USER:	**GRAY, ILKA K (ixg)**
FOLDER:	**K984146 - 245 pages (FOI:10000645)**
COMPANY:	**I-FLOW CORP. (IFLOW)**
PRODUCT:	**SET, ADMINISTRATION, INTRAVASCULAR (FPA)**
SUMMARY:	**Product: PARAGON INFUSION**

DATE REQUESTED:	**Tue Feb 02 24:00:00 2010**
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CORPORATION

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K984146

SUMMARY OF SAFETY AND EFFECTIVENESS

November 11, 1998

Trade Name: Paragon Infusion Kit

Common Name: Infusion Pump Kit

Classification Name: Pump, Infusion

All questions and/or comments concerning this document should be made to:

Robert J. Bard, Esq., R.A.C.
Vice President of Regulatory and Legal Affairs

I-Flow Corporation
20202 Windrow Drive
Lake Forest, CA 92630

Telephone: 949.206.2700
Fax: 949.206.2600

1.0 GENERAL INFORMATION

1.1 Purpose of Submission

1.1.1 This submission is intended to notify the Federal Food and Drug Administration that I-Flow Corporation intends to market a new intended use for the Paragon Infusion System (K923875), originally identified as the SideKick 50 Plus and SideKick 100 Plus. The Paragon will be marketed as a kit, the Paragon Infusion Kit, including labeling changes and additional components.

1.1.2 Trade Name: Paragon Infusion Kit

1.1.3 Common Name: Infusion Pump Kit

1.1.4 Classification Name: Pump, Infusion

1.1.5 Classification Panel: General Hospital and Personal Use Device

1.2 Statement of Equivalence

1.2.1 The Paragon Infusion Kit includes components that are legally marketed (either pre-amendment devices or devices that have been granted permission to market via premarket notification regulation).

1.2.2 The Paragon pump and administration set are the same as used in K923875.

1.2.3 The Paragon Kit is substantially equivalent to the I-Flow Paragon Infusion System (K923875), the I-Flow PainBuster Infusion Kit (K980558, K982946), the Sgarlato Pain Control Infusion Pump (PCIP) (K896422) and the I-Flow Homepump C-Series (K944692).

2.0 PHYSICAL SPECIFICATIONS AND DESCRIPTIONS

2.1 Description of the Paragon Infusion Kit

2.1.1 The Paragon Infusion Kit is identical to the I-Flow PainBuster Infusion Kit with the exception of the Paragon pump and administration set replacing the PainBuster pump.

2.1.2 The kit is comprised of a Paragon pump and administration set (K923875) and various kit components such as catheter, needle, syringe, Y adapter, dressing, tape, gauze and carry case.

2.1.2.1 The PainBuster kit contains all the above components except for an elastomeric pump with integrated administration set instead of the Paragon pump and administration set.

2.1.3 The Paragon administration set is intended to attach to the kit catheter at the distal end of the set to provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

2.1.4 The Paragon administration set is a disposable device intended for single patient use. The Paragon pump is reusable.

2.1.5 The Paragon is suitable for use as an ambulatory device and is intended for use in the hospital, home environment or alternative care sites.

2.2 Description of Paragon Pump

2.2.1 The Paragon pump consists of two cylindrical shells. The top half of the pump has internal threads which mate to the external threads of the bottom half of the pump.

2.2.2 The top incorporates a pressure plate which applies a load to the pliable drug bag. The load is applied to the drug bag by way of two opposing springs which act upon a scissors mechanism. The spring/scissors mechanism creates a near constant pressure in the drug bag.

2.2.3 The bottom half of the pump is slotted to allow for positioning of the administration set.

2.2.4 When the top and bottom halves of the pump are fully threaded together, the pressure plate contacts the drug bag and acts as the pressurizing element.

2.2.5 This premarket notification proposes no changes to the Paragon pump.

2.3 Description of Paragon Administration Set

2.3.1 The Paragon administration set consists of a PVC drug bag attached to the administration line.

2.3.2 Each administration set consists of fixed diameter flow control tubing or glass orifice.

2.3.3 The flow control tubing or glass orifice is cut to a specific length L. When the PVC drug bag is pressured by the Paragon pump, the delivery times are defined by the inside diameter of the flow control orifice.

2.3.3.1 The delivery time characteristic is derived from the flow rate of the device which is in turn approximated by Poiseulle's equation:

$$Q = \frac{\Delta \rho \pi D^4}{128 \mu L}$$

2.3.3.2 Where Q is the flow rate, ρ is the pressure drop across the orifice, D is the inside diameter of the flow controlling orifice, μ is the dynamic viscosity of the fluid and L is the length of the orifice. The equation provides an approximation of the actual delivery time.

2.4 Product Configuration

2.4.1 The Paragon pump:

2.4.1.1 PG100000P: 100 ml volume

2.4.2 The Paragon administration sets:

2.4.2.1 PG100005: 100 ml volume, 0.5 ml/hr flow rate

2.4.2.2 PG100010: 100 ml volume, 1.0 ml/hr flow rate

2.4.2.3 PG100020: 100 ml volume, 2.0 ml/hr flow rate

2.4.2.4 PG100040: 100 ml volume, 4.0 ml/hr flow rate

2.4.2.5 PG100100: 100 ml volume, 10.0 ml/hr flow rate

2.4.2.6 PG100020Y: 100 ml volume, 2.0 ml/hr flow rate, dual orifice, dual catheter with Y adapter

2.4.2.6.1 The dual orifice set consists of a standard Paragon set with dual orifice downstream from the Y adapter. Each orifice allows 2 ml/hr flow rate.

2.4.3 Each model consists of a kit with the following components:

2.4.3.1 Paragon pump (optional).

2.4.3.1.1 The reusable Paragon pump may be packaged and sold separately from the disposable kit components.

2.4.3.2 Paragon administration set.

2.4.3.3 Catheter:

2.4.3.3.1 18 to 22 G catheter, 11 to 40 in. length, polyamide, nylon, FEP (fluorinated ethylene propylene) polymer, silicone, polyurethane or Teflon.

2.4.3.3.2 A catheter connector is included to connect the catheter to the distal luer of the administration set.

2.4.3.3.3 The B. Braun Perifix® Epidural Catheter Set is an example of the type of catheter that may be used with the Paragon Infusion Kit.

2.4.3.3.3.1 Product code: EC20-0.

2.4.3.3.3.2 510(k) number: K813186.

2.4.3.4 Needle:

2.4.3.4.1 14 to 18 G, 1 ½ to 3 ¼ in. length, stainless steel.

2.4.3.4.2 The needle may be a catheter over needle as in the Angiocath™ example below.

2.4.3.4.3 The Angiocath catheter introducer needle is an example of the type of catheter introducer needle that may be used with the Paragon Infusion Kit.

2.4.3.4.3.1 Product code: 382258.

2.4.3.5 Syringe (optional):

2.4.3.5.1 60 cc plastic, luer lock syringe.

2.4.3.5.2 The syringe is used to fill the Paragon drug bag with medication.

2.4.3.5.3 The B-D 60 cc syringe is an example of the type of syringe that may be included in the Paragon Kit.

2.4.3.5.3.1 Product Code: 309663.

2.4.3.6 Dressing (optional):

2.4.3.6.1 The dressing is used to hold the catheter and/or flow restrictor in place.

2.4.3.6.2 The OpSite™ is an example of the type of dressing that may be used in the Paragon Kit.

2.4.3.6.2.1 Product Code: 4973.

2.4.3.7 Carry Case (optional):

2.4.3.7.1 The carry case is used to hold the Paragon pump while delivering medication.

2.4.3.7.1.1 I-Flow part numbers 1400749, 1400752 or 1400758.

2.4.3.8 Antiseptic Skin Swabs (optional):

2.4.3.8.1 The antiseptic skin swabs are used to prep the skin area of the patient prior to inserting the catheter.

2.4.3.8.2 The Alcohol Prep Pads or Iodophor PVP Scrub Swabsticks manufactured by Clinipad Corporation are examples of the type of antiseptic skin swabs that may be used in the Paragon Kit.

2.4.3.8.2.1 Model number: CL0110.

2.4.3.8.2.2 Model number: CL1244.

2.4.3.9 Tape (optional):

2.4.3.9.1 The tape may be used to the secure catheter, flow control tubing or gauze.

2.4.3.9.2 The Transpore™ Surgical Tape manufactured by 3M is an example of the type of tape that may be used in the Paragon Kit.

2.4.3.9.2.1 Model number: 3M1527-1.

2.4.3.10 Gauze (optional):

2.4.3.10.1 The gauze may be used to secure the catheter or flow control tubing.

2.4.3.10.2 The Kling® Conforming Gauze manufactured by Johnson and Johnson is an example of the type of gauze which may be used in the Paragon Kit.

2.4.3.10.2.1 Model number: JJ6923.

2.4.3.11 Y Adapter (optional)

2.4.3.11.1 The Y adapter is used for an additional catheter for a large wound or multiple wound sites.

2.4.3.11.2 The Flexible Y Fitting by Qosina is an example of the type of Y Adapter that may be used in the Paragon Kit.

2.4.3.11.2.1 Model number: 81120.

2.5 Components and Materials

The pump and administration sets used in the Paragon Infusion Kit are currently available models of the Paragon Infusion System (K923875). No changes will be made to the Paragon pump or administration sets.

All kit components other than the pump and administration set are identical to those used in the PainBuster infusion system submitted under K980558, K982946.

The Paragon administration set is a disposable device intended for single patient use. The Paragon pump is reusable.

2.6 Power Requirements

2.6.1 The Paragon pump is a mechanical pump that utilizes spring energy for power. No additional external power source is required.

3.0 OPERATIONAL SPECIFICATIONS AND DESCRIPTIONS

3.1 Standard Operating Conditions:

Priming/Residual Volume:	< 5 ml
Operating Temperature:	31°C skin temperature (90°F)
Test Solution:	0.9% NaCl
Operating Pressure:	6.0 psi pressure source
Head Height:	0"
Accuracy:	±10% at 95% confidence interval

3.2 **Flow Rate Performance Data**: Testing occurred at standard operating conditions. All models produced an average flow rate within the ±10% accuracy claim.

	100 ml x 0.5 ml/hr	100 ml x 1 ml/hr	100 ml x 2 ml/hr	100 ml x 4 ml/hr	100 ml x 10 ml/hr
Average Flow Rate (ml/hr)	0.53	0.99	1.99	4.14	10.30
Std. Dev.	0.01	0.03	0.07	0.10	0.38
N	5	5	5	5	10

100 ml x 0.5 ml/hr: A five (5) piece sample produced an average flow rate of 0.53 ml/hr. The resulting average is well within its ±10% accuracy claim. The fastest infusion had an average flow rate of 0.54 ml/hr and the slowest infusion had an average flow rate of 0.51 ml/hr.

100 ml x 1.0 ml/hr: A five (5) piece sample produced an average flow rate of 0.99 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 1.04 ml/hr and the slowest infusion had an average flow rate of 0.96 ml/hr.

100 ml x 2.0 ml/hr: A five (5) piece sample produced an average flow rate of 1.99 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 2.05 ml/hr and the slowest infusion had an average flow rate of 1.90 ml/hr.

100 ml x 4.0 ml/hr: A five (5) piece sample produced an average flow rate of 4.14 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 4.24 ml/hr and the slowest infusion had an average flow rate of 3.99 ml/hr.

100 ml x 10.0 ml/hr: A ten (10) piece sample produced an average flow rate of 10.30 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 10.80 ml/hr and the slowest infusion had an average flow rate of 9.65 ml/hr.

Back Pressure (Head Height) Comparison: Approximately 0.57 psi pressure difference results per 16" head height. Thus, a 10% flow rate change may occur for each 16" head height difference from nominal assuming a 6 psi pressure source.

3.3 **Drug Delivery Comparison**: Local anesthetics have densities similar to normal saline (e.g. 1.002 to 1.005 for Ropivacaine HCl vs. 1.0045 for normal saline) and should not affect flow rate. Product labeling includes a statement as to delivery times and the possible deviation from nominal due to drug viscosity.

3.4 **Safety / Alarm Functions**

3.4.1 The Paragon pump and administration set provide a continuous fixed flow and as such is not subject to fluid runaway conditions similar to that of some electronic pumps.

3.4.2 The Paragon pump will not be recommended for any application that exceeds the minimum internal pressure of the system.

3.4.3 If for any reason the patient needs to stop his or her infusions, each administration set is supplied with a pinch clamp to stop the infusion.

3.4.4 This device contains no alarms or indicators for flow other than visual.

3.4.5 This device contains no alarms or indicators to detect air in line or an occlusion; however, each set may include an integrated air-eliminating filter.

4.0 BIOLOGICAL SPECIFICATIONS

4.1 Biological testing is in conformance with ISO 10993 Part 1 for all fluid path components of the Paragon administration set.

5.0 CHEMICAL AND DRUG SPECIFICATIONS

5.1 Compatibility

5.1.1 There are no specific drugs referenced in the labeling for the Paragon Infusion Kit.

5.1.2 The Paragon Infusion Kit is intended for use with general local anesthetics and epidural medications.

5.2 Drug Stability

5.2.1 There are no drugs included in the Paragon Infusion Kit.

6.0 INTENDED USE

6.1 The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management.

6.2 Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

6.3 The Paragon pump is re-usable. The disposable Paragon administration set is single patient use only.

6.4 No testing has been conducted to determine the efficacy of the Paragon for the delivery of blood, blood products, lipids or fat emulsions. The Paragon is not intended for the delivery of blood, blood products, lipids or fat emulsions.

6.5 The Paragon is suitable for use as an ambulatory device and is intended for use in the hospital, home environment or alternative care sites.

7.0 PACKAGING

7.1 The Paragon Kit consists of an inner pouch or tray with Tyvek lid stock surrounded by a header bag with an ETO Tyvek strip.

7.2 The Paragon administration set may be packaged in either a Tyvek pouch or Form/Fill/Seal.

7.3 The Paragon Kit components are placed in the inner tray or pouch.

7.4 Packaging is suitable for either radiation or ETO sterilization.

8.0 STERILIZATION INFORMATION

Note: The kit components of the Paragon Infusion Kit may be purchased non-sterile and packaged by I-Flow or sterile from the manufacture. The Paragon administration set and non-sterile purchased components shall be sterilized as follows:

8.1 The methods of sterilization are gamma radiation (Cobalt 60) or ETO gas.

9.0 COMPARISON TO LEGALLY MARKETED DEVICES

See Table 1 that follows this section for more specific information.

9.1 Intended Use

9.1.1 The Paragon Infusion Kit, the PainBuster Infusion Kit and the Sgarlato Pain Control Infusion Pump (PCIP) have the same intended use:

9.1.1.1 To provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

9.1.2 The predicate Paragon Infusion System and Homepump C-Series are intended for general infusion use, including chemotherapy and pain management.

9.2 Device Descriptions

9.2.1 The Paragon Infusion Kit

9.2.1.1 The Paragon Infusion Kit is identical to the predicate PainBuster Infusion Kit with the exception of the Paragon pump and administration set replacing the PainBuster pump.

9.2.1.2 The Paragon Infusion Kit uses the same mechanical, reusable Paragon pump as the predicate Paragon Infusion System.

9.2.1.3 The Paragon Infusion Kit uses the same Paragon Administration Set as the Paragon Infusion System.

9.2.2 The Paragon Infusion System

9.2.2.1 The Paragon Infusion Kit uses the same pump and administration sets as the Paragon Infusion System (K923875).

9.2.3 The Sgarlato Pain Control Infusion Pump (PCIP)

9.2.3.1 The Sgarlato PCIP consists of a kit very similar to the Paragon and PainBuster Infusion Kit. These kits consist of an infusion pump and administration set, catheter, needle, syringe, Y adapter, carry case, dressing, tape and gauze.

9.2.3.2 The Sgarlato kit uses a disposable, spring driven syringe pump with integrated administration set.

9.2.4 The Homepump C-Series

9.2.4.1 The Homepump C-Series consists of a disposable, elastomeric infusion pump with integrated administration set.

9.2.5 Specifications

9.2.5.1 The Paragon Infusion Kit, PainBuster Infusion Kit and Sgarlato PCIP have similar fill volumes and flow rates, see Table 1.

9.2.6 Flow Control

9.2.6.1 The Paragon Infusion Kit and all its predicate devices use either a glass orifice or PVC tubing to control the flow rate.

9.2.7 Materials

9.2.7.1 The Paragon Infusion Kit uses the same Paragon Administration Set as the Paragon Infusion System. All fluid path materials of the Paragon Administration Set are in conformance with ISO 10993 Part 1.

9.2.8 Based upon the data presented in this section 9.0 and Table 1, I-Flow Corporation has determined that the Paragon Infusion Kit is substantially equivalent to the named predicate devices.

Table 1
Comparison to Legally Marketed Devices

Comparison Element	Paragon Infusion Kit (subject device)	SE[1] Paragon Infusion System (K923875)	SE[1] PainBuster Infusion Kit (K980558, K982946)	SE[1] Sgarlato PCIP (K896422)	SE[1] Homepump C-Series (K944692)
Intended Use	To provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.	General infusion use, including chemotherapy and pain management.	To provide continuous infusion of a local anesthetic directly into the intraoperative site for postoperative pain management.	To provide continuous infusion of a local anesthetic directly into the surgical wound site for postoperative pain management.	General infusion use, including chemotherapy and pain management.
Routes of Administration	Percutaneous, subcutaneous, intramuscular and epidural	Intravenous	Percutaneous and subcutaneous	Percutaneous, subcutaneous and epidural	Intravenous, intra-arterial, epidural or subcutaneous
Contraindications	Not intended for intravenous or intra-arterial delivery. Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for intravenous, intra-arterial or epidural delivery. Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for rapid infusions. Not intended for intravenous infusion.	Not intended for delivery of blood, blood products, lipids or fat emulsions.
Reuse Capability	Re-usable pump, single patient use disposable administration set	Re-usable pump, single patient use disposable administration set	Disposable, single patient use	Disposable, single patient use	Disposable, single patient use
Description	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.
Fill Volumes	100 ml	100 ml	50 to 270 ml	50 to 100 ml	50 to 500 ml
Flow Rates	0.5, 1.0, 2.0, 4.0 or 10.0 ml/hr	0.5 to 200 ml/hr	0.5, 1.0, 2.0, 5.0 or 10.0 ml/hr	0.5, 1.0 or 2.0 ml/hr	0.5 to 500 ml/hr
Pump Type	Mechanical spring	Mechanical spring	Elastomeric Pump	Spring driven syringe pump	Elastomeric Pump
Power Requirements	None	None	None	None	None
Pump Mechanism	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.
Pressure Source	Mechanical spring energy	Mechanical spring energy	Strain energy of elastomeric membranes	Mechanical spring energy	Strain energy of elastomeric membranes
Fluid Reservoir	PVC drug bag	PVC drug bag	Thermoplastic (Krayton) elastomeric membrane	Polypropylene plastic syringe	Thermoplastic (Krayton) elastomeric membrane
Administration Set					
Flow Control	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.
Safety / Alarm Functions	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.

[1]SE = Substantially Equivalent

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB - 9 1999

Robert J. Bard, Esq., R.A.C.
Vice President Regulatory and Legal Affairs
I-Flow Corporation
20202 Window Drive
Lake Forest, California 92630

Re: K984146
Trade Name: Paragon Infusion
Regulatory Class: II
Product Code: FPA
Dated: November 11, 1998
Received: November 19, 1998

Dear Mr. Bard:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Good Manufacturing Practice for Medical Devices: General (GMP) regulation (21 CFR Part 820) and that, through periodic GMP inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4692. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html".

Sincerely yours,

Timothy A. Ulatowski
Director
Division of Dental, Infection Control,
and General Hospital Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number (if known): K984146

Device Name: Paragon Infusion Kit

Indications for Use:

1. The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management. Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUED ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Dental, Infection Control,
and General Hospital Devices

510(k) Number K984146

Prescription Use ✓ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB - 9 1999

Robert J. Bard, Esq., R.A.C.
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Sincerely yours,

Timothy A. Ulatowski
Director
Division of Dental, Infection Control,
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Office of Device Evaluation
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Enclosure

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1. The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management. Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUED ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Dental, Infection Control,
and General Hospital Devices
510(k) Number K984146

Prescription Use ✓ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

3

(Optional Format 1-2-96)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food And Drug Administration

m: Reviewer(s) - Name(s) HUNG TRINH

Memorandum

ject: 510(k) Number K984146

The Record - It is my recommendation that the subject 510(k) Notification:

- ☐ Refused to accept.
- ☐ Requires additional information (other than refuse to accept).
- ☐ Accepted for review _____.
- ☑ Is substantially equivalent to marketed devices.
- ☐ NOT substantially equivalent to marketed devices.
  - De Novo Classification Candidate? ☐ YES ☐ NO
- ☐ Other (e.g., exempt by regulation, not a device, duplicate, etc.)

Is this device subject to Postmarket Surveillance?	☐ YES	☑ NO
Is this device subject to the Tracking Regulation?	☐ YES	☑ NO
Was clinical data necessary to support the review of this 510(k)?	☐ YES	☑ NO
Is a prescription device?	☑ YES	☐ NO
Was this 510(k) reviewed by a Third Party?	☐ YES	☑ NO
Special 510(k)?	☐ YES	☑ NO
Abbreviated 510(k)?	☐ YES	☑ NO

This 510(k) contains:

Truthful and Accurate Statement ☐ Requested ☑ Enclosed
(required for originals received 3-14-95 and after)

☑ A 510(k) summary OR ☐ A 510(k) statement

☐ The required certification and summary for class III devices

☑ The indication for use form (required for originals received 1-1-96 and after)

Material of Biological Origin ☐ YES ☐ NO

The submitter requests under 21 CFR 807.95 (doesn't apply for SEs):

Confidentiality ☐ Confidentiality for 90 days ☐ Continued Confidentiality exceeding 90 days

Predicate Product Code with class: Additional Product Code(s) with panel (optional):

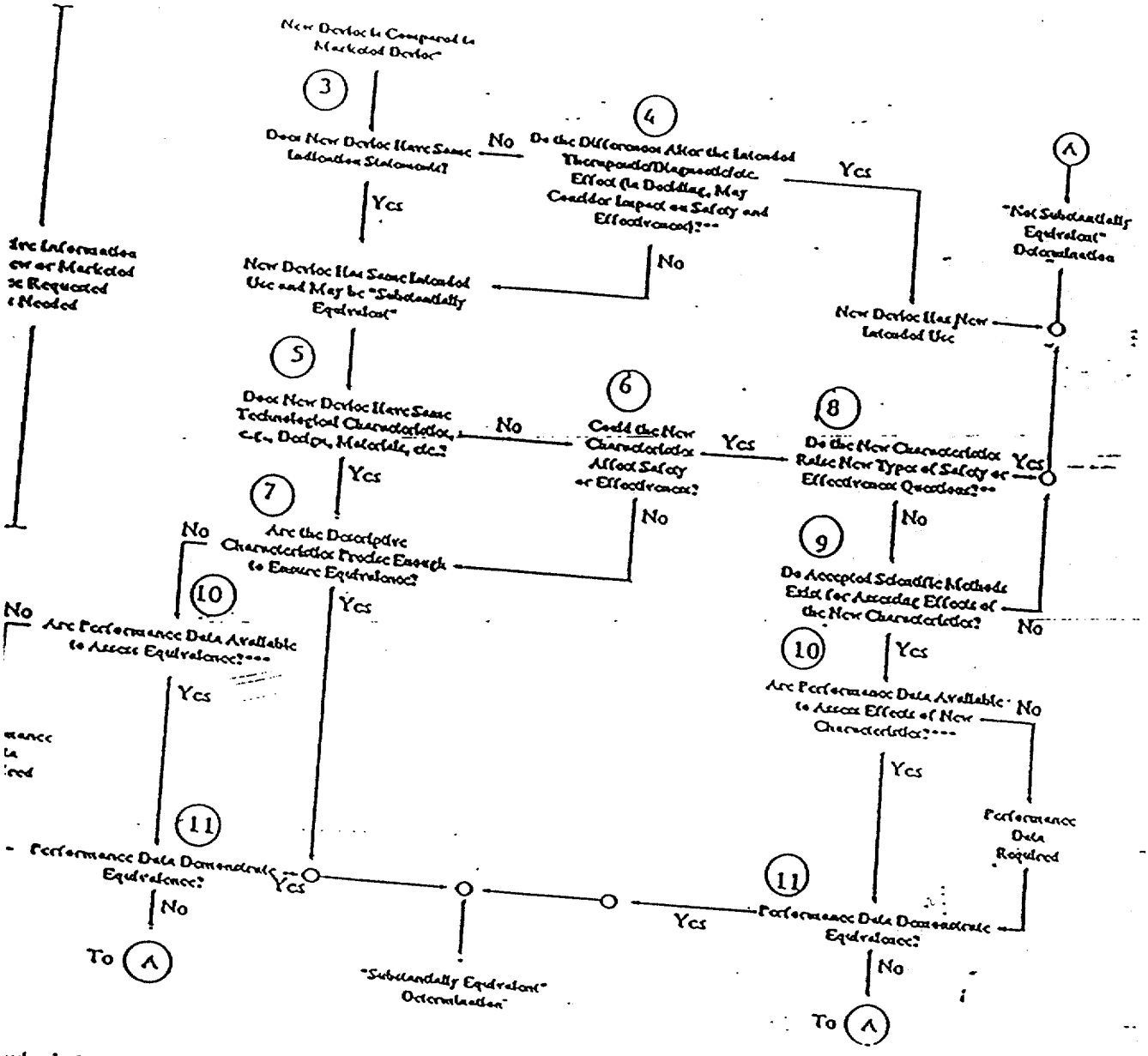
80 FRA class II

Patricia Cicirelli (Branch Chief) HFZ-83 (Branch Code) 2/5/99 (Date)

4

view: (Division Director) 2/8/99 (Date)

510(k) "SUBSTANTIAL EQUIVALENCE" DECISION-MAKING PROCESS (DETAILED)



ubmissions compare new devices to marketed devices. FDA requests additional information if the relationship marketed and "predicate" (pre-Amendments or reclassified post-Amendments) devices is unclear.

ision is normally based on descriptive information alone, but limited testing information is sometimes required.

y be in the 510(k), other 510(k)s, the Center's classification files, or the literature.

MEMO TO THE RECORD
510(K) REVIEW

DATE: 2/1/99
FROM: Hung Trinh
DOCUMENT: ~~K984063~~ K984146
COMPANY NAME: I-Flow Corp
DEVICE NAME: Paragon Infusion Kit

OFFICE: HFZ-480
DIVISION:DDIG/GHDB

Contact point: Robert Bard, VC Regulatory and Legal Affairs
949-206-2700
949-206-2600 (fx)

NARRATIVE DEVICE DESCRIPTION

1. **SUMMARY DESCRIPTION OF THE SUBMISSION UNDER REVIEW:**
The firm intends to market a new intended use for the Paragon Infusion System (K923875), originally identified as the SideKick 50 Plus and SideKick 100 Plus. The subject device will be marketed as a kit, which includes labeling changes and additional components.

2. **INTENDED USE:**
The device is intended to provide continuous infusion of a local anesthetic directly into an intraoperative (soft tissue/body cavity) site for general surgery for postoperative pain management. Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

3. **DEVICE DESCRIPTION:**

A. **Life-supporting or life-sustaining:** no
B. **Implant (short-term or long-term):** no
C. **Is the device sterile?** yes
If yes, is sterility information provided? yes
Gamma radiation (cobalt 60) or ETO gas. Gamma radiation validation methodology is by ANSI/AAMI ST32-1191/EN 552; dosage from 25 to 35 kGy. ETO sterilization complies with ANSI/AAMI/ISO 11135-1994/EN550
D. **Is the device for single use?** Single patient use
E. **Is the device for prescription use?** yes
If yes, is prescription labeling included? yes
F. **Is the device for home use or portable?** yes
G. **Does the device contain drug or biological product as a component?** no
H. **Is this device a kit?** no
I. **Software-driven:** no
J. **Electrically Operated:** no
K. **Applicable standards to which conformance has been demonstrated (e.g., IEC, ANSI, ASTM, etc.):** no
L. **Device(s) to which equivalence is claimed, manufacturer, and 510(k) number or preamendment status:**
I-Flow Paragon Infusion System (K923875)

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PainBuster Infusion Kit (K980558, K982946)
Home pump C-Series (K944692)
Sgarlato Pain Control Infusion Pump (PCIP) (K896422)

M. Submission provides comparative specifications yes
comparative in vitro data no
performance data yes
animal testing no
clinical testing no
biocompatibility testing no (same material as predicates)

N. Provide a statement of how the device is either similar to and/or different from other marketed devices, plus data (if necessary) to support the statement. Provide a summary about the devices design, materials, physical properties and toxicology profile if important.

The sponsor claims that device is the same as the I-Flow PainBuster Infusion Kit with the exception of the Paragon Pump and administration set replacing the PainBuster Pump. The kit is comprised of a Paragon pump and administration set (K923875) and various kit components such as catheter, needle, syringe, Y adapter, dressing, tape, gauze and carry case.

Comparative specs:

Comparison Element	Paragon Infusion Kit	Paragon Infusion System	PainBuster Infusion kit	Sgarlato PCIP
Bolus Volume	0.5 ml; ±10% @ 95% confidence interval	N/a	o.5 ml	0-1.0 ml
Bolus Lockout time	6 or 15 min; ±15% @ 95% confidence interval	N/a	6, 15, 60 min	15, 30,, 60, 120 min
Flow rates	0.5 to 10 ml/hr; ±10% @ 95% confidence interval	0.5 - 200 ml/hr	0.5 to 10 ml/hr	0.5 – 500 ml/hr
Fill Volume	100 ml	100 ml	50 to 270 ml	50 to 100 ml
Pressure source	Mechanical spring energy of the pump	Mechanical spring energy of the pump	Strain energy of elastomeric membranes	Mechanical Spring
Fluid Reservoir	PVC drug bag	PVC drug bag	Thermoplastic (Krayton) Elastomeric membrane	Polypropylene Plastic syringe
Catheter	Nylon, polyamide FEP polymer, silicon, Polyurethane or teflon	N/a	Nylon, polyamide FEP polymer, Polyurethane or teflon	polyamide

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Needle	Stainless steel	N/a	Stainless steel	Stainless steel
Syringe (optional)	Polypropylene, synthetic rubber, medical silicone	N/a	Polypropylene, synthetic rubber, medical silicone	
Y Adapter (optional)	PVC, Surgimedics or ABS, Qosina	N/a	PVC, Surgimedics or ABS Qosina	

A more detailed comparison is available on page 18 of 19.

O. Does the submission include a summary of safety and effectiveness information upon which an equivalence determination is based? yes

P. RECOMMENDATION:

I believe that this device is equivalent to: 80 FPA

Classification should be based on:

880.5440 Intravascular (IV) administration set **Class:** II

If the device is substantially equivalent to a class III device, does the submission include: (1) certification that a reasonable search of all information known, or otherwise available, about the generic type of device has been performed and (2) a summary description of the types of safety and effectiveness problems associated with the type of device and a citation to the literature, or other sources of information, upon which they have based the description? n/a

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"SUBSTANTIAL EQUIVALENCE" (SE) DECISION MAKING DOCUMENTATION

K984146

Reviewer: Hung Trinh

Division/Branch: DDIGD/GHDB

Device Name: Paragon Infusion Kit

Product To Which Compared (510(K) Number If Known):

		YES	NO	
1.	Is Product A Device	X		If **NO** = Stop
2.	Is Device Subject To 510(k)?	X		If **NO** = Stop
3.	Same Indication Statement?	X		If **YES** = Go To 5
4.	Do Differences Alter The Effect Or Raise New Issues of Safety Or Effectiveness?			If **YES** = Stop **NE**
5.	Same Technological Characteristics?	X		If **YES** = Go To 7
6.	Could The New Characteristics Affect Safety Or Effectiveness?			If **YES** = Go To 8
7.	Descriptive Characteristics Precise Enough?		X	If **NO** = Go To 10 If **YES** = Stop **SE**
8.	New Types Of Safety Or Effectiveness Questions?			If **YES** = Stop **NE**
9.	Accepted Scientific Methods Exist?			If **NO** = Stop **NE**
10. Performance Data Available?		X		If **NO** = Request Data
11. Data Demonstrate Equivalence?		X		Final Decision: **SE**

Note: In addition to completing the form on the LAN, "yes" responses to questions 4, 6, 8, and 11, and every "no" response requires an explanation.

9

20202 Windrow Dr
Lake Forest, CA 92630
Tel: 949.206.2670
Fax: 949.206.2603

I-Flow Corporation

Fax

To:	Hung Trinh	**From:**	Robert J Bard, Esq.
Fax:	301.480.3002	**Pages:**	6
Phone:	301.594.1287 x 130	**Date:**	02/02/99
Re:	K984063, K984146, K984638	**CC:**	

x **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

● **Comments:** The documents accompanying this facsimile transmission contains information which may be legally privileged and confidential. The information is intended only for the use of the recipient named below. If you have received this facsimile in error, please immediately notify us by telephone to arrange for return of the original documents to us. Any disclosure, copying, distribution or the taking of any action in reliance on the contents of this faxed information is strictly prohibited.

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I-FLOW CORPORATION
20202 Windrow Drive
Lake Forest, CA 92630
(800) 448-3569 (949) 206-2700
Fax (949) 206-2600

February 2, 1999

VIA FACSIMILE

Hung Trinh
Food and Drug Administration
Center for Devices and Radiological Health
Office Device Evaluation
9200 Corporate Blvd.
Rockville, Maryland 20850

Re: K984063
K984146
K984638

Dear Mr. Trinh:

Pursuant to our conversation of February 2, 1999, I have made the following changes to the above referenced premarket notifications.

K984063 The **Indications for Use** description has been changed to a single statement. Lines 3, 4 and 5 have been deleted and Line 2 has been incorporated into Line 1.

No other changes have been made to premarket notification K984063.

K984146 A supplemental submission was made on January 13, 1999 to include synovial infusions as an additional indication for use. The basis of this supplemental submission was the finding of a predicate device (the McKinley Outbound K982256) that included (b)(4) (b)(4) as an indication for use.

I-Flow has agreed to remove the January 13 revision from our submission based on your statement that the McKinley will not be allowed to have an indication for use that includes (b)(4) (b)(4) Based on your statement, I-Flow believes the Office of Device Evaluation will require McKinley to modify their Indications for Use Statement and that the posting on the FDA 510(k) webpage will be changed.

//

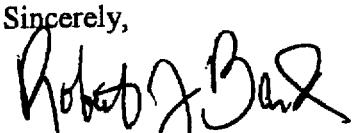
The **Indications for Use** description has been changed to a single statement including both Lines 1 and 2.

K984638 The **Indications for Use** description has been changed to a single statement including both Lines 1 and 2.

No other changes have been made to premarket notification K984638.

If you have any additional issues specific to the above identified premarket notifications, either to the information provided or in general, I can be reached at 949.206.2670 or 800.206.2700.

Sincerely,



Robert J. Bard, Esq., R.A.C.
Vice President, Regulatory and Legal Affairs

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510(k) Number (if known): K984146

Device Name: Paragon Infusion Kit

Indications for Use:

1. The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management. Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUED ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

(Optional Format 1-2-96)

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Internal Administrative Form

	YES	NO
1. Did the firm request expedited review?		✓
2. Did we grant expedited review?		✓
3. Have you verified that the Document is labeled Class III for GMP purposes?		✓
4. If, not, has POS been notified?		✓
5. Is the product a device?	✓	
6. Is the device exempt from 510(k) by regulation or policy?		✓
7. Is the device subject to review by CDRH?	✓	
8. Are you aware that this device has been the subject of a previous NSE decision?		✓
9. If yes, does this new 510(k) address the NSE issue(s), (e.g., performance data)?		✓
10. Are you aware of the submitter being the subject of an integrity investigation?		✓
11. If, yes, consult the ODE Integrity Officer.		✓
12. Has the ODE Integrity Officer given permission to proceed with the review? (Blue Book Memo #I91-2 and Federal Register 90N0332, September 10, 1991.		✓

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Screening Checklist
For all Premarket Notification 510(k) Submissions

Device Name: Paragon Infusion	K984144
Submitter (Company): I-Flow Corp.	

Items which should be included *(circle missing & needed information)*	SPECIAL YES	SPECIAL NO	ABBREVIATED YES	ABBREVIATED NO	TRADITIONAL YES	TRADITIONAL NO	✓ IF ITEM IS NEEDED AND IS MISSING
1. Cover Letter clearly identifies Submission as:							
a) "Special 510(k): Device Modification"	GO TO #2,4		GO TO # 3,4,5		GO TO #4,5	✓	
b) "Abbreviated 510(k)"							
c) Traditional 510(k)							
2. "SPECIALS" - ONLY FOR MODIFICATIONS TO MANUFACTURER'S OWN CLASS II, III OR RESERVED CLASS I DEVICE							
a) Name & 510(k) number of legally marketed (unmodified) predicate device							
b) *STATEMENT - INTENDED USE AND INDICATIONS FOR USE OF MODIFIED DEVICE AS DESCRIBED IN ITS LABELING HAVE NOT CHANGED**			* If no - STOP not a special				
c) *STATEMENT - FUNDAMENTAL SCIENTIFIC TECHNOLOGY OF THE MODIFIED DEVICE HAS NOT CHANGED**			* If no - STOP not a special				
d) Design Control Activities Summary							
i) Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis							
ii) Based on the Risk Analysis, an identification of the verification and/or validation activities required, including methods or tests used and acceptance criteria to be applied							
iii) A declaration of conformity with design controls. The declaration of conformity should include:							
1) A statement signed by the individual responsible, that, as required by the risk analysis, all verification and validation activities were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met							
2) A statement signed by the individual responsible, that manufacturing facility is in conformance with design control procedure requirements as specified in 21 CFR 820.30 and the records are available for review.							

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→ → → CONTINUE TO SECTION 4 ← ← ←

	SPECIALS		ABBREVIATED		TRADITIONAL		✓ IF ITEM IS NEEDED AND IS MISSING
	YES	NO	YES	NO	YES	NO	
3. ABBREVIATED 510(K): SPECIAL CONTROLS/CONFORMANCE TO RECOGNIZED STANDARDS							
a) For a submission, which relies on a guidance document and/or special control(s), a summary report that describes how the guidance and/or special control(s) was used to address the risks associated with the particular device type							
b) If a manufacturer elects to use an alternate approach to address a particular risk, sufficient detail should be provided to justify that approach.							
c) For a submission, which relies on a recognized standard, a declaration of conformity to the standard. The declaration should include the following:							
i) An identification of the applicable recognized consensus standards that were met							
ii) A specification, for each consensus standard, that all requirements were met, except for inapplicable requirements or deviations noted below							
iii) An identification, for each consensus standard, of any way(s) in which the standard may have been adapted for application to the device under review, e.g., an identification of an alternative series of tests that were performed							
iv) An identification, for each consensus standard, of any requirements that were not applicable to the device							
v) A specification of any deviations from each applicable standard that were applied							
vi) A specification of the differences that may exist, if any, between the tested device and the device to be marketed and a justification of the test results in these areas of difference							
vii) Name/address of test laboratory/certification body involved in determining the conformance of the device with applicable consensus standards and a reference to any accreditations for those organizations							
d) Data/information to address issues not covered by guidance documents, special controls, and/or recognized standards							

→ → → CONTINUE TO SECTION 4 ← ← ← 16

4. GENERAL INFORMATION: REQUIRED IN ALL 510(K) SUBMISSIONS	SPECIALS		ABBREVIATED		TRADITIONAL		✓ IF ITEM IS NEEDED AND IS MISSING
	YES	NO	YES	NO	YES	NO	
a) trade name, classification name, establishment registration number, address of manufacturer, device class					✓		
b) OR a statement that the device is not yet classified	FDA - may be a classification request; see coordinator						
c) identification of legally marketed equivalent device	NA				✓		
d) compliance with Section 514 - performance standards	NA				✓		
e) address of manufacturer					✓		
f) Truthful and Accurate Statement					✓		
g) Indications for Use enclosure					✓		
h) SMDA Summary or Statement *(FOR ALL DEVICE CLASSES)*							
i) Class III Certification & Summary *(FOR ALL CLASS III DEVICES)*							
j) Description of device (or modification) including diagrams, engineering drawings, photographs, service manuals					✓		
k) Proposed Labeling:					✓		
i) package labeling (user info)					✓		
ii) statement of intended use					✓		
iii) advertisements or promotional materials					✓		
i) MRI compatibility (if claimed)							
m) Comparison Information (similarities and differences) to named legally marketed equivalent device (table preferred) should include:					✓		
i) labeling					✓		
ii) intended use					✓		
iii) physical characteristics							
iv) anatomical sites of use							
v) performance (bench, animal, clinical) testing	NA						
vi) safety characteristics	NA						
n) If kit, kit certification							
5. Additional Considerations: (may be covered by Design Controls)							
a) Biocompatibility data for all patient-contacting materials, OR certification of identical material/formulation:						✓	
i) component & material						✓	
ii) identify patient-contacting materials						✓	
iii) biocompatibility of final sterilized product						✓	
b) Sterilization and expiration dating information:					✓		
i) sterilization method					✓		
ii) SAL					✓		
iii) packaging					✓		
iv) specify pyrogen free					✓		
v) ETO residues					✓		
vi) radiation dose					✓		
c) Software validation & verification:						✓	
i) hazard analysis						✓	
ii) level of concern						✓	
iii) development documentation						✓	
iv) certification						✓	

Items shaded under "NO" are necessary for that type of submission. Circled items and items with checks in the "Needed & Missing" column must be submitted before acceptance of the document.

Passed Screening ✓ Yes ____ No

Date: NOV 23 1998

Reviewer: _____

Concurrence by Review Branch: _____

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
Document Mail Center (HFZ-401)
9200 Corporate Blvd.
Rockville, Maryland 20850

November 19, 1998

I-FLOW CORP.
20202 WINDROW DR.
LAKE FOREST, CA 92630
ATTN: ROBERT J. BARD

510(k) Number: K984146
Received: 19-NOV-1998
Product: PARAGON INFUSION

The Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), has received the Premarket Notification you submitted in accordance with Section 510(k) of the Federal Food, Drug, and Cosmetic Act (Act) for the above referenced product. We have assigned your submission a unique 510(k) number that is cited above. Please refer prominently to this 510(k) number in any future correspondence that relates to this submission. We will notify you when the processing of your premarket notification has been completed or if any additional information is required. YOU MAY NOT PLACE THIS DEVICE INTO COMMERCIAL DISTRIBUTION UNTIL YOU RECEIVE A LETTER FROM FDA ALLOWING YOU TO DO SO.

On January 1, 1996, FDA began requiring that all 510(k) submitters provide on a separate page and clearly marked "Indication For Use" the indication for use of their device. If you have not included this information on a separate page in your submission, please complete the attached and amend your 510(k) as soon as possible. Also if you have not included your 510(k) Summary or 510(k) Statement, or your Truthful and Accurate Statement, please do so as soon as possible. There may be other regulations or requirements affecting your device such as Postmarket Surveillance (Section 522(a)(1) of the Act) and the Device Tracking regulation (21 CFR Part 821). Please contact the Division of Small Manufacturers Assistance (DSMA) at the telephone or web site below for more information.

Please remember that all correspondence concerning your submission MUST be sent to the Document Mail Center (HFZ-401) at the above letterhead address. Correspondence sent to any address other than the Document Mail Center will not be considered as part of your official premarket notification submission. Because of equipment and personnel limitations, we cannot accept telefaxed material as part of your official premarket notification submission, unless specifically requested of you by an FDA official. Any telefaxed material must be followed by a hard copy to the Document Mail Center (HFZ-401).

You should be familiar with the manual entitled, "Premarket Notification 510(k) Regulatory Requirements for Medical Devices" available from DSMA. If you have other procedural or policy questions, or want information on how to check on the status of your submission (after 90 days from the receipt date), please contact DSMA at (301) 443-6597 or its toll-free number (800) 638-2041, or at their Internet address http://www.fda.gov/cdrh/dsmamain.html or me at (301) 594-1190.

Sincerely yours,

Marjorie Shulman
Consumer Safety Officer
Premarket Notification Staff
Office of Device Evaluation
Center for Devices and Radiological Health

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K984146

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
Premarket Submission Cover Sheet

Date of Submission: 11/11/98

FDA Document Number:

Section A — Type of Submission

- [X] 510(k)
- [ ] 510(k) Add'l information
- [ ] IDE
- [ ] IDE Amendment
- [ ] IDE Supplement
- [ ] IDE Report
- [ ] PMA
- [ ] PMA Amendment
- [ ] PMA Report
- [ ] PMA Supplement - Regular
- [ ] PMA Supplement - Special
- [ ] PMA Supplement - 30 day
- [ ] PMA Supplement - Panel Track

Section B1 — Reason for Submission — 510(k)s Only

- [ ] New device
- [X] Additional or expanded indications
- [ ] Change in technology, design, materials, or manufacturing process
- [ ] Other reason (specify):

Section B2 — Reason for Submission — PMAs Only

- [ ] New device
- [ ] Withdrawal
- [ ] Additional or expanded indications
- [ ] Licensing agreement
- [ ] Change in design, component, or specification:
  - [ ] Software
  - [ ] Color Additive
  - [ ] Other (specify below)
- [ ] Location change:
  - [ ] Manufacturer
  - [ ] Sterilizer
  - [ ] Packager
  - [ ] Distributor
- [ ] Labeling change:
  - [ ] Indications
  - [ ] Instructions
  - [ ] Performance Characteristics
  - [ ] Shelf life
  - [ ] Trade name
  - [ ] Other (specify below)
- [ ] Process change:
  - [ ] Manufacturer
  - [ ] Sterilizer
  - [ ] Packager
- [ ] Report submission:
  - [ ] Annual or periodic
  - [ ] Post-approval study
  - [ ] Adverse reaction
  - [ ] Device defect
  - [ ] Amendment
- [ ] Response to FDA correspondence (specify below)
- [ ] Request for applicant hold
- [ ] Request for removal of applicant hold
- [ ] Request for extension
- [ ] Request to remove or add manufacturing site
- [ ] Change in ownership
- [ ] Change in correspondent
- [ ] Other reason (specify):

RECEIVED 98 11 10 FDA/CDRH/ODE/DHO

Section B3 — Reason for Submission — IDEs Only

- [ ] New device
- [ ] Addition of institution
- [ ] Expansion / extension of study
- [ ] IRB certification
- [ ] Request hearing
- [ ] Request waiver
- [ ] Termination of study
- [ ] Withdrawal of application
- [ ] Unanticipated adverse effect
- [ ] Change in:
  - [ ] Correspondent
  - [ ] Design
  - [ ] Informed consent
  - [ ] Manufacturer
  - [ ] Manufacturing
  - [ ] Protocol – feasibility
  - [ ] Protocol– other
  - [ ] Sponsor
- [ ] Response to FDA letter concerning:
  - [ ] Conditional approval
  - [ ] Deemed approved
  - [ ] Deficient final report
  - [ ] Deficient progress report
  - [ ] Deficient investigator report
  - [ ] Disapproval
  - [ ] Request extension of time to respond to FDA
  - [ ] Request meeting
- [ ] Emergency use:
  - [ ] Notification of emergency use
  - [ ] Additional information
- [ ] Report submission:
  - [ ] Current investigator
  - [ ] Annual progress
  - [ ] Site waiver limit reached
  - [ ] Final
- [ ] IOL submissions only:
  - [ ] Change in IOL style
  - [ ] Request for protocol waiver
- [ ] Other reason (specify):

SK-10

10 CFR 9

	FDA Document Number:

Section C — Product Classification

Product code: 80 FRN	C.F.R. Section: 880.5725	Device class: ☐ Class I ☒ Class II ☐ Class III ☐ Unclassified
Classification panel: General Hospital and Personal Use Device		

Section D — Information on 510(k) Submissions

Product codes of devices to which substantial equivalence is claimed:

1 80 FRN	2 80 MEB	3	4
5	6	7	8

Summary of, or statement concerning, safety and effectiveness data:
☒ 510(k) summary attached
☐ 510(k) statement

Information on devices to which substantial equivalence is claimed:

510(k) Number	Trade or proprietary or model name	Manufacturer
1 K923875	1 Paragon Infusion System	1 I-Flow Corp.
2 K980558 & K982946	2 PainBuster Infusion Kit	2 I-Flow Corp.
3 K896422	3 Pain Control Infusion Pump (PCIP)	3 Sgarlato Laboratories, Inc.
4 K944692	4 Homepump C-Series	4 I-Flow Corp.
5	5	5
6	8	8

Section E — Product Information — Applicable to All Applications

Common or usual name or classification name:

Pump, Infusion

Trade or proprietary or model name	Model number
1 Paragon Infusion Kit	1
2	2
3	3
4	4
5	5
6	6

FDA document numbers of all prior related submissions (regardless of outcome):

1	2	3	4	5	6
7	8	9	10	11	12

Data included in submission: ☐ Laboratory testing ☐ Animal trials ☐ Human trials

Indications (from labeling):

The Paragon Infusion Kit is intended to provide continuous infusion of a local anesthetic directly into an intraoperative site for general surgery for postoperative pain management.

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	FDA Document Number:

Section F — Manufacturing / Packaging / Sterilization Sites

☒ Original ☐ Add ☐ Delete	FDA establishment registration number: (b)(4)	☒ Manufacturer ☐ Contract manufacturer	☐ Contract sterilizer ☐ Repackager / relabeler

Company / Institution name: I-Flow Corporation

Division name (if applicable):	Phone number (include area code): (949)206-2700 ext. 2670
Street address: 20202 Windrow Drive	FAX number (include area code): (949)206-2603

City:	State / Province:	Country:	ZIP / Postal Code:
Lake Forest	CA	U.S.A.	92630

Contact name: Robert J. Bard, Esq., R.A.C.

Contact title: Vice President of Regulatory and Legal Affairs

☐ Original ☐ Add ☐ Delete	FDA establishment registration number:	☐ Manufacturer ☐ Contract manufacturer	☐ Contract sterilizer ☐ Repackager / relabeler

Company / Institution name:

Division name (if applicable):	Phone number (include area code): ( )
Street address:	FAX number (include area code): ( )

City:	State / Province:	Country:	ZIP / Postal Code:

Contact name:

Contact title:

☐ Original ☐ Add ☐ Delete	FDA establishment registration number:	☐ Manufacturer ☐ Contract manufacturer	☐ Contract sterilizer ☐ Repackager / relabeler

Company / Institution name:

Division name (if applicable):	Phone number (include area code): ( )
Street address:	FAX number (include area code): ( )

City:	State / Province:	Country:	ZIP / Postal Code:

Contact name:

Contact title:

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	FDA Document Number:

Section G **Applicant or Sponsor**

Company / Institution name: I-Flow Corporation	FDA establishment registration number: (b)(4)
Division name (if applicable):	Phone number (include area code): (949) 206-2700 ext. 2670
Street address: 20202 Windrow Drive	FAX number (include area code): (949) 206-2603

City:	State / Province:	Country:	ZIP / Postal Code:
Lake Forest	CA	U.S.A.	92630

Signature:

Name: Robert J. Bard, Esq., R.A.C.

Title: Vice President of Regulatory and Legal Affairs

Section H **Submission correspondent (if different from above)**

Company / Institution name:	
Division name (if applicable):	Phone number (include area code): ( )
Street address:	FAX number (include area code): ( )

City:	State / Province:	Country:	ZIP / Postal Code:

Contact name:

Contact title:

Your voluntary completion of this Premarket Submission Cover Sheet will not affect any FDA decision concerning your submission, but will help FDA's Center for Devices and Radiological Health process your submission more efficiently. The information you provide should apply *only* to a single accompanying submission. Please do not send cover sheets for any previous submissions. See the instructions for additional information on completing the cover sheet. If you have a question concerning completion of the cover sheet, please contact the Division of Small Manufacturers Assistance at (800) 638-2041 or (301) 443-6597.

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I-FLOW
CORPORATION

20202 Windrow Drive
Lake Forest, CA 92630
(800) 448-3569 (949) 206-2700
Fax (949) 206-2600

Premarket Notification - 510(k)

Via Federal Express
November 11, 1998

Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Document Mail Center HFZ - 401
9200 Corporate Blvd.
Rockville, Maryland 20850

Reviewing Staff:
In accordance with §510(k) of the Federal Food, Drug, and Cosmetic Act and in conformance with Title 21 CFR §807.81, I-Flow Corporation is submitting this premarket notification for the *Paragon Infusion Kit* prior to the introduction into interstate commerce for commercial distribution.

The *Paragon Infusion Kit* is substantially equivalent to the existing I-Flow Paragon Infusion System (K923875), the I-Flow PainBuster Infusion Kit (K980558, K982946), the Sgarlato Pain Control Infusion Pump (PCIP) (K896422) and the I-Flow Homepump C-Series (K944692).

All questions and/or comments concerning this document should be made to:

Robert J. Bard, Esq., R.A.C.
Vice President Regulatory and Legal Affairs

I-Flow Corporation
20202 Windrow Drive
Lake Forest, CA 92630
Telephone: 949.206.2700
Fax: 949.206.2600

Sincerely,

Robert J. Bard, Esq., R.A.C.
Vice President Regulatory and Legal Affairs

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I-FLOW
CORPORATION

20202 Windrow Drive
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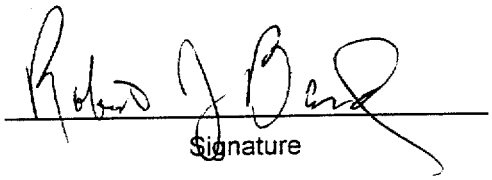
PREMARKET NOTIFICATION
TRUTHFUL AND ACCURATE STATEMENT
(As required by 21 CFR 807.87(j))

I certify that, in my capacity as the Vice President of Regulatory and Legal Affairs of I-Flow Corporation, I believe to the best of my knowledge, that all data and information submitted in the premarket notification for the Paragon Infusion Kit are truthful and accurate and that no material fact has been omitted.



Signature

Robert J Bard, Vice President of Regulatory and Legal Affairs
Name Title

I-Flow Corporation
Company Dated

Premarket Notification - 510(k) Number

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I-FLOW
CORPORATION

20202 Windrow Drive
Lake Forest, CA 92630
(800) 448-3569 (949) 206-2700
Fax (949) 206-2600

510(k) Number (if known): _____

Device Name: Paragon Infusion Kit

Indications for Use:

1. The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management.

2. Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUED ON ANOTHER PAGE IF NEEDED)

_____ _____ _____ _____ _____ _____

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

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(Optional Format 1-2-96)

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1.0 GENERAL INFORMATION

1.1 Purpose of Submission

1.1.1 This submission is intended to notify the Federal Food and Drug Administration that I-Flow Corporation intends to market a new intended use for the Paragon Infusion System (K923875), originally identified as the SideKick 50 Plus and SideKick 100 Plus. The Paragon will be marketed as a kit, the Paragon Infusion Kit, including labeling changes and additional components.

1.1.2 Trade Name: Paragon Infusion Kit

1.1.3 Common Name: Infusion Pump Kit

1.1.4 Classification Name: Pump, Infusion

1.1.5 Classification Panel: General Hospital and Personal Use Device

1.2 Statement of Equivalence

1.2.1 The Paragon Infusion Kit includes components that are legally marketed (either pre-amendment devices or devices that have been granted permission to market via premarket notification regulation).

1.2.2 The Paragon pump and administration set are the same as used in K923875.

1.2.3 The Paragon Kit is substantially equivalent to the I-Flow Paragon Infusion System (K923875), the I-Flow PainBuster Infusion Kit (K980558, K982946), the Sgarlato Pain Control Infusion Pump (PCIP) (K896422) and the I-Flow Homepump C-Series (K944692).

2.0 PHYSICAL SPECIFICATIONS AND DESCRIPTIONS

2.1 Description of the Paragon Infusion Kit

2.1.1 The Paragon Infusion Kit is identical to the I-Flow PainBuster Infusion Kit with the exception of the Paragon pump and administration set replacing the PainBuster pump.

2.1.2 The kit is comprised of a Paragon pump and administration set (K923875) and various kit components such as catheter, needle, syringe, Y adapter, dressing, tape, gauze and carry case.

2.1.2.1 The PainBuster kit contains all the above components except for an elastomeric pump with integrated administration set instead of the Paragon pump and administration set.

2.1.3 The Paragon administration set is intended to attach to the kit catheter at the distal end of the set to provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

2.1.4 The Paragon administration set is a disposable device intended for single patient use. The Paragon pump is reusable. 27

2.1.5 The Paragon is suitable for use as an ambulatory device and is intended for use in the hospital, home environment or alternative care sites.

2.1.6 See Appendix A for drawings and Appendix B and C for labeling of the Paragon Infusion Kit.

2.2 Description of Paragon Pump

2.2.1 The Paragon pump consists of two cylindrical shells. The top half of the pump has internal threads which mate to the external threads of the bottom half of the pump.

2.2.2 The top incorporates a pressure plate which applies a load to the pliable drug bag. The load is applied to the drug bag by way of two opposing springs which act upon a scissors mechanism. The spring/scissors mechanism creates a near constant pressure in the drug bag.

2.2.3 The bottom half of the pump is slotted to allow for positioning of the administration set.

2.2.4 When the top and bottom halves of the pump are fully threaded together, the pressure plate contacts the drug bag and acts as the pressurizing element.

2.2.5 This premarket notification proposes no changes to the Paragon pump.

2.3 Description of Paragon Administration Set

2.3.1 The Paragon administration set consists of a PVC drug bag attached to the administration line.

2.3.2 Each administration set consists of fixed diameter flow control tubing or glass orifice.

2.3.3 The flow control tubing or glass orifice is cut to a specific length L. When the PVC drug bag is pressured by the Paragon pump, the delivery times are defined by the inside diameter of the flow control orifice.

2.3.3.1 The delivery time characteristic is derived from the flow rate of the device which is in turn approximated by Poiseulle's equation:

$$Q = \frac{\Delta \rho \pi D^4}{128 \mu L}$$

2.3.3.2 Where Q is the flow rate, ρ is the pressure drop across the orifice, D is the inside diameter of the flow controlling orifice, μ is the dynamic viscosity of the fluid and L is the length of the orifice. The equation provides an approximation of the actual delivery time.

2.4 Product Configuration

See Appendix A for drawings and Appendix B and C for labeling.

2.4.1 The Paragon pump:

2.4.1.1 PG100000P: 100 ml volume

2.4.2 The Paragon administration sets:

2.4.2.1 PG100005: 100 ml volume, 0.5 ml/hr flow rate
2.4.2.2 PG100010: 100 ml volume, 1.0 ml/hr flow rate
2.4.2.3 PG100020: 100 ml volume, 2.0 ml/hr flow rate
2.4.2.4 PG100040: 100 ml volume, 4.0 ml/hr flow rate
2.4.2.5 PG100100: 100 ml volume, 10.0 ml/hr flow rate

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2.4.2.6 PG100020Y: 100 ml volume, 2.0 ml/hr flow rate, dual orifice, dual catheter with Y adapter

2.4.2.6.1 The dual orifice set consists of a standard Paragon set with dual orifice downstream from the Y adapter. Each orifice allows 2 ml/hr flow rate.

2.4.3 Each model consists of a kit with the following components:

2.4.3.1 Paragon pump (optional).

2.4.3.1.1 The reusable Paragon pump may be packaged and sold separately from the disposable kit components.

2.4.3.2 Paragon administration set.

2.4.3.3 Catheter:

2.4.3.3.1 18 to 22 G catheter, 11 to 40 in. length, polyamide, nylon, FEP (fluorinated ethylene propylene) polymer, silicone, polyurethane or Teflon.

2.4.3.3.2 A catheter connector is included to connect the catheter to the distal luer of the administration set.

2.4.3.3.3 The B. Braun Perifix® Epidural Catheter Set is an example of the type of catheter that may be used with the Paragon Infusion Kit.

2.4.3.3.3.1 Product code: EC20-0.

2.4.3.3.3.2 510(k) number: K813186.

2.4.3.4 Needle:

2.4.3.4.1 14 to 18 G, 1 ½ to 3 ¼ in. length, stainless steel.

2.4.3.4.2 The needle may be a catheter over needle as in the Angiocath™ example below.

2.4.3.4.3 The Angiocath catheter introducer needle is an example of the type of catheter introducer needle that may be used with the Paragon Infusion Kit.

2.4.3.4.3.1 Product code: 382258.

2.4.3.5 Syringe (optional):

2.4.3.5.1 60 cc plastic, luer lock syringe.

2.4.3.5.2 The syringe is used to fill the Paragon drug bag with medication.

2.4.3.5.3 The B-D 60 cc syringe is an example of the type of syringe that may be included in the Paragon Kit.

2.4.3.5.3.1 Product Code: 309663.

2.4.3.6 Dressing (optional):

2.4.3.6.1 The dressing is used to hold the catheter and/or flow restrictor in place.

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2.4.3.6.2 The OpSite™ is an example of the type of dressing that may be used in the Paragon Kit.

2.4.3.6.2.1 Product Code: 4973.

2.4.3.7 Carry Case (optional):

2.4.3.7.1 The carry case is used to hold the Paragon pump while delivering medication.

2.4.3.7.1.1 I-Flow part numbers 1400749, 1400752 or 1400758.

2.4.3.8 Antiseptic Skin Swabs (optional):

2.4.3.8.1 The antiseptic skin swabs are used to prep the skin area of the patient prior to inserting the catheter.

2.4.3.8.2 The Alcohol Prep Pads or Iodophor PVP Scrub Swabsticks manufactured by (b)(4) (b)(4) are examples of the type of antiseptic skin swabs that may be used in the Paragon Kit.

2.4.3.8.2.1 Model number: CL0110.

2.4.3.8.2.2 Model number: CL1244.

2.4.3.9 Tape (optional):

2.4.3.9.1 The tape may be used to the secure catheter, flow control tubing or gauze.

2.4.3.9.2 The Transpore™ Surgical Tape manufactured by (b)(4) is an example of the type of tape that may be used in the Paragon Kit.

2.4.3.9.2.1 Model number: 3M1527-1.

2.4.3.10 Gauze (optional):

2.4.3.10.1 The gauze may be used to secure the catheter or flow control tubing.

2.4.3.10.2 The Kling® Conforming Gauze manufactured by (b)(4) (b)(4) is an example of the type of gauze which may be used in the Paragon Kit.

2.4.3.10.2.1 Model number: JJ6923.

2.4.3.11 Y Adapter (optional)

2.4.3.11.1 The Y adapter is used for an additional catheter for a large wound or multiple wound sites.

2.4.3.11.2 The Flexible Y Fitting by Qosina is an example of the type of Y Adapter that may be used in the Paragon Kit.

2.4.3.11.2.1 Model number: 81120 (see I-Flow part number 5000755 for assembly).

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2.5 Components and Materials

The pump and administration sets used in the Paragon Infusion Kit are currently available models of the Paragon Infusion System (K923875). No changes will be made to the Paragon pump or administration sets.

All kit components other than the pump and administration set are identical to those used in the PainBuster infusion system submitted under K980558, K982946.

The Paragon administration set is a disposable device intended for single patient use. The Paragon pump is reusable.

2.5.1 Non-fluid path components

- 2.5.1.1 Fill Valve Luer Cap: (b)(4) (b)(4)
- 2.5.1.2 Distal Luer Cap: (b)(4) (b)(4)
- 2.5.1.3 Pinch Clamp: (b)(4) (b)(4)
- 2.5.1.4 Dressing/Tape/Gauze/Skin Preps.
- 2.5.1.5 Carry Case: Nylon.

2.5.2 Fluid path components

- 2.5.2.1 Filter (optional): Manufactured by (b)(4) (b)(4) The filter is (b) (b)(4) (b)(4) (b)(4)
- 2.5.2.2 Filter (optional):
  - 2.5.2.2.1 (b)(4) (b)(4)
  - 2.5.2.2.2 (b)(4) (b)(4)
- 2.5.2.3 Distal Male Luer Adapter: (b)(4) (b)(4)
- 2.5.2.4 Tubing (Make-up): (b)(4) (b)(4)
- 2.5.2.5 Tubing (Flow Control): (b)(4) (b)(4)
- 2.5.2.6 Glass Orifice (optional): (b)(4) (b)(4)
  - 2.5.2.6.1 (b)(4) (b)(4)
- 2.5.2.7 Drug Bag: (b)(4) (b)(4)
- 2.5.2.8 Fill Valve
  - 2.5.2.8.1 Housing: (b)(4) (b)(4)
  - 2.5.2.8.2 Disk: (b)(4) (b)(4)
  - 2.5.2.8.3 Luer: (b)(4) (b)(4)

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2.5.2.9 Catheter: (b)(4) (b)(4) (b)(4) (b)(4)

2.5.2.10 Needle: (b)(4) (b)(4)

2.5.2.11 Syringe: (b)(4) (b)(4)

2.5.2.12 Y Adapter: (b)(4) (b)(4)

2.5.2.13 Solvent Bonding: (b)(4) (b)(4)

2.6 Pumping Mechanism

2.6.1 The Paragon pumping mechanism is identical to the original Paragon pump submitted under K923875.

2.6.2 The pressure that pumps the fluid comes from the mechanical spring energy applying force to the drug bag.

2.7 Administration Sets and Drug Reservoir

2.7.1 The administration sets used in the Paragon Infusion Kit are currently available models of the Paragon Infusion System (K923875). No changes will be made to the Paragon administration sets.

2.7.2 The Paragon administration set consists of a PVC drug bag attached to the administration line.

2.8 Power Requirements

2.8.1 The Paragon pump is a mechanical pump that utilizes spring energy for power. No additional external power source is required.

3.0 OPERATIONAL SPECIFICATIONS AND DESCRIPTIONS

3.1 Standard Operating Conditions:

Priming/Residual Volume:	< 5 ml
Operating Temperature:	31°C skin temperature (90°F)
Test Solution:	0.9% NaCl
Operating Pressure:	6.0 psi pressure source
Head Height:	0"
Accuracy:	±10% at 95% confidence interval

3.2 **Flow Rate Performance Data**: Testing occurred at standard operating conditions. All models produced an average flow rate within the ±10% accuracy claim.

	100 ml x 0.5 ml/hr	100 ml x 1 ml/hr	100 ml x 2 ml/hr	100 ml x 4 ml/hr	100 ml x 10 ml/hr
Average Flow Rate (ml/hr)	0.53	0.99	1.99	4.14	10.30
Std. Dev.	0.01	0.03	0.07	0.10	0.38
N	5	5	5	5	10

100 ml x 0.5 ml/hr: A five (5) piece sample produced an average flow rate of 0.53 ml/hr. The resulting average is well within its ±10% accuracy claim. The fastest infusion had an average flow rate of 0.54 ml/hr and the slowest infusion had an average flow rate of 0.51 ml/hr.

100 ml x 1.0 ml/hr: A five (5) piece sample produced an average flow rate of 0.99 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 1.04 ml/hr and the slowest infusion had an average flow rate of 0.96 ml/hr.

100 ml x 2.0 ml/hr: A five (5) piece sample produced an average flow rate of 1.99 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 2.05 ml/hr and the slowest infusion had an average flow rate of 1.90 ml/hr.

100 ml x 4.0 ml/hr: A five (5) piece sample produced an average flow rate of 4.14 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 4.24 ml/hr and the slowest infusion had an average flow rate of 3.99 ml/hr.

100 ml x 10.0 ml/hr: A ten (10) piece sample produced an average flow rate of 10.30 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 10.80 ml/hr and the slowest infusion had an average flow rate of 9.65 ml/hr.

Graphical representation of the data can be found in Charts #1 through #5.

Back Pressure (Head Height) Comparison: Approximately 0.57 psi pressure difference results per 16" head height. Thus, a 10% flow rate change may occur for each 16" head height difference from nominal assuming a 6 psi pressure source.

3.3 **Drug Delivery Comparison**: Local anesthetics have densities similar to normal saline (e.g. 1.002 to 1.005 for Ropivacaine HCl vs. 1.0045 for normal saline) and should not affect flow rate. Product labeling includes a statement as to delivery times and the possible deviation from nominal due to drug viscosity.

3.4 **Safety / Alarm Functions**

3.4.1 The Paragon pump and administration set provide a continuous fixed flow and as such is not subject to fluid runaway conditions similar to that of some electronic pumps.

3.4.2 The Paragon pump will not be recommended for any application that exceeds the minimum internal pressure of the system.

3.4.3 If for any reason the patient needs to stop his or her infusions, each administration set is supplied with a pinch clamp to stop the infusion.

3.4.4 This device contains no alarms or indicators for flow other than visual.

3.4.5 This device contains no alarms or indicators to detect air in line or an occlusion; however, each set may include an integrated air-eliminating filter.

4.0 BIOLOGICAL SPECIFICATIONS

4.1 Biological testing is in conformance with ISO 10993 Part 1 for all fluid path components of the Paragon administration set.

4.2 The Paragon administration set is categorized as follows:

4.2.1 Device Category: External Communicating Device.

4.2.2 Body Contact: Tissue/Bone/Dentin Communicating

4.2.3 Contact Duration: Prolonged.

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Chart #1
Paragon Infusion Kit
Incremental Flow Rate Profile
100 ml fill volume
0.5 ml/hr flow rate (NS)

CUMULATIVE AVERAGE FLOW

Time (hrs)

Sample	
(b)(4)	(b)(4)
Min	
Max	
N	
Avg.	
Std. Dev	

*Incremental flow rate is the average flow rate between time values.

**For QC test criteria, the average flow rate is measured at a minimum of (b)(4) into delivery.

Incremental Flow Rate (ml/hr)

(b)(4)

Time (hrs)

(b)(4)

Chart #2
Paragon Infusion Kit
Incremental Flow Rate Profile
100 ml fill volume
1.0 ml/hr flow rate (NS)

Sample	Time (hrs)	CUMULATIVE AVERAGE FLOW
(b)(4)	(b)(4)	
Min		
Max		
N		
Avg.		
Std. Dev.		

*Incremental flow rate is the average flow rate between time values.

**For QC test criteria, the average flow rate is measured at a minimum of (b)(4) into delivery.

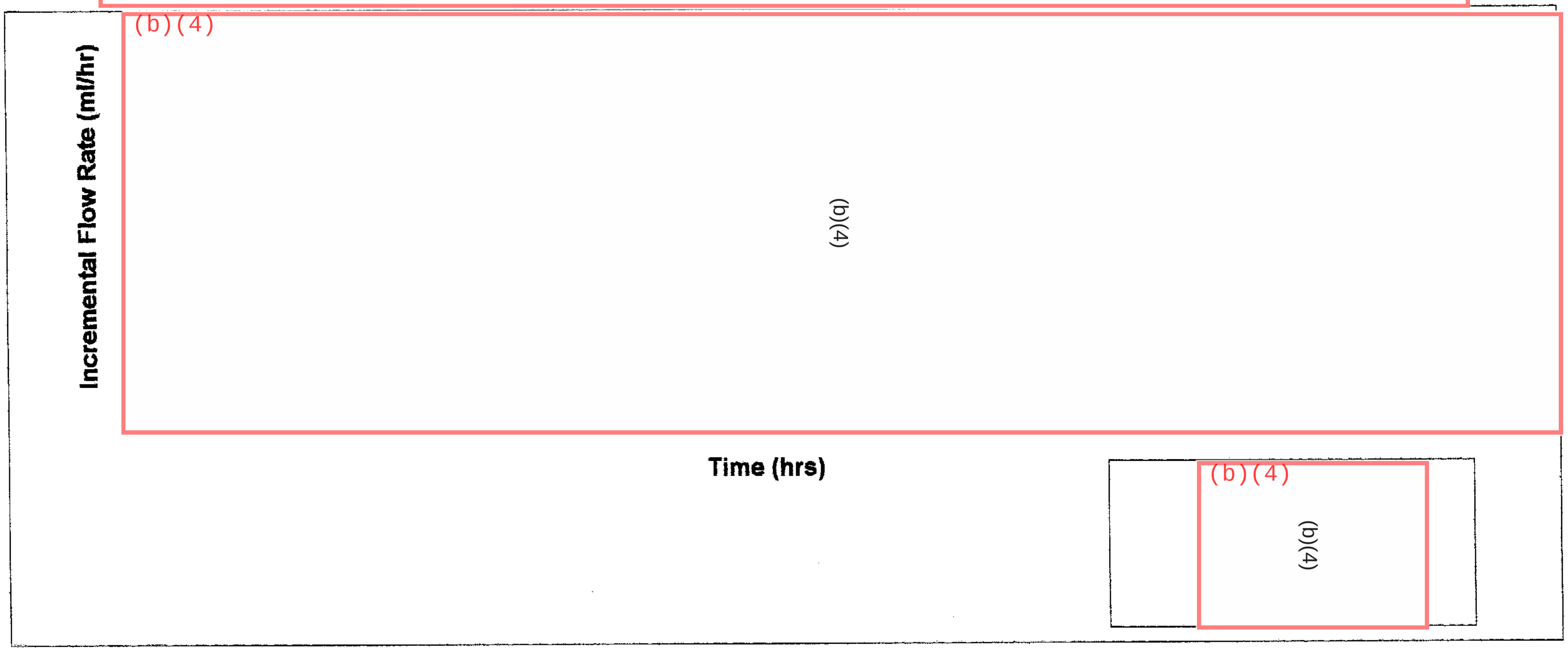

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Chart #3
Paragon Infusion Kit
Incremental Flow Rate Profile
100 ml fill volume
2.0 ml/hr flow rate (NS)

CUMULATIVE AVERAGE FLOW

Time (hrs)

Sample	(b)(4)
(b)(4)	
Min	
Max	
N	
Avg.	
Std. Dev.	

*Incremental flow rate is the average flow rate between time values.

**For QC test criteria, the average flow rate is measured at a minimum of (b)(4) into delivery.

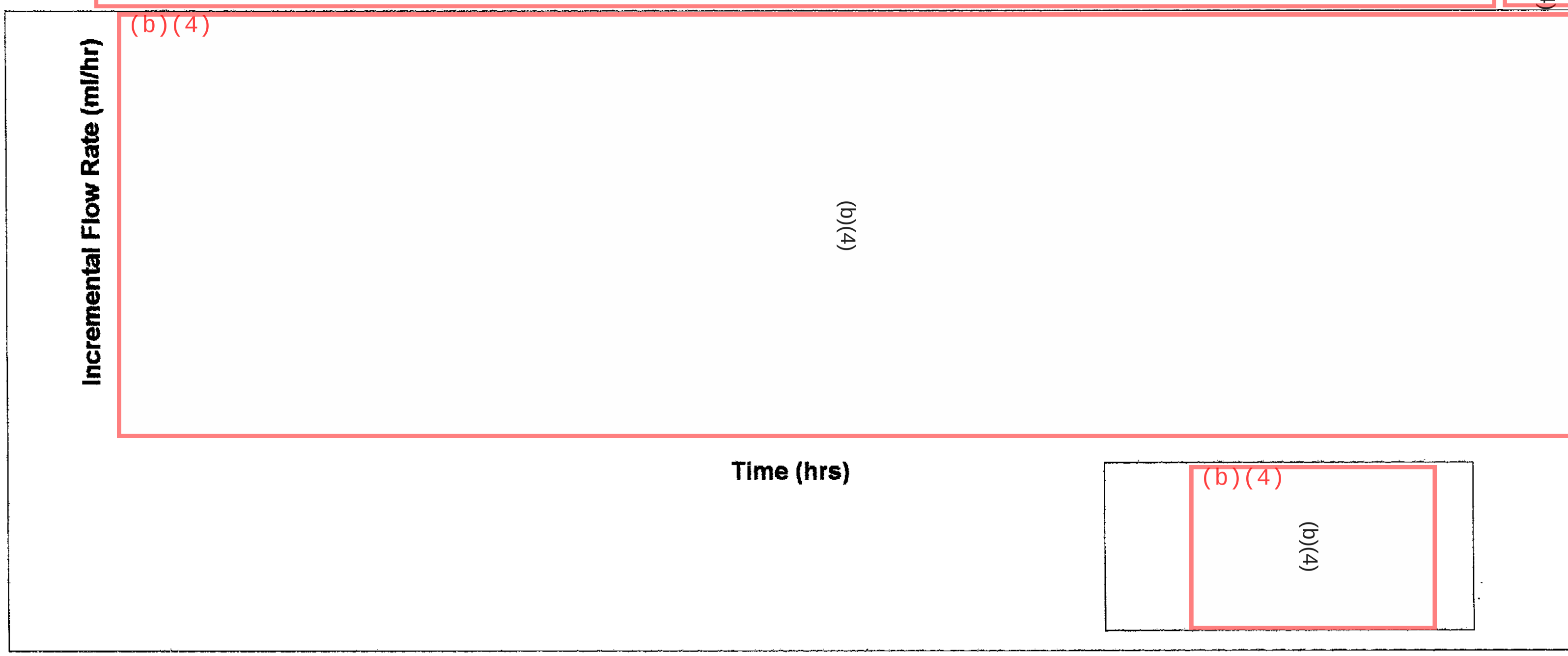

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Chart #4
Paragon Infusion Kit
Incremental Flow Rate Profile
100 ml fill volume
4.0 ml/hr flow rate (NS)

Sample	Time (hrs)	CUMULATIVE AVERAGE FLOW
(b)(4)	(b)(4)	
Min		
Max		
N		
Avg.		
Std. Dev		

*Incremental flow rate is the average flow rate between time values.

**For QC test criteria, the average flow rate is measured at a minimum of (b)(4) into delivery.

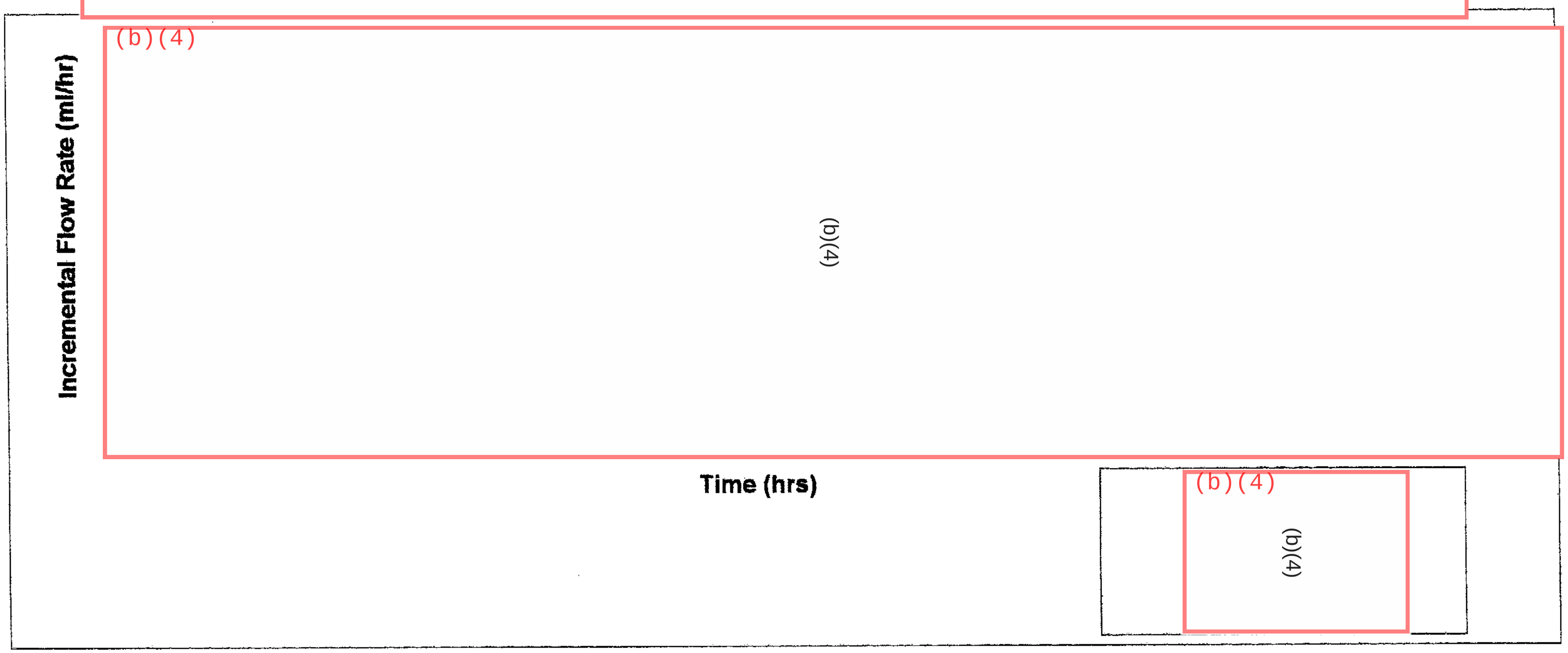
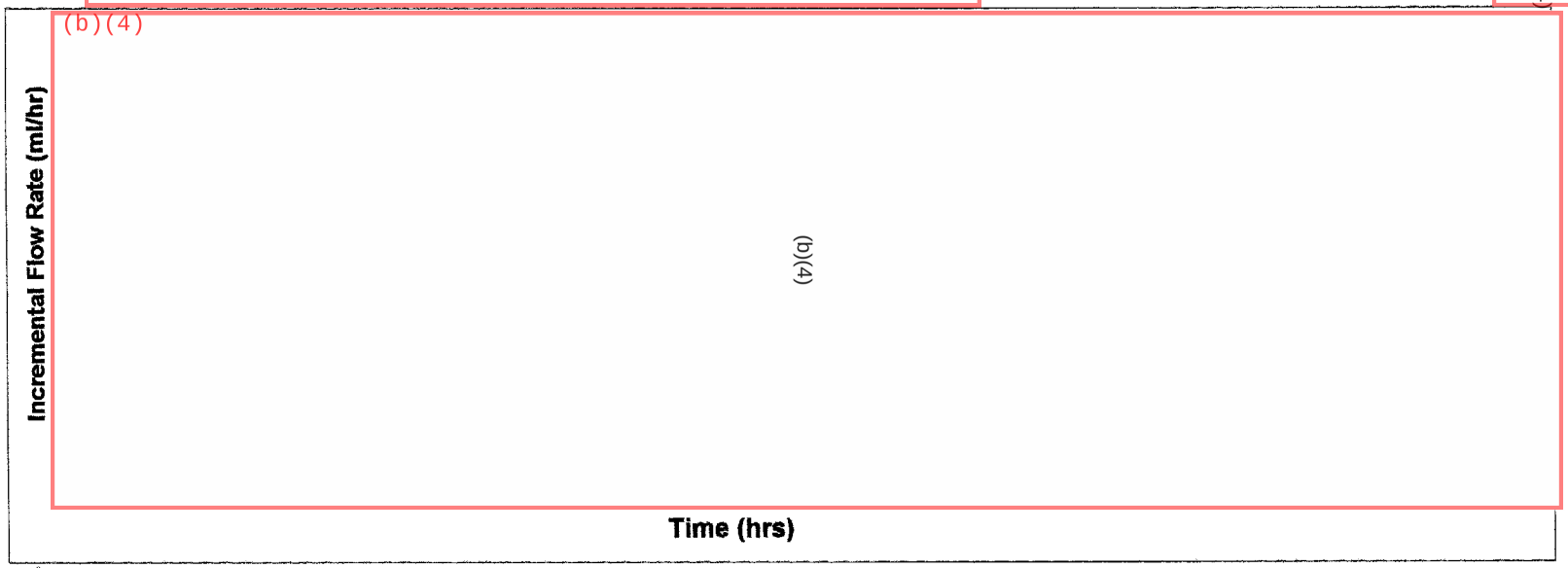


Chart #5
Paragon Infusion Kit
Incremental Flow Rate Profile
100 ml fill volume
10.0 ml/hr flow rate (NS)

CUMULATIVE AVERAGE FLOW RATE AT 2 hrs**
10.35
10.64
9.65
10.80
10.71
10.22
10.00
10.60
10.00
10.06
9.65
10.80
10
10.30
0.38

*Incremental flow rate is the average flow rate between time values.

**For QC test criteria, the average flow rate is measured at a minimum of (b)(4) (b) nto delivery.



5.0 CHEMICAL AND DRUG SPECIFICATIONS

5.1 Compatibility

5.1.1 There are no specific drugs referenced in the labeling for the Paragon Infusion Kit.

5.1.2 The Paragon Infusion Kit is intended for use with general local anesthetics and epidural medications.

5.2 Drug Stability

5.2.1 There are no drugs included in the Paragon Infusion Kit.

6.0 INTENDED USE

6.1 The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management.

6.2 Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

6.3 The Paragon pump is re-usable. The disposable Paragon administration set is single patient use only.

6.4 No testing has been conducted to determine the efficacy of the Paragon for the delivery of blood, blood products, lipids or fat emulsions. The Paragon is not intended for the delivery of blood, blood products, lipids or fat emulsions.

6.5 The Paragon is suitable for use as an ambulatory device and is intended for use in the hospital, home environment or alternative care sites.

7.0 LABELS AND LABELING

7.1 I-Flow Corporation believes the proposed labels and labeling, where appropriate, meets the requirements of 21 CFR Part 801 as it relates to a determination of intended use and adequate directions for use.

7.2 The Paragon Directions for Use labeling:

7.2.1 Provides comprehensive directions for preparation and use for the Paragon.

7.2.2 Describes the routes of administration as it relates to intended use.

7.2.3 Describes the fluid types that may be administered by the pump as it relates to intended use.

7.2.4 Contains warning information.

7.2.5 Contains the prescription statement required under 801.109 (b)(1).

7.2.6 Includes the specifications of the Paragon. The specifications include the priming volume, residual volume, accuracy and operating conditions.

7.3 Identification labels and labeling

7.3.1 I-Flow has developed product identification labeling for the Paragon Infusion Kit. Refer to Appendix B for examples.

7.4 Packaging labels

7.4.1 Contains the prescription statement required under 801.109(b)(1).

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7.5 Appendix B and C contains example labeling of the following:

7.5.1 Labeling for pump, administration set, catheter, needle, syringe and dressing.

7.6 Appendix D contains predicate labeling for the Paragon Infusion System, PainBuster Infusion Kit, Sgarlato Pain Control Infusion Pump (PCIP) and the Homepump C-Series.

8.0 STANDARDS

8.1 There are currently no standards established for mechanical infusion pumps.

9.0 PACKAGING

9.1 The components of the Paragon Infusion Kit may be purchased as sterile, finished devices or purchased in bulk, non-sterile and packaged by I-Flow.

9.2 The Paragon Kit consists of an inner pouch or tray with Tyvek lid stock surrounded by an optional header bag with an ETO Tyvek strip.

9.3 The Paragon administration set may be packaged in either a Tyvek pouch or Form/Fill/Seal.

9.4 The Paragon Kit components are placed in the inner tray or pouch.

9.5 Packaging is suitable for either radiation or ETO sterilization.

9.6 The Paragon Infusion Kit will be packaged 1 or 5 kits per case.

9.7 Package aging tests have been conducted on the inner pouch packaging material. The results of bacterial dust challenge testing has determined that the Tyvek pouches/trays used to package the disposable Paragon administration set maintain sterility in excess of three years.

10.0 STERILIZATION INFORMATION

Note: The kit components of the Paragon Infusion Kit may be purchased non-sterile and packaged by I-Flow or sterile from the manufacture. The Paragon administration set and non-sterile purchased components shall be sterilized as follows:

10.1 The methods of sterilization are gamma radiation (Cobalt 60) or ETO gas.

10.2 Sterilization validation methodology is by ANSI/AAMI ST32-1991 / EN552 Method 1 for gamma radiation.

10.2.1 The gamma radiation dose validated for this product is 25 to 35 KGy (2.5 to 3.5 Mrad).

10.3 Sterilization validation methodology is by ANSI/AAMI/ISO 11135-1994 / EN550 for ETO gas sterilization.

10.3.1 For ETO sterilized product, the maximum levels of gas residuals for ethylene oxide, ethylene chlorohydrin and ethylene glycol are consistent with the FDA proposed rule, 43 FR 27482 (June 23, 1978).

10.3.2 The maximum residual limits are 25 ppm for ethylene oxide, 25 ppm for ethylene chlorohydrin, and 250 ppm for ethylene glycol.

10.4 The sterile product under review here will have a sterilization assurance level (SAL) of 10^{-6}. Sterility testing is by spore strip for ETO. Under AAMI Method 1 for Gamma sterilized product, no sterility test is required.

40

10.5 The Paragon Infusion Kit has not been tested for pyrogenicity and is not indicated for blood path use.

11.0 REFERENCES

11.1 Appendix E contains the following articles:

11.1.1 Armitage, E. N. Local anaesthetic techniques for prevention of postoperative pain. *British Journal of Anaesthesia*, 1986: 58: 790 - 800.

11.1.2 McClure, J. H. Continuous infusion techniques for postoperative pain relief. *Anaesthesiology*, 1993: 6: 819 - 822.

11.1.3 Dahl, J. B., et al. Wound infiltration with local anaesthetics for postoperative pain relief. *Acta Anaesthesiologica Scandinavica*, 1994: 38: 7 - 14.

11.1.4 Wilkes, R. A., & Thomas, W. G. Bupivacaine infusion for iliac crest donor sites. *Journal of Bone and Joint Surgery*, 1994: 76-B (3): 503.

11.1.5 Rawal, N., et al. Postoperative patient controlled regional analgesia at home. Poster presented at American Society of Anesthesiologists, 1997.

11.1.6 Nyhammar, E., Hohansson, S. Chemical Stability of Meropenem in Portable Infusion Pumps. National Corporation of Swedish Pharmacies, Central Laboratory, Stockholm, Sweden.

11.1.7 Rawal, N., et al. Postoperative patient-controlled local anesthetic administration at home. *Anesthesia and Analgesia*, 1998: 86: 86 - 89.

11.1.8 Baker, J. W., & Tribble, C. G. Pleural anesthetics given through an epidural catheter secured inside a chest tube. *Annals of Thoracic Surgery*, 1991: 51: 138, 139.

11.1.9 American Hospital Formulary Service (AHFS) Drug Information (1998 ed., pp. 2659 - 2661). Bethesda, MD: American Society of Health-System Pharmacists.

11.1.10 Trissel, L. A. (1994). *Handbook on Injectable Drugs* (8th ed., pp. 127, 128). Bethesda, MD: American Society of Hospital Pharmacists' Special Projects Division.

11.1.11 Enneking, F.K., Scarborough, M.T., Radson, E.A. Local anesthetic infusion through nerve sheath catheters for analgesia following upper extremity amputation. *Regional Anesthesia,* 1997: 22(4): 351-356.

11.1.12 Partridge, B.L., Stabile, B.E. The effects of incisional bupivacaine on postoperative narcotic requirements, oxygen saturation and length of stay in the post-anesthesia care unit. *Acta Anaesthesiogica Scandinavica.* 1990: 34: 486-491.

11.1.13 Khoury, G.F., Chen, C.N., Garland, D.E., Stein, C. Intra-articular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. *Anesthesiology,* 1992: 77: 263-266.

11.1.14 Raja, S.N., Dickstein, R.E., Johnson, C.A. Comparison of postoperative analgesic effects of intra-articular bupivacaine and morphine following arthroscopic knee surgery. *Anesthesiology.* 1992: 77: 1143-1147.

41

11.1.15 Shenfeld, O., Eldar, G., Lotan, G., Avigad, I., Goldwasser, B. Intraoperative irrigation with bupivacaine for analgesia after orchiopexy and herniorrhaphy in children. *The Journal of Urology.* 1995: 153: 185-187.

11.1.16 Tverskoy, M., Cozacov, C., Ayache, M. Bradley, E., Kissin, I. Postoperative Pain after Inguinal Herniorrhaphy with Different Types of Anesthesia. *Anesthesia and Analgesia.* 1990: 70: 29-35.

11.1.17 Oakley, M., Smith, J., Anderson, J., Fenton-Lee, D. Randomized Placebo-controlled Trial of Local Anaesthetic Infusion in Day-case Inguinal Hernia Repair. *British Journal of Surgery.* 1998: 85: 797-799.

11.1.18 Drug insert for Naropin (ropivacaine HCl).

11.1.19 Drug insert for Marcaine (bupivacaine HCl).

12.0 COMPARISON TO LEGALLY MARKETED DEVICES

See Table 1 that follows this section for more specific information.

12.1 Intended Use

12.1.1 The Paragon Infusion Kit, the PainBuster Infusion Kit and the Sgarlato Pain Control Infusion Pump (PCIP) have the same intended use:

12.1.1.1 To provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

12.1.2 The predicate Paragon Infusion System and Homepump C-Series are intended for general infusion use, including chemotherapy and pain management.

12.2 Device Descriptions

12.2.1 The Paragon Infusion Kit

12.2.1.1 The Paragon Infusion Kit is identical to the predicate PainBuster Infusion Kit with the exception of the Paragon pump and administration set replacing the PainBuster pump.

12.2.1.2 The Paragon Infusion Kit uses the same mechanical, reusable Paragon pump as the predicate Paragon Infusion System.

12.2.1.3 The Paragon Infusion Kit uses the same Paragon Administration Set as the Paragon Infusion System.

12.2.2 The Paragon Infusion System

12.2.2.1 The Paragon Infusion Kit uses the same pump and administration sets as the Paragon Infusion System (K923875).

12.2.3 The Sgarlato Pain Control Infusion Pump (PCIP)

12.2.3.1 The Sgarlato PCIP consists of a kit very similar to the Paragon and PainBuster Infusion Kit. These kits consist of an infusion pump and administration set, catheter, needle, syringe, Y adapter, carry case, dressing, tape and gauze.

12.2.3.2 The Sgarlato kit uses a disposable, spring driven syringe pump with integrated administration set.

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12.2.4 The Homepump C-Series

12.2.4.1 The Homepump C-Series consists of a disposable, elastomeric infusion pump with integrated administration set.

12.2.5 Specifications

12.2.5.1 The Paragon Infusion Kit, PainBuster Infusion Kit and Sgarlato PCIP have similar fill volumes and flow rates, see Table 1.

12.2.6 Flow Control

12.2.6.1 The Paragon Infusion Kit and all its predicate devices use either a glass orifice or PVC tubing to control the flow rate.

12.2.7 Materials

12.2.7.1 The Paragon Infusion Kit uses the same Paragon Administration Set as the Paragon Infusion System. All fluid path materials of the Paragon Administration Set are in conformance with ISO 10993 Part 1.

12.2.8 Based upon the data presented in this section 12.0 and Table 1, I-Flow Corporation has determined that the Paragon Infusion Kit is substantially equivalent to the named predicate devices.

Table 1
Comparison to Legally Marketed Devices

Comparison Element	Paragon Infusion Kit (subject device)	SE[1] Paragon Infusion System (K923875)	SE[1] PainBuster Infusion Kit (K980558, K982946)	SE[1] Sgarlato PCIP (K896422)	SE[1] Homepump C-Series (K944692)
Intended Use	To provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.	General infusion use, including chemotherapy and pain management.	To provide continuous infusion of a local anesthetic directly into the intraoperative site for postoperative pain management.	To provide continuous infusion of a local anesthetic directly into the surgical wound site for postoperative pain management.	General infusion use, including chemotherapy and pain management.
Routes of Administration	Percutaneous, subcutaneous, intramuscular and epidural	Intravenous	Percutaneous and subcutaneous	Percutaneous, subcutaneous and epidural	Intravenous, intra-arterial, epidural or subcutaneous
Contraindications	Not intended for intravenous or intra-arterial delivery. Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for intravenous, intra-arterial or epidural delivery. Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for rapid infusions. Not intended for intravenous infusion.	Not intended for delivery of blood, blood products, lipids or fat emulsions.
Reuse Capability	Re-usable pump, single patient use disposable administration set	Re-usable pump, single patient use disposable administration set	Disposable, single patient use	Disposable, single patient use	Disposable, single patient use
Description	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.
Fill Volumes	100 ml	100 ml	50 to 270 ml	50 to 100 ml	50 to 500 ml
Flow Rates	0.5, 1.0, 2.0, 4.0 or 10.0 ml/hr	0.5 to 200 ml/hr	0.5, 1.0, 2.0, 5.0 or 10.0 ml/hr	0.5, 1.0 or 2.0 ml/hr	0.5 to 500 ml/hr
Pump Type	Mechanical spring	Mechanical spring	Elastomeric Pump	Spring driven syringe pump	Elastomeric Pump
Power Requirements	None	None	None	None	None
Pump Mechanism	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.
Pressure Source	Mechanical spring energy	Mechanical spring energy	Strain energy of elastomeric membranes	Mechanical spring energy	Strain energy of elastomeric membranes
Fluid Reservoir	PVC drug bag	PVC drug bag	Thermoplastic (Krayton) elastomeric membrane	Polypropylene plastic syringe	Thermoplastic (Krayton) elastomeric membrane
Administration Set					
Flow Control	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.
Safety / Alarm Functions	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.

[1]SE = Substantially Equivalent

Comparison Element	Paragon Infusion Kit (subject device)	SE[1] Paragon Infusion System (K923875)	SE[1] PainBuster Infusion Kit (K980558, K982946)	SE[1] Sgarlato PCIP (K896422)	SE[1] Homepump C-Series (K944692)
Non-fluid Path Components					
Fill Valve Luer Cap					
Distal Luer Cap					
Pinch Clamp					
Dressing (optional)					
Tape (optional)					
Gauze (optional)					
Carry Case (optional)					
Fluid Path Components					
Distal Male Luer Adapter					
Tubing (make-up)					
Tubing (flow control)					
Glass Orifice (optional)					
Orifice Sleeve					
Filter (optional)					
Filter Housing					
Filter Membrane					
Filter Air Vent					
Drug Bag					
Fill Valve/Port					
Housing					
Disk					
Luer					
Catheter					
Needle					
Syringe (optional)					
Y Adapter (optional)					
Packaging (sterile)					
Sterilization					
Product Code	80 FRN	80 FRN	80 MEB	80 FRN	80 MEB

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[1]SE = Substantially Equivalent

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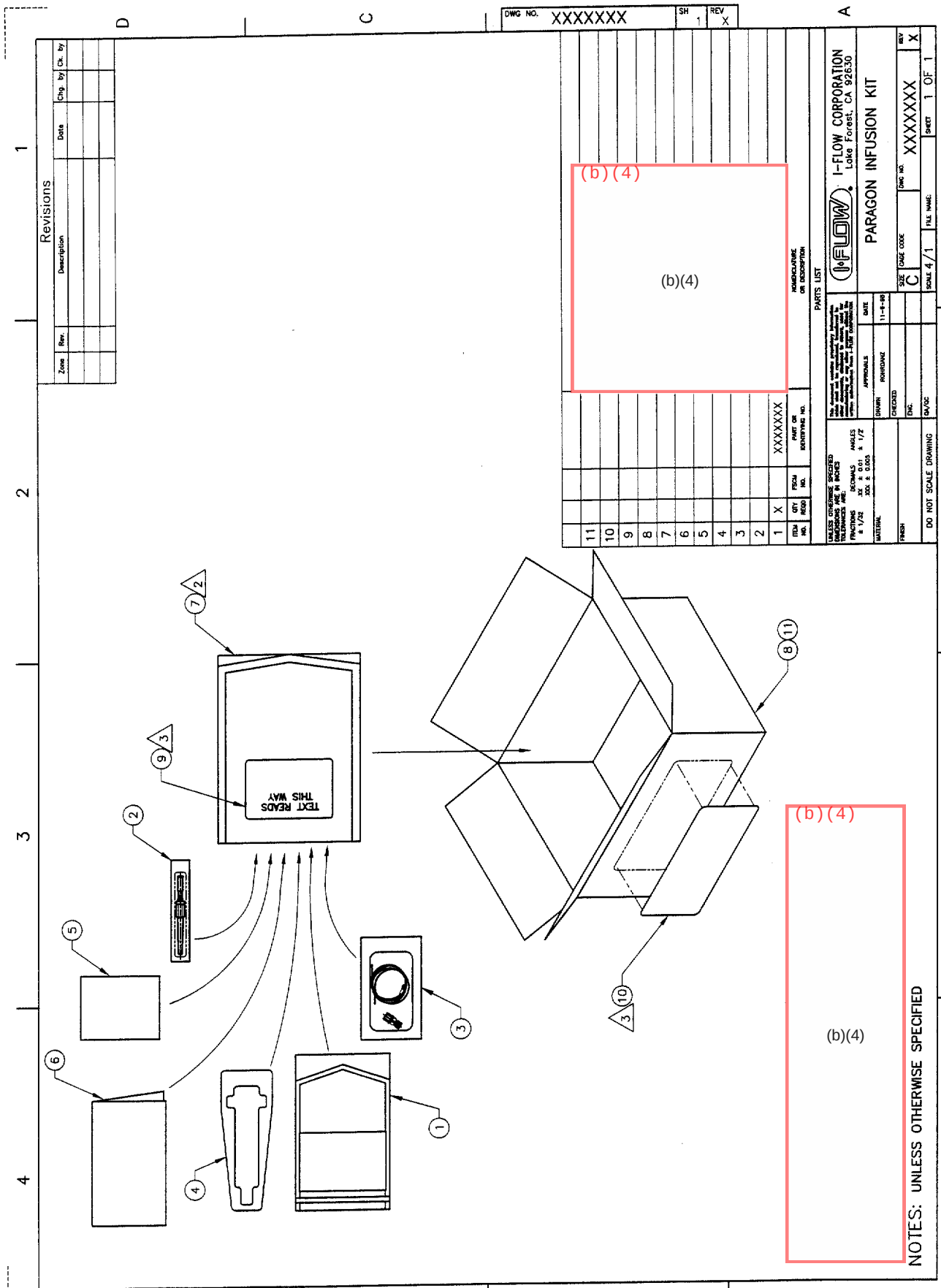
Appendix A

Paragon Infusion Kit Drawings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SH 1
REV X
Revisions
Zone
Rev.
Description
Date
Chg. by
Ck. by
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PARTS LIST
ITEM NO.
QTY REQD
PART OR IDENTIFYING NO.
NOMENCLATURE OR DESCRIPTION
XXXXXXX
I-FLOW CORPORATION
Lake Forest, CA 92630
PARAGON INFUSION KIT
XXXXXXX
SIZE C
SCALE 4/1
SHEET 1 OF 1
DRAWN
CHECKED
ENG.
QA/QC
APPROVALS
DATE
MATERIAL
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DO NOT SCALE DRAWING
TEXT READS THIS WAY
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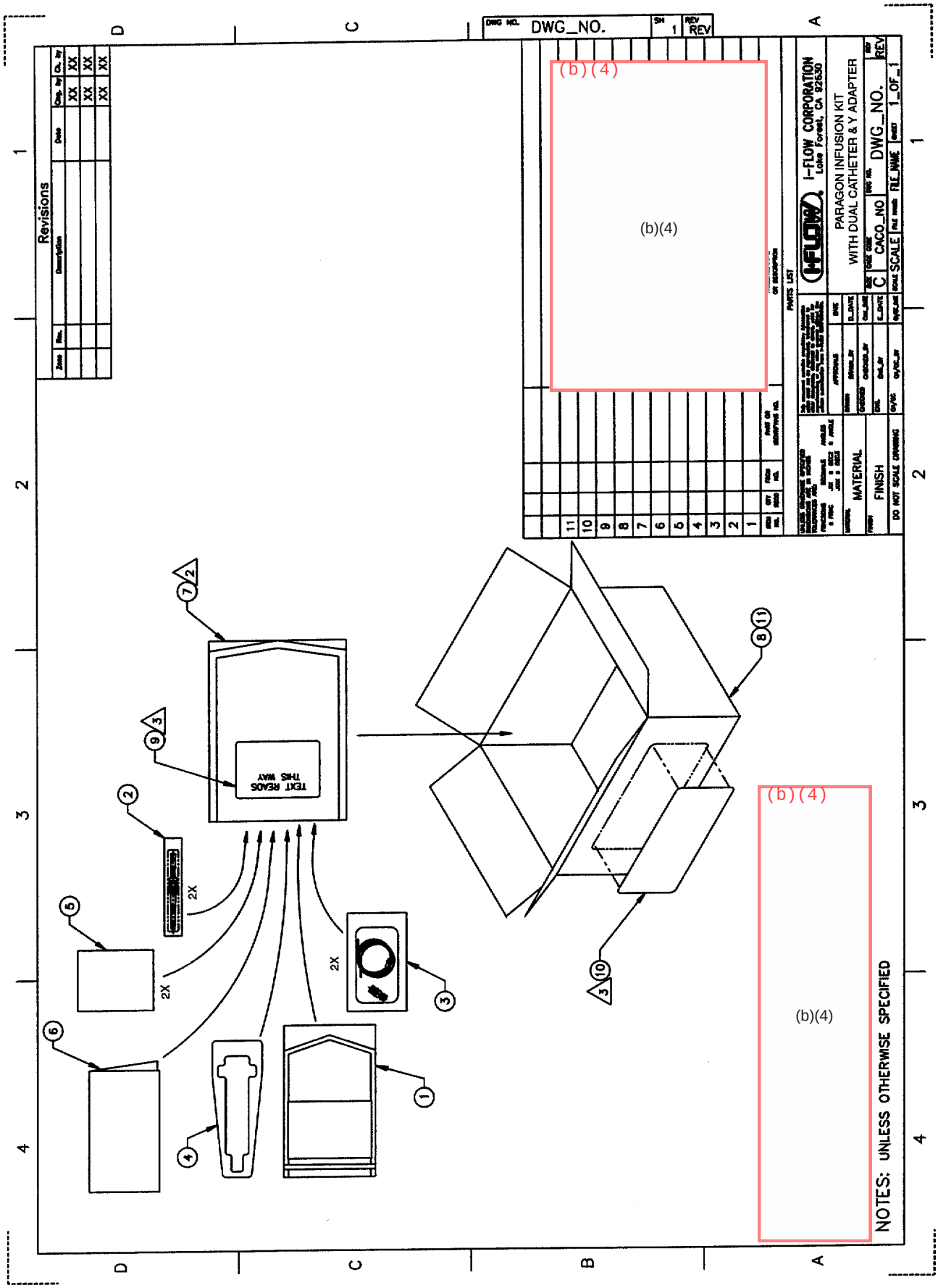
NOTES: UNLESS OTHERWISE SPECIFIED


DWG_NO.
REV
(b)(4)
I-FLOW CORPORATION
Lake Forest, CA 92630
PARAGON INFUSION KIT
WITH DUAL CATHETER & Y ADAPTER
DWG_NO.
REV
CACO_NO
SCALE
FILE_NAME
1_OF_1
Revisions
Description
Date
Chk. by
Qa. by
XX
PARTS LIST
MATERIAL
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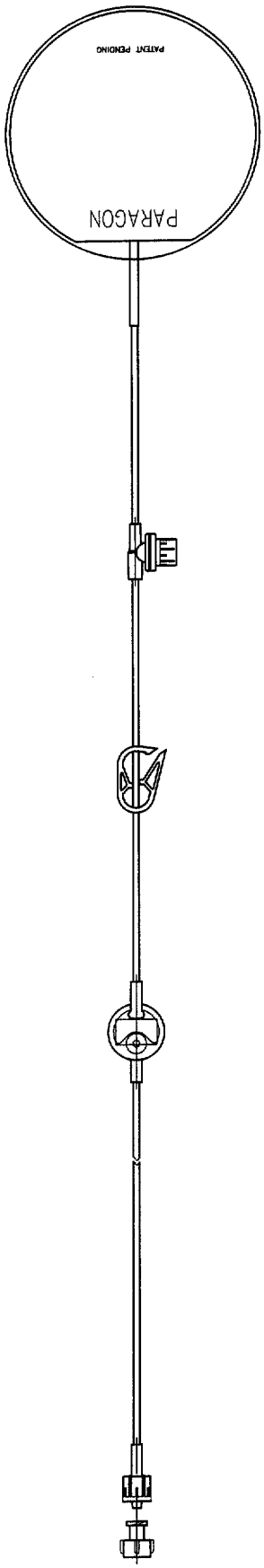
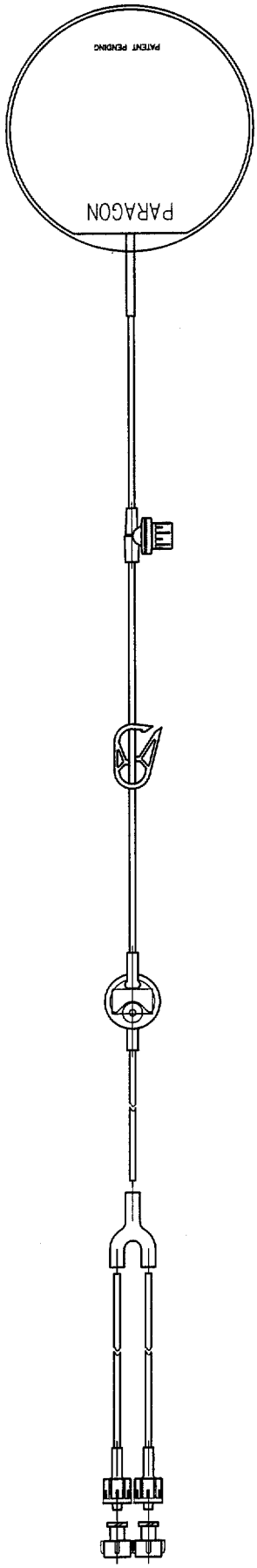
DO NOT SCALE DRAWING
TEXT READS THIS WAY
2X
NOTES: UNLESS OTHERWISE SPECIFIED

PARAGON ADMINISTRATION SET



PARAGON ADMINISTRATION SET
WITH DUAL ORIFICES



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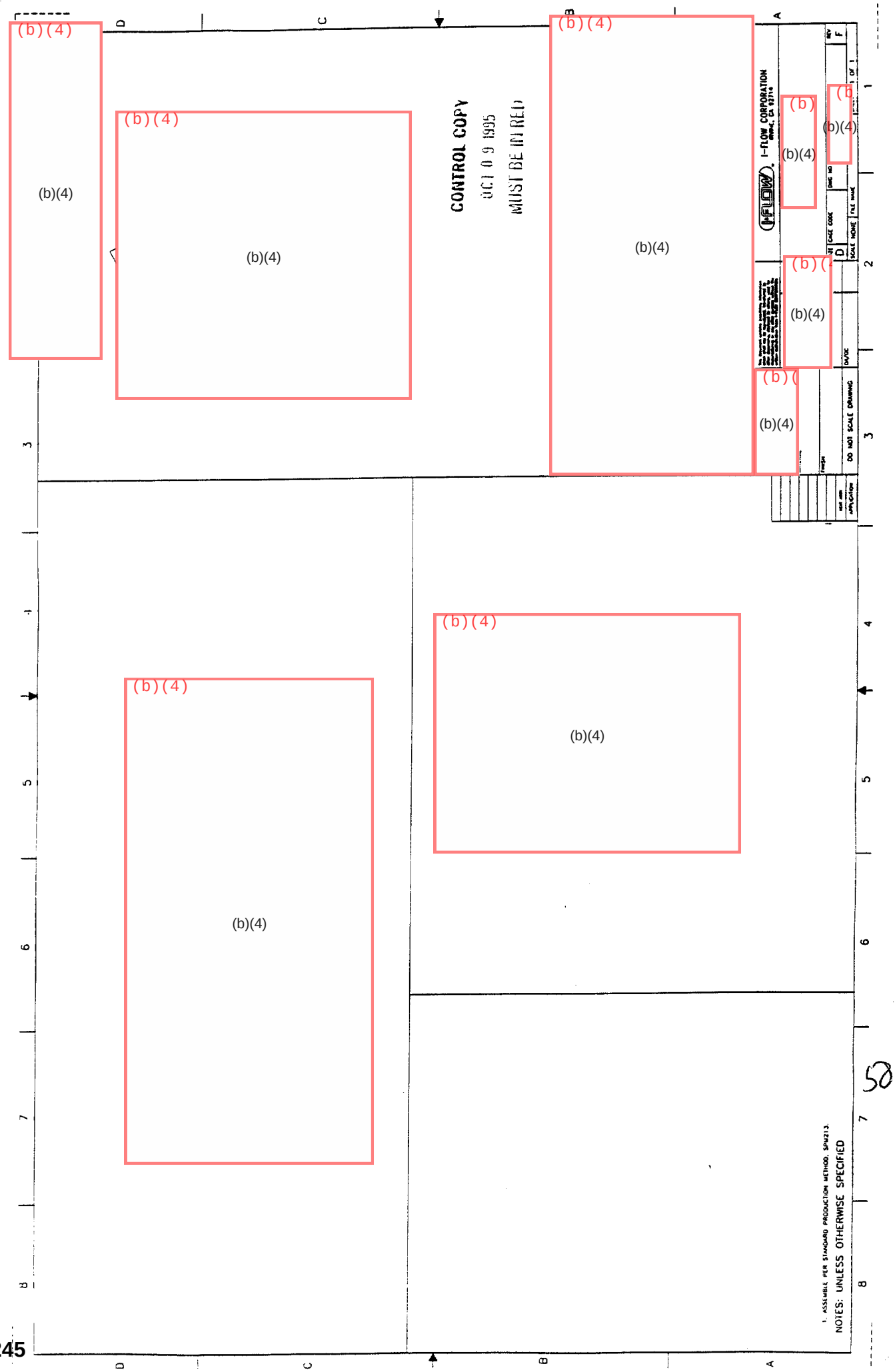
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MUST BE RETURNED
I-FLOW CORPORATION
DO NOT SCALE DRAWING
NOTES: UNLESS OTHERWISE SPECIFIED
1. ASSEMBLE PER STANDARD PRODUCTION METHOD, SPM213.

Part Specification For	I-Flow Corporation	Date: 4-16-92

I-FLOW P/N: 1100968	Rev: b

Part Description: FLEXIBLE Y FITTING

Revisions	Description	Date	Chg.By	Ck.By
A	PRODUCTION RELEASE DCO 974	4-16-92	KJS	SET
B	REVISED PER DCO 1614	1-25-94	EB	

Qualified Manufacturers [X] or Equivalent [ ] no substitutions

Manufacturer	MFG P/N
QOSINA CORP	81120
SURGIMEDICS	012500-000

Suggested source	Vendor P/N

NOTES:

I-FLOW
ORIGINAL
DOCUMENTATION

59

Approvals

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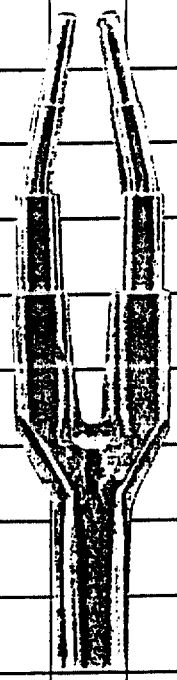
Plastisol

1 cm

Plastisol Components are made from liquid PVC resin with durometer of 65–69 Shore A hardness.

Qosina offers two versions of a Universal Y connector—2.5 inches and 3.5 inches long. The stem internal dimension is 1/4 inch. The internal leg dimensions are undersized to insure a tight non-glued fit for tubing sizes of 3/32 inch, 1/8 inch, 3/16 inch and 1/4 inch.



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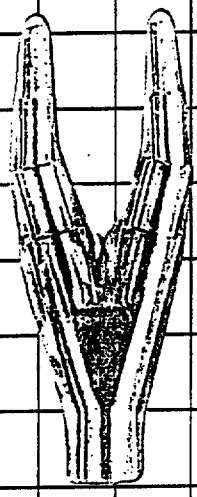

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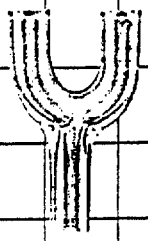
QOSINA CORP
150-Q EXECUTIVE DRIVE, EDGEWOOD, NEW YORK 11717
PHONE (516) 242-3000 FAX (516) 242-3230
ELIZABETH SEIMS
DIRECTOR OF SALES

Horseshoe Y connectors have the same internal dimensions on all three openings:



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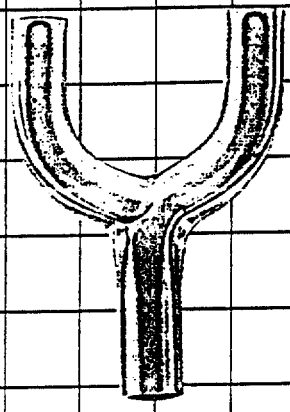

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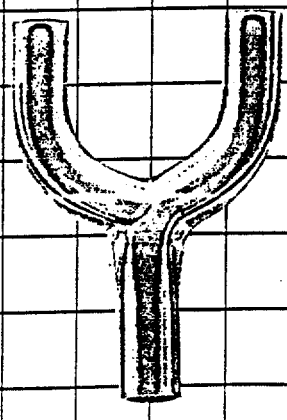

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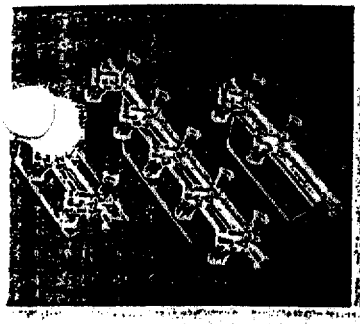
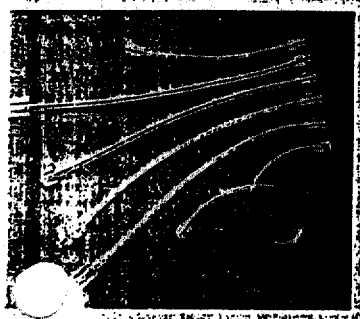
Qosina gladly welcomes the opportunity to quote other sizes and design configurations.





Manifolds

Surgimedics/TMP Manifolds are completely clear and free of glued joints, with a one-piece straight-through body that reveals air bubbles, emboli or other irregularities that can hide in opaque models. Ten manifold variations are available, with two, three, four or five ports, for a full range of uses in ICU/CCU, surgery monitoring, cardiac catheterization, drug administration and other specialty procedures.

Dip-Molded "Y" Connectors

Surgimedics/TMP Dip-Molded "Y" Connectors, manufactured of Class VI medical approved ingredients, are popular for their utility in soft tubing connections, irrigation, blood administration, dialysis, perfusion circuits and other applications. Standard connectors are available in seven interior dimensions, from .120" to .375". Special connectors allow users to clip one or both legs to accommodate fittings of 1/6", 3/32", 5/32" and 7/32".

Insert Molded Lines

Surgimedics/TMP Insert Molded Lines are clear with fittings made from medical grade PVC. Their luer lock devices eliminate the need for solvents or adhesives. Lines come in a variety of types from micro-bore to IV sizes, in both PVC and polyethylene-lined/PVC models, and for a range of low-to high-pressure uses. Engineered to meet exacting demands, the lines have gained wide use in blood pressure monitoring, drug infusion, anesthesia/capnography, radiology, respiratory care, enteral feeding, chemotherapy, cardiac therapy and diabetic treatment.

At Surgimedics/TMP, we follow exacting procedures and use only the finest medical-grade materials in the manufacturing of medical/surgical products. Used as directed, standard catalog items are guaranteed to deliver reliable, superior performance under normal operating room conditions.

Products are frequently available in multiple colors, with custom imprinting and coding, in bulk, sterile and packaged expressly to meet a user's needs. Moreover, Surgimedics/TMP design engineers take pleasure in working with clinicians as well as fabricators in the development of new products, from concept to final form.

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REVISIONS

LTR.	DESCRIPTION	DATE	BY
E	(b)(4) AJ-94	9-12-90	RCR

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SURGIMEDICS

TMP TEXAS MEDICAL PRODUCTS, INC.
A wholly owned subsidiary of SURGIMEDICS, INC.

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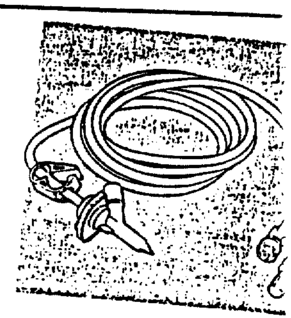
Disposable Transducer Domes & Luer Loc

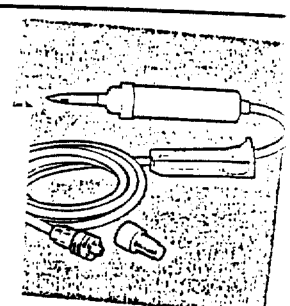
Sterile Part Number	Package	Price Each	Description	Bulk Part Number	500-999	1000-4999	5000-10,000
014480	25/Ctn	$2.70	Bentley/Linden Assembled	*014480-120	$2.60	$2.55	$2.50
014482	25/Ctn	2.70	Bentley/Luer Assembled	*014482-120	2.60	2.55	2.50
014484	25/Ctn	2.70	Gould/Linden Assembled	*014484-120	2.60	2.55	2.50
014486	25/Ctn	2.70	Gould/Luer Assembled	*014486-120	2.60	2.55	2.50
014488	25/Ctn	2.70	B & H/Linden Assembled	*014488-120	2.60	2.55	2.50
014490	25/Ctn	2.70	B & H/Luer Assembled	*014490-120	2.60	2.55	2.50

Contrast Media Se



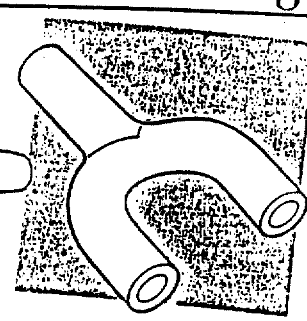
Sterile Part Number	Package	Price Each	Description	Bulk Part Number	500-999	1000-4999	5000-10,000
Contrast Media Sets							
014061	25/Ctn	$1.60	72" w/Vented Spike, pinch	014061-120	$1.40	$1.05	$ .89
*014063	25/Ctn	1.65	96" w/Vented Spike, pinch	014063-121	1.45	1.10	.95
*014064	25/Ctn	1.60	72" w/Non-Vented Spike, pinch	014064-120	1.40	1.05	.89
014065	10/Ctn	1.83	72" w/Vented Drip Chamber, rlr	014065-120	2.06	1.50	1.30
014067	10/Ctn	1.70	Flush Line w/Non-Vented Drip Chamber	014067-120	1.95	1.45	1.20
*014068	25/Ctn	1.60	72" w/Vented Spike, rlr	014068-120	1.40	1.05	.89
*014069	25/Ctn	1.60	72" w/Non-Vented Spike, rlr	014069-120	1.40	1.05	.89

Solution Administration Set



Sterile Part Number	Package	Price Each	Description	Bulk Part Number	500-999	1000-4999	5000-10,000
Solution Administration Sets							
014070	25/Ctn	$1.47	Single Set 60" Macro	014070-121	$1.40	$1.20	$1.00
014071	25/Ctn	1.47	Single Set 60" Micro	014071-121	1.40	1.25	1.05
014074	25/Ctn	2.20	2-Way Set 48"	014074-120	2.15	1.90	1.75
014077	25/Ctn	2.95	3-Way Set 48"	014077-120	2.90	2.60	2.50

Plastisol "Y" Fittings



Part Number	Description	500-999	1000-4999	5000-10,000
Plastisol "Y" Fittings				
Bulk	8 weeks			
012500	.120" ID	$ .27	$ ~~.21~~ .22	$ .17
012501	.140" ID	.28	.21	.17
012502	.160" ID	.29	.22	.18
012503	.187" ID	.32	.24	.20
012504	.250" ID	.33	.25	.20
*012505	.345" ID	.49	.36	.29
*012506	.375" ID	.49	.36	.29
012552	Universal "Y"	.25	.19	.15

*1000 Pieces Minimum

55

*Denotes Non-Stock — Special Order

Plastisol Dipped Parts

Norton products that solve problems

Because we control every step of the manufacturing process... from formulation and compounding of raw materials through extrusion, molding, assembly, packaging, and final distribution ...we can offer more flexibility, more experience, and more expertise in responding to your needs. Our theme "Norton Can Do!" is more than just a promotional statement... it's a commitment and a promise we are ready to fulfill. "Can Do!" means that you can rely on Norton to provide solutions to your problems... not just products.

Standard Manufacturing Tolerances

1. Parts with an ID of .075" to .375" have an ID tolerance of ±.005" and a wall tolerance of ±.015".
2. Parts with an ID of .375" to .625" have an ID tolerance of ±.010" and a wall tolerance of ±.020".
3. Parts with an ID of .625" to 1.00" have an ID tolerance of ±.010" and a wall tolerance of ±.030". There may be higher wall thickness in areas of restricted run-off.
4. The maximum length without specially built tanks is 13".
5. The trim lengths are toleranced at ±1/16 of an inch up to 2" and ±1/8" on longer parts.

Plastisol Typical Physical Properties

Property	Formulation 85-4	97-1	98-1	99-1
Hardness, Shore A, 15s	57	53	55	56
Tensile strength, psi	2013	1876	1824	1858
Ultimate elongation, %	394	410	438	427
Tensile stress, 100% elongation, %	870	706	683	643
Tensile stress, 200% elongation, %	1334	1119	1075	1070
Tensile stress, 300% elongation, %	1691	1487	1435	1420
Tear resistance, lb./in.	176	137	144	140
Specific gravity, 23°/23°C	1.20	1.19	1.19	1.19
Water absorption, % absorbed	0.16	0.34	0.29	0.30
Color	Clear	Clear	Gray	Blue

Standard Plastisol "Y" Fitting Dimensions

.120", .140", .160", 3/16", 1/4"

These compounds are medical grade, Class VI approved Plastisol. Customer needs can be met through development of other compounds by research group.

To order please contact your Norton representative or Norton medical products distributor. Write to us at

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NORTON HEALTH CARE PRODUCTS
P.O. BOX 350, ORRVILLE, OHIO 44667
1-800-321-0001 Customer S...

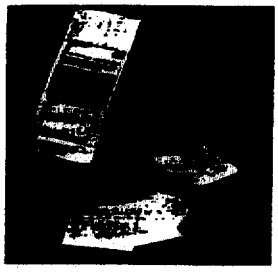
MEDICAL SPECIALTIES DISTRIBUTORS

Versalon® Nonwoven All-Purpose Sponges

Ideal for applying ointments, prepping, wiping needles, cleaning slides and more. Rayon/polyester blend construction. Cost-effective sponge. Highly absorbent. Virtually lint-free. Tray of 50.

Sterile 2's in Peel-Back Package

ORDER NO.	DESCRIPTION	QUANTITY
KE8042	2" x 2", 4-ply	cs/3000
KE8043	3" x 3", 4-ply	cs/2400
KE8046	3" x 4", 4-ply	cs/1200
KE8044	4" x 4", 4-ply	cs/1200



STERI-DRAPES

3M Healthcare

Steri-Drape™ Surgical Drapes

Steri-Drape™ plastic drapes feature dependable 3M adhesive. Helps maintain sterile field around surgical site and isolates endogenous sources of contamination. Steri-Drape™ blue fabric drapes are constructed of impermeable fabric, and provide effective adjuncts to any drape system. Available in a wide range of sizes and styles.

ORDER NO.	DESCRIPTION	QUANTITY
3M1000	17⅞" x 11¾"	bx/10
3M1010	17⅞" x 23½"	bx/10

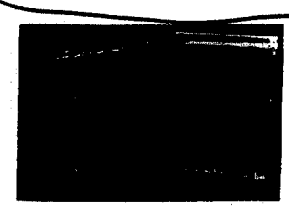
SWABS/SKIN PREPS & TOWELETTES

Clinipad Corporation

Alcohol Prep Pads

70% isopropyl alcohol impregnated in non-woven applicators, packaged in hermetically sealed, foil pouches. 70% isopropyl alcohol is used as a topical antiseptic/anti-infective agent prior to administering injections. The sterile labeled products are all processed in accordance with U.S.P. sterility testing procedures.

ORDER NO.	DESCRIPTION	QUANTITY
CL0110	Medium, 1¼" x 1½", bx/200	cs/2000
CL0110R	Medium, 1¼" x 1½", bx/100	cs/2000
CL0210	Large, 1¾" x 2", bx/100	cs/1000



Acetone Alcohol Prep Pads

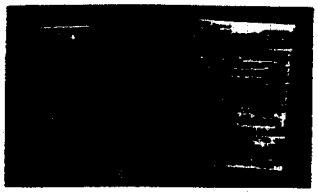
70% isopropyl alcohol combined with 10% acetone impregnated on a non-woven applicator, packaged in a hermetically-sealed, foil-laminated pouch.

ORDER NO.	DESCRIPTION	QUANTITY
CL0310	1¾" x 1½", bx/100	cs/1000

Aqueous Towelettes

Towelette saturated with purified water and 0.9% benzyl alcohol, and packaged in a hermetically-sealed, foil-laminated pouch.

ORDER NO.	DESCRIPTION	QUANTITY
CL2388	8" x 5¼", bx/100	cs/1000



Pouches, Towelettes, and Prep Pads

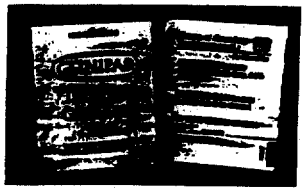
Broad range of products including antiseptics, skin protectants and cosmetic items. Unit-of-use packaging eliminates waste and cross-contamination. Color coded.

ORDER NO.	DESCRIPTION	QUANTITY
CL2389	Castile soap towelettes	cs/1000
CL2391	Refreshing towelettes	cs/1000
CL2395	Antiseptic towelettes	cs/1000
CL3941	Povidone iodine solution, 1 oz	cs/200
CL8133	Protective dressing	cs/1000

Tincture of Green Soap Towelettes

A folded towelette saturated with green soap tincture solution and packaged in a hermetically-sealed, foil-laminated pouch.

ORDER NO.	DESCRIPTION	QUANTITY
CL2396	8" x 5¼"	cs/1000



Iodophor Triples Towelettes

Poloxamer iodine is saturated on three folded towelettes, packaged in a hermetically sealed, foil-laminated pouch. Bulk case.

ORDER NO.	DESCRIPTION	QUANTITY
CL2590	2¼" x 1", unfolded 6" x 4¾"	cs/1500

Liquid Castile Soap Pouches

A hermetically-sealed mylar pouch filled with the highest quality castile soap.

ORDER NO.	DESCRIPTION	QUANTITY
CL3932	4" x 2"	cs/500

Dressing & Wound Care

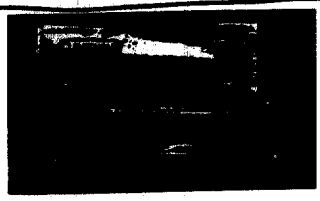
TO PLACE YOUR ORDER CALL 1-800-967-6400

Clinipad Corporation (continued)

Iodophor PVP Scrub Swabsticks

4" swabsticks saturated with povidone iodine scrub antiseptic, a solution consisting of povidone iodine and a nonionic detergent packaged in a hermetically-sealed, foil-laminated pouch.

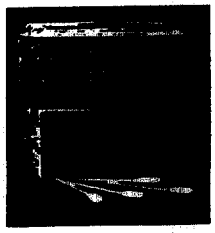
ORDER NO.	DESCRIPTION	QUANTITY
CL1242	Single swab, bx/50	cs/500
CL1244	Triple swab, bx/25	cs/250



Lemon Glycerin Swabsticks

4" swabsticks saturated with a lemon flavored glycerine and a pleasant tasting, odorless liquid packaged in a hermetically-sealed, foil-laminated pouch. Appropriate for general mouth care.

ORDER NO.	DESCRIPTION	QUANTITY
CL1225	Triple swab, bx/25	cs/250

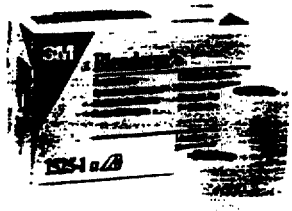


TAPES

Blenderm™ Surgical Tape

Features a waterproof backing that protects against outside contamination. It is recommended for occlusive skin test patches and protective dressings. This hypoallergenic, plastic surgical tape adheres securely to body contours.

ORDER NO.	DESCRIPTION	QUANTITY
3M1525-1	1" x 5 yd, cs/10 bx	bx/12
3M1525-2	2" x 5 yd, cs/10 bx	bx/6



Durapore™ Surgical Tape

Durapore™ surgical tape is a multipurpose specialty dressing tape for applications where strength is required. This hypoallergenic silk tape features a strong, durable backing and excellent adhesion to provide security for the most critical taping needs. The permeable backing permits moisture build-up.

ORDER NO.	DESCRIPTION	QUANTITY
3M1538-0	½" x 10 yd, cs/10 bx	bx/24
3M1538-1	1" x 10 yd, cs/10 bx	bx/12
3M1538-2	2" x 10 yd, cs/10 bx	bx/6
3M1538-3	3" x 10 yd, cs/10 bx	bx/4

Microfoam™ Surgical Tape

Stretchable, hypo-allergenic tape for pressure dressings. Made of surgical foam coated with firm adhesive. Used for orthopedic rehabilitation dressings, post-surgical dressings, and relief of edema and distention non-irritating. Tears easily. Stretched.

ORDER NO.	DESCRIPTION	QUANTITY
3M1528-1	1" x 5½ yd, cs/10 bx	bx/12
3M1528-2	2" x 5½ yd, cs/10 bx	bx/6
3M1528-3	3" x 5½ yd, cs/10 bx	bx/4
3M1528-4	4" x 5½ yd, cs/10 bx	bx/3

Micropore™ Surgical Tape

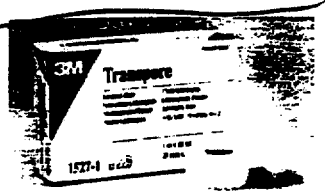
This hypo-allergenic paper tape is porous to enable moisture to escape without reducing adhesion. Easy to remove and leaves minimal tape residue.

ORDER NO.	DESCRIPTION	QUANTITY
3M1530-0	½" x 10 yd, cs/10 bx	bx/24
3M1530-1	1" x 10 yd, cs/10 bx	bx/12
3M1530-2	2" x 10 yd, cs/10 bx	bx/6
3M1530-3	3" x 10 yd, cs/10 bx	bx/4
3M1533-1	1" x 10 yd, tan, cs/10 bx	bx/12
3M1533-2	2" x 10 yd, tan, cs/10 bx	bx/6
3M1535-1	1" x 10 yd, dispenser pack, cs/10 bx	bx/12
3M1535-2	2" x 10 yd, dispenser pack, cs/10 bx	bx/6

Transpore™ Surgical Tape

Lightweight, clear plastic tape. For securing pressure dressings over movable joints. Hypo-allergenic adhesive, leaves no residue. Uniformly perforated for ventilation. Conforms well and tears easily. X-ray transparent.

ORDER NO.	DESCRIPTION	QUANTITY
3M1527-0	½" x 10 yd, cs/10 bx	bx/24
3M1527-1	1" x 10 yd, cs/10 bx	bx/12
3M1527-2	2" x 10 yd, cs/10 bx	bx/6
3M1527-3	3" x 10 yd, cs/10 bx	bx/4
3M1527S-1	1" x 1½ yd, single use, cs/5 bx	bx/100
3M1527S-2	2" x 1½ yd, single use, cs/5 bx	bx/50



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MEDICAL SPECIALTIES DISTRIBUTORS

Medi-Rip® Self-Adherent Bandages

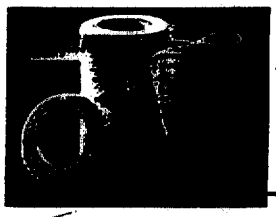
Cotton self-adherent bandage with elastic support securely sticks to itself, but never to skin or hair. Tears easily to exact length needed. Lightweight, cool and comfortable. Individually wrapped in 5 yard lengths.

ORDER NO.	DESCRIPTION	QUANTITY
CC0510	1", non-sterile, cs/4 bx	bx/24
CC0520	2", non-sterile, cs/8 bx	bx/12
CC0530	3", non-sterile, cs/8 bx	bx/12
CC0540	4", non-sterile, cs/8 bx	bx/12
CC0560	6", non-sterile, cs/4 bx	bx/12

Co-Wrap™

Self-adherent – never needs pins, clips or tape. Patient-friendly cotton stays cool, comfortable and gentle. Low cost – just pennies per application. User-friendly – each roll is easy to start and finish with no waste.

ORDER NO.	DESCRIPTION	QUANTITY
CC2910	1" x 5 yds, tan, cs/4 bx	bx/24
CC2920	2" x 5 yds, tan, cs/8 bx	bx/12
CC2930	3" x 5 yds, tan, cs/8 bx	bx/12
CC2940	4" x 5 yds, tan, cs/8 bx	bx/12
CC2960	6" x 5 yds, tan, cs/8 bx	bx/12



Johnson & Johnson

Kling® Conforming Gauze

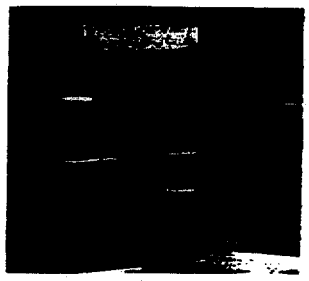
Ideal for securing dressings, IV's, splints, or for providing mild compression and support. Maximum freedom of movement without constriction. Gentle stretch for easy application. Conforms to difficult contours. Stays in place with minimal taping. Bandage clings to itself. Individually packaged.

ORDER NO.	DESCRIPTION	QUANTITY
JJ6922	2", sterile, pk/12	cs/96
JJ6923	3", sterile, pk/12	cs/72
JJ6924	4", sterile, pk/12	cs/72
JJ6926	6", sterile, pk/12	cs/48

Sof-Kling™ Conforming Bandages

Sof-Kling™ Conforming Bandage is a one-ply rayon/polyester blend bandage that conforms, stretches and adheres to itself. This low-linting bandage is highly absorbent. Individually packaged.

ORDER NO.	DESCRIPTION	QUANTITY
JJ6992	2" x 65", sterile, pk/12	cs/96
JJ6993	3" x 75", sterile, pk/12	cs/72
JJ6994	4" x 75", sterile, pk/12	cs/72
JJ6996	6" x 85", sterile, pk/12	cs/48



Kendall Healthcare

Conform® Stretch Bandages

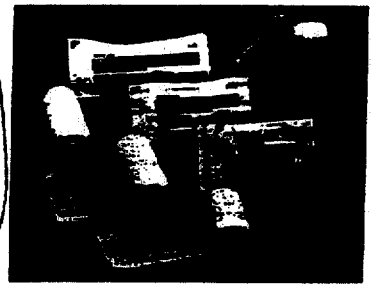
One-ply cotton/polyester blend crocheted bandage. Provides softness, conformability, low lint, high absorbency. Ideal for securing dressings, IV's and splints or for providing mild compression or support. Holds securely to any body contour; allows for movement and some soft tissue swelling. Stays in place with minimal taping. Stretched.

Non-Sterile, Bulk

ORDER NO.	DESCRIPTION	QUANTITY
KE2239	1" x 4.1 yds, bg/24	cs/96
KE2242	2" x 4.1 yds, bg/12	cs/96
KE2244	3" x 4.1 yds, bg/12	cs/96
KE2247	4" x 4.1 yds, bg/12	cs/96
KE2249	6" x 4.5 yds, bg/12	cs/48

Sterile in Soft Pouch

ORDER NO.	DESCRIPTION	QUANTITY
KE2230	1" x 4.1 yds, bg/12	cs/96
KE2231	2" x 4.1 yds, bg/12	cs/96
KE2232	3" x 4.1 yds, bg/12	cs/96
KE2236	4" x 4.1 yds, bg/12	cs/96
KE2238	6" x 4.5 yds, bg/12	cs/48



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Appendix B

Paragon Infusion Kit Labeling

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PARAGON INFUSION KIT

Directions for Use

NOMENCLATURE

1. PARAGON Infuser ❶
2. Fluid Level Indicator ❷
3. 1.2 micron air-eliminating filter ❸
4. PARAGON Administration Set ❹
5. Flow Rate Label ❺
6. Luer Lock ❻
7. End of Infusion Indicator ⓱

INTENDED USE

The Paragon Infusion Kit is intended to provide a continuous infusion of a local anesthetic directly into an intraoperative site for general surgery for postoperative pain management. The routes of administration include percutaneous, subcutaneous, intramuscular and epidural.

CONTRAINDICATIONS

Not for intravenous or intra-arterial drug delivery.
Not for blood, blood products, lipids or fat emulsions delivery.

CAUTION

1. Do not use the administration set if the sterile pouch is opened or damaged. If either protective cap is missing or not in place, the sterility of the administration set is no longer guaranteed.
2. It is recommended that the administration set be changed in accordance with established guidelines.
3. Do not resterilize administration set. Administration sets are intended for single patient use only. The fluid pathway is sterile and nonpyrogenic.
4. Epidural administration of analgesics is limited to use with indwelling catheters specifically indicated for either short-term or long-term analgesic drug delivery. Do not use Y adapter with epidural delivery.
5. If the device is to be used for epidural analgesic drug administration, it should be labeled to differentiate from other routes of administration. When using this device for epidural drug administration, make certain only drugs recommended for this route of administration are used.
6. **This product contains natural rubber latex which may cause allergic reactions. Individuals with known natural rubber latex sensitivities should not use this product.**

INTRODUCTION

The *PARAGON* is a drug delivery system consisting of a reusable mechanical infuser and specially designed administration sets. The *PARAGON* provides precise delivery of medications requiring slow and continuous infusions.

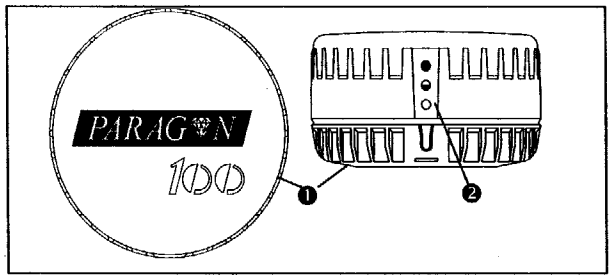
THE *PARAGON* ADMINISTRATION SET

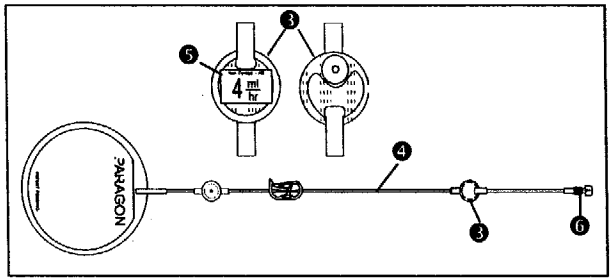
Administration sets are made of PVC. Each set is approximately 127 cm long. A 1.2 micron air-eliminating filter is built into all administration sets. The flow rate at which the drug flows to the patient is controlled by a flow restrictor built into the end of each set. Flow rates for each set are printed on a label located on the air-eliminating filter. ❺

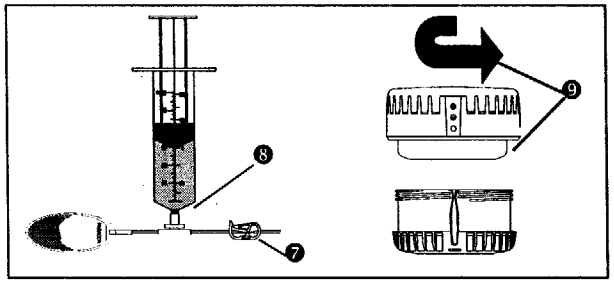
FILLING THE *PARAGON* DRUG BAG - USE ASEPTIC TECHNIQUE

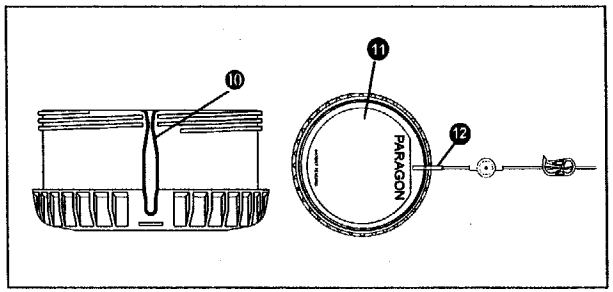
1. Remove the drug bag with attached administration set from its package.
2. Move the flow clamp next to the filling valve and close the clamp. ❼
3. Fill a sterile syringe with the solution to be dispensed into the drug bag.
4. Connect the tip of the syringe to the filling valve and inject the solution into the drug bag. ❽ Refill the syringe and repeat if necessary.

   NOTE: The *PARAGON* Infuser is designed to hold a total of 100 ml of fluid. The maximum fill volume is 120 ml. If the amount of fluid exceeds 120 ml, it may be difficult to engage the threads on the top and bottom of the









THE CARRYING CASE

The carrying case can be worn on a belt, over the shoulder, or around the waist.

1. Place the *PARAGON* Infuser in the carrying case so that the bottom of the infuser can be seen through the clear plastic window. ⓲
2. Lift the Velcro strap and slide the administration set down so that the set exits the carrying case at the side window opening. ⓳ Close the strap. (Positioning the infuser in this way allows for the viewing of the Fluid Level Indicator.)
3. The front flap of the carrying case lifts up to reveal a clear plastic window, allowing for the viewing of the End of Infusion Indicator. ⓴
4. If necessary, a small lock can be placed through the larger of the two holes on the zipper, and then through the cloth loop on the side of the carrying case. (This may discourage tampering with the infuser during an infusion.) ㉑

CARE OF THE *PARAGON*

The *PARAGON* Infuser is durable and is intended to be used for repeated drug deliveries. After each patient use, the exposed surfaces, except the threads, may be wiped clean using isopropyl alcohol or a 10% bleach solution.

NOTE: Do not submerge the *PARAGON* Infuser in a bleach solution. After cleaning, if the *PARAGON* is difficult to twist together, place a small drop of lubricating ointment (such as K-Y™ Jelly) on a small section of the threads on the bottom of the infuser. Twist the top of the infuser onto the bottom to spread out the ointment. ㉒

IMPORTANT

1. Only *PARAGON* administration sets distributed by I-Flow Corporation are authorized for use with this product. I-Flow Corporation accepts no responsibility for performance, or the liability for damages, caused by the misuse of this product when used with unauthorized administration sets.
2. This product uses DEHP plasticized PVC. Certain solutions may be incompatible with the PVC material used in the administration set. Consult the drug package insert and other available sources of information for a more thorough understanding of possible incompatibility problems.

The *PARAGON* Infuser Specifications

Size: 5.8 cm high; 10.2 cm in diameter

Weight: 260 g

Flow Rates: 0.5, 1, 2, 4 and 10 ml/hr

Delivery Accuracy: ±10% at 95% confidence interval.

Priming volume: Allow 1 ml for loss during priming.

Residual volume: Approximately 4 ml

NOTES

1. The infusion rates for each administration set are indicated on the administration set label.
2. Actual infusion rates may vary from the specified range due to:
   - viscosity and/or drug concentration.
   - temperatures above or below the operating conditions.
   - the positioning of the *PARAGON* Infuser above or below the infusion

PARAGON Infuser.
5. Remove air from the drug bag by aspirating with a syringe attached to the filling valve. Squeezing the sides of the drug bag when pulling back on the syringe will aid in removing the air.
6. Be certain to replace the cap on the filling valve.
7. Do not place labels on the drug bag. Labels may be wrapped around the set.

LOADING THE DRUG BAG INTO THE *PARAGON* INFUSER
1. Twist open the top and bottom halves of the *PARAGON* Infuser. ❾
2. Before placing the drug bag into the *PARAGON* Infuser, slide the thin portion of the administration set through the slot found on the bottom of the infuser. ❿
3. Center the bag in the bottom and press all around the edge of the bag to fully seat the bag in the bottom. Make sure there are no wrinkles in the bag. ⓫
4. Pull gently on the thick portion of the tubing so that it is fully extended and seated at the bottom of the slot. ⓬
5. Twist the top and bottom halves of the *PARAGON* Infuser together until they meet. ⓭

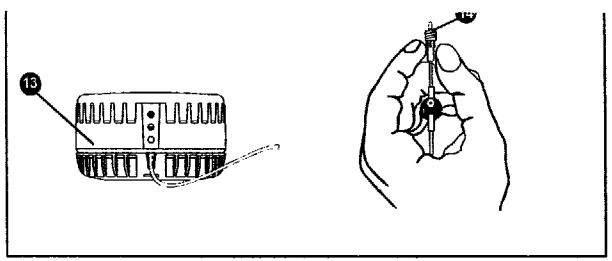
PRIMING THE ADMINISTRATION SET
1. Using appropriate aseptic technique, remove the cap from the Luer lock at the end of the set. Open the clamp on the set tubing. The medication will flow toward the end of the Luer lock.
2. Confirm that fluid is flowing by observing the formation of a drop at the end of the Luer lock. It may take 10 minutes for a drop to form when priming the 0.5 ml/hr set. ⓮
3. Pinch the clamp closed and replace the cap.

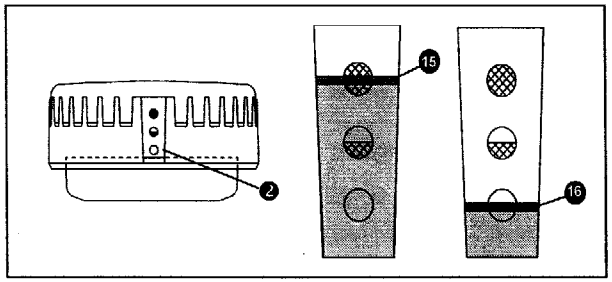
PLACING THE CATHETER
1. Insert introducer needle through the skin (approximately 3-5 cm away from wound site) then push introducer needle into the surgical wound site.
2. Insert the marked end of the catheter though the hub of the introducer needle.
3. Remove introducer needle while holding catheter tightly in place. Assure catheter placement in wound site.
4. Attach the catheter connector to the unmarked end of the catheter. Tighten until catheter cannot be removed.
5. Attach the catheter connector to the set tubing.
5. Tape catheter securely in place.
6. Apply appropriate dresssing to catheter site.

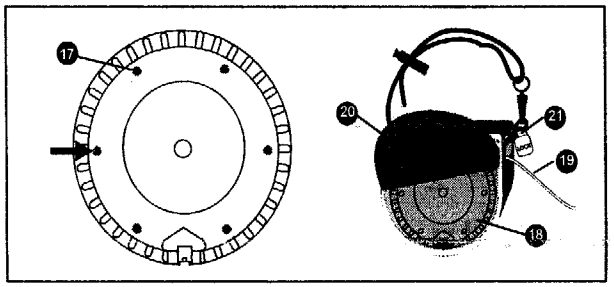
STARTING THE INFUSION
1. Start the infusion by opening the clamp on the administration set. The infusion will begin immediately.
2. Secure flow restrictor to skin and apply desired dressing. The flow restrictor must not be in contact with cold therapy pads.

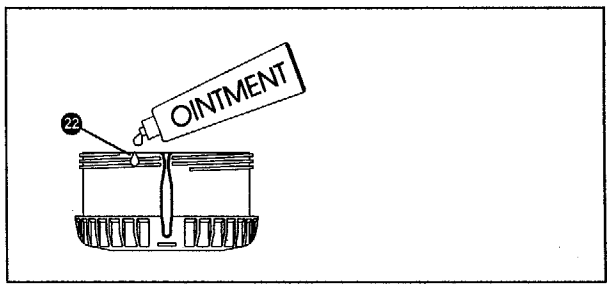
THE FLUID LEVEL INDICATOR
1. The window with the markings on the side of the infuser is used to estimate how far the infusion has progressed. ❷
2. When the *PARAGON* drug bag is filled to its capacity of 100-120 ml, the top of the pressure plate will be aligned with the top round marker. ⓯
3. As the infusion progresses, the plate will move to the bottom marker indicating the bag is nearly empty. ⓰

THE END OF THE INFUSION
The infusion is complete when at least three (out of the six) small blue dots appear through the bottom of the *PARAGON* Infuser. ⓱









3. The *PARAGON* System has been calibrated using Normal Saline as the diluent and skin contact temperature (32°C, 90°F) as the operating environment. When using Normal Saline and skin temperature the *PARAGON* System will flow at the specified nominal rate. The use of other diluents or operating temperatures other than the above will affect the nominal flow rate. For example, if 5% Dextrose (D5W) is used as the final diluent, the *PARAGON* System will flow at 10% below the nominal rate due to higher solution viscosity and the refill time will be 10% longer.

CAUTION
1. **Prompt removal of the catheter is advised after infusion is complete to reduce risk of infection.**
2. **FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.**

U.S. and Foreign Patents Pending

Manufactured by:
I-Flow Corp.
Lake Forest, CA 92630
Printed in the U.S.A.

European Representative:
MPS Medical Product Service GmbH
Borngasse 20, 35619 Braunfels, Germany
CE 0123
130XXXXA
11/98

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I-FLOW CORPORATION, LAKE FOREST, CA U.S.A.

CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF PG100005

PART NO. 5001200

PARAGON INFUSION KIT
100 ml Vol x 0.5 ml/hr

PACKAGE IS NOT STERILE, INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 100 ml Vol, 0.5 ml/hr Administration Set
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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I-Flow Corporation
Lake Forest, CA 92630 U.S.A.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF PG100010

PART NO. 5001201

PARAGON INFUSION KIT
100 ml Vol x 1 ml/hr

PACKAGE IS NOT STERILE, INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 100 ml Vol, 1 ml/hr Administration Set
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF PG100020

PART NO. 5001202

PARAGON INFUSION KIT
100 ml Vol x 2 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 100 ml Vol, 2 ml/hr Administration Set
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF PG100040

PART NO. 5001203

PARAGON INFUSION KIT
100 ml Vol x 4 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 100 ml Vol, 4 ml/hr Administration Set
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF PG100100

PART NO. 5001204

PARAGON INFUSION KIT
100 ml Vol x 10 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 100 ml Vol, 10 ml/hr Administration Set
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000780

PARAGON ADMINISTRATION SET
100 ml Vol x 0.5 ml/hr

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000781

PARAGON ADMINISTRATION SET
100 ml Vol x 1 ml/hr

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000782

PARAGON ADMINISTRATION SET
100 ml Vol x 2 ml/hr

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000783

PARAGON ADMINISTRATION SET
100 ml Vol x 4 ml/hr

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000784

PARAGON ADMINISTRATION SET
100 ml Vol x 10 ml/hr

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF PG100005

PART NO. 5001200

PARAGON INFUSION KIT
100 ml Vol x 0.5 ml/hr



LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF PG100010

PART NO. 5001201

PARAGON INFUSION KIT
100 ml Vol x 1 ml/hr

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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1303061A

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF PG100020

PART NO. 5001202

PARAGON INFUSION KIT
100 ml Vol x 2 ml/hr




CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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Fabrique par / Fabricado por:
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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF PG100040

PART NO. 5001203

PARAGON INFUSION KIT
100 ml Vol x 4 ml/hr

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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I-FLOW CORPORATION, LAKE FOREST, CA U.S.A.

CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF PG100100

PART NO. 5001204

PARAGON INFUSION KIT
100 ml Vol x 10 ml/hr

LOT

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF PG100000

PART NO. 5001299

PARAGON PUMP
100 ml Vol



LOT

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1303999A

Skin Contact – NS

$0.5 \frac{ml}{hr}$

Skin Contact – NS

$1 \frac{ml}{hr}$

Skin Contact – NS

$2 \frac{ml}{hr}$

Skin Contact – NS

$4 \frac{ml}{hr}$

Skin Contact – NS

$10 \frac{ml}{hr}$

Appendix C

Kit Component Labeling

PEEL OPEN

PERIFIX PERIFIX PERIFIX

PEEL OPEN

PERIFIX®
Epidural Catheter Set

PRODUCT CODE
EC20-C
333530

Contents of unopened, undamaged package are:
STERILE

DISPOSABLE - Destroy after single use. Do not clean or resterilize.
Store at controlled room temperature.

CONTENTS:
One - Marked 20 GA. x 39.3 in. (100 cm) Radiopaque Polyamide Epidural Catheter with Closed Tip and Three Lateral Sideports
One - Catheter Threading Assist Guide
One - Screw Cap Luer Lock Catheter Connector

CAUTION: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

B|BRAUN

B. Braun Medical Inc.
Bethlehem, PA 18018
Assembled and packaged in U.S.A.
Components made in U.S.A. and Germany

P-2000 REV. 3/98

891430 EXP 1/02

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PERIFIX® Epidural Catheter Directions

Contents of unopened, undamaged package are:

STERILE

DISPOSABLE - Destroy after single use. Do not clean or resterilize.
Store at controlled room temperature.

CAUTION: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

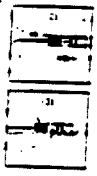
DIRECTIONS: Use Aseptic Technique.

Following puncture and verification of the Epidural Space, introduce the catheter tip through the Epidural Needle using the:

(1) Threading Assist Guide. The guide will increase longitudinal stability of the catheter.

CAUTION: DO NOT WITHDRAW CATHETER THROUGH NEEDLE BECAUSE OF THE POSSIBLE DANGER OF SHEARING.

Insert catheter to desired depth. Catheter markings: 5.5 cm (1 ring), 10.5 cm (2 rings), 15.5 cm (3 rings) in 1 cm increments, 20.5 cm (4 rings). The solid wide warning mark indicates exit of catheter from needle when using the Threading Assist Guide and a PERIFIX® Epidural Needle. The catheter will exit 1 cm before the warning mark when not using the Threading Assist Guide.



Remove needle and Threading Assist Guide over catheter while holding catheter tightly in place.

(2) Introduce distal end of catheter as far as possible in central opening of transparent screw cap of catheter connector.

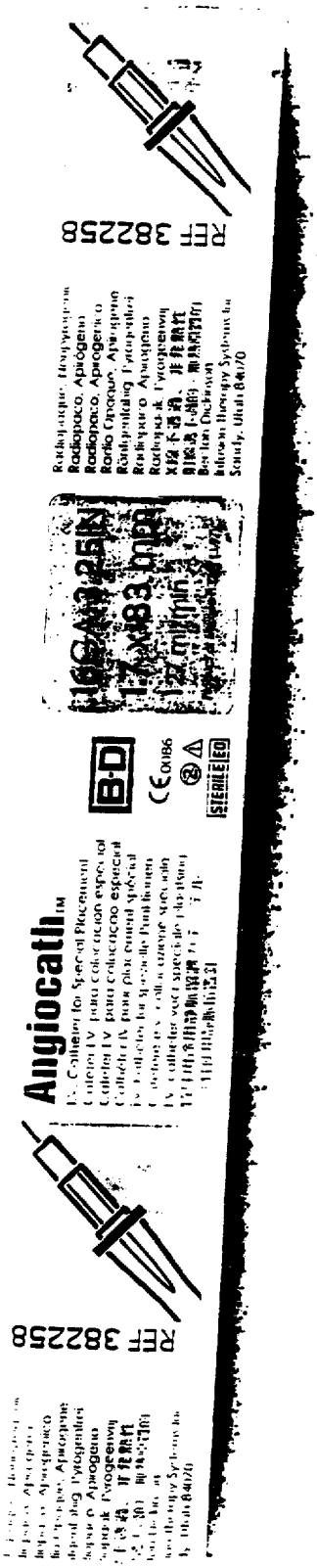
(3) Tighten screw cap until catheter can no longer be withdrawn. Administer test dose. Administer anesthetic as needed.

B|BRAUN

B. Braun Medical Inc.
Bethlehem, PA 18018

A4808076 P-3060 REV. 8/95

78


Angiocath
REF 382258
REF 382258
B-D
STERILE EO

60cc Syringe
LATEX FREE
delines...Do not reshield used needles

LUER LOK®

Discard after single use • Sterile

BECTON DICKINSON & CO.
FRANKLIN LAKES NJ
07417-1884

T TAB ◀PEEL AT TAB ◀PEEL AT TAB ◀PEEL AT TAB

Reorder No. 309663
60cc Syringe
DG615(4)

B-D® 60cc Syringe
LATEX FREE
Follow CDC guidelines...Do not reshield used needles

Disc
sing
Ster

BECTO
FRANK
07417-

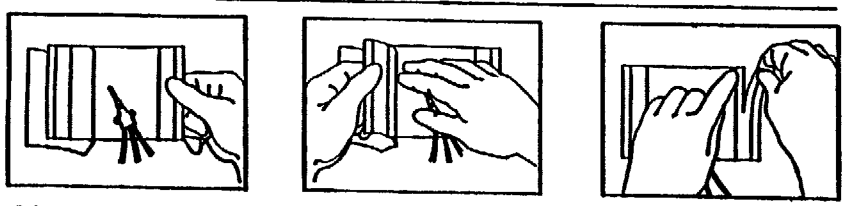
◀PEEL AT TAB ◀PEEL AT TAB ◀PEEL AT TAB ◀PEEL AT TAB ◀PEE

Appendix C
PainBuster Syringe Label
B-D Luer Lock®

Smith+Nephew

4 in x 5 in (10 cm x 13 cm) **#4973**

High MVP Transparent Dressing



Single use. Sterile unless opened or damaged.

Customer Action Center: 1 800 876-1261
Smith & Nephew United, Inc., Largo, FL 34643
***Trademark of Smith & Nephew**

PP 08908

OpSite V3000 Central

TAPE HANDLE

+H19549731B

81

Appendix D

Predicate Labeling

I-FLOW

PARAGON USER'S GUIDE

Directions for Use

NOMENCLATURE

1. *PARAGON* Infuser ❶
2. Fluid Level Indicator ❷
3. 1.2 micron air-eliminating filter ❸
4. *PARAGON* Administration Set ❹
5. Flow Rate Label ❺
6. Luer Lock ❻
7. End of Infusion Indicator ❼

CAUTION

1. Do not use the administration set if the sterile pouch is opened or damaged. If either protective cap is missing or not in place, the sterility of the administration set is no longer guaranteed.
2. Not for blood or blood products delivery. It is recommended that the administration set be changed every 24-48 hours or in accordance with CDC guidelines or institutional policies.
3. Do not resterilize administration set. Administration sets are intended for single patient use only. The fluid pathway is sterile and nonpyrogenic.

INTRODUCTION

The *PARAGON* is a drug delivery system consisting of a reusable mechanical infuser and specially designed administration sets. The *PARAGON* provides precise delivery of medications requiring slow and continuous infusions, such as chemotherapeutics and analgesics. The *PARAGON* also infuses medications which require faster delivery, such as antibiotics.

THE *PARAGON* ADMINISTRATION SET

Administration sets are made of PVC. Each set is approximately 127 cm long. A 1.2 micron air-eliminating filter is built into all administration sets. The flow rate at which the drug flows to the patient is controlled by a flow restrictor built into the end of the set. Flow rates for each set are printed on the air-eliminating filter label. ❸

FILLING THE *PARAGON* IV BAG - USE ASEPTIC TECHNIQUE

1. Remove the IV bag with attached administration set from its package.
2. Move the flow clamp next to the filling valve and close the clamp. ❹
3. Fill a sterile syringe with the solution to be dispensed into the IV bag.
4. Connect the tip of the syringe to the filling valve and inject the solution into the IV bag. ❺ Refill the syringe and repeat if necessary.
   NOTE: The *PARAGON* infuser is designed to hold a total of 100 ml of fluid. The maximum fill volume is 110 ml. If the amount of fluid exceeds 110 ml, it may be difficult to engage the threads on the top and bottom of the *PARAGON* infuser.
5. Remove air from the IV bag by aspirating with a syringe attached to the filling valve. Squeezing the sides of the IV bag when pulling back on the syringe will aid in removing the air.
6. Be certain to replace the cap on the filling valve.
7. Do not place labels on the IV bag. Labels may be wrapped around the set.

LOADING THE IV BAG INTO THE *PARAGON* INFUSER

1. Twist open the top and bottom halves of the *PARAGON* infuser. ❻
2. Before placing the IV bag into the *PARAGON* infuser, slide the thin portion of the administration set through the slot found on the bottom of the infuser. ❼
3. Center the bag in the bottom and press all around the edge of the bag to fully seat the bag in the bottom. Make sure there are no wrinkles in the bag. ❽
4. Pull gently on the thick portion of the tubing so that it is fully extended and seated at the bottom of the slot. ❾
5. Twist the top and bottom halves of the *PARAGON* infuser together until they meet. ❿

PRIMING THE ADMINISTRATION SET

1. Using appropriate aseptic technique, remove the cap from the luer lock at the end of the set. Open the clamp on the IV tubing. The medication will flow toward the end of the luer lock.
2. Confirm that fluid is flowing by observing the formation of a drop at the end of the luer lock. It may take 10 minutes for a drop to form when priming the 0.5 ml/hr set. ⓫
3. Pinch the clamp closed and replace the cap.

STARTING THE INFUSION

1. Attach the administration set to the IV site. Secure the connection against the skin.
2. Start the infusion by opening the clamp on the administration set. The infusion will begin immediately.

THE FLUID LEVEL INDICATOR

1. The window with the markings on the side of the infuser is used to estimate how far the infusion has progressed. ⓬
2. When the *PARAGON* IV bag is filled to its capacity of 100-110 ml, the top of the pressure plate will be aligned with the top round marker. ⓭
3. As the infusion progresses, the plate will move to the bottom marker indicating the bag is nearly empty. ⓮

THE END OF THE INFUSION

The infusion is complete when at least three (out of the six) small blue dots appear through the bottom of the *PARAGON* infuser. ⓯

THE CARRYING CASE

The carrying case can be worn on a belt, over the shoulder, or around the waist.

1. Place the *PARAGON* infuser in the carrying case so that the bottom of the infuser can be seen through the clear plastic window. ⓰
2. Lift the Velcro strap and slide the administration set down so that the set exits the carrying case at the side window opening. ⓱ Close the strap. (Positioning the infuser in this way allows for the viewing of the Fluid Level Indicator.)
3. The front flap of the carrying case lifts up to reveal a clear plastic window, allowing for the viewing of the End of Infusion Indicator. ⓲
4. If necessary, a small lock can be placed through the larger of the two holes on the zipper, and then through the cloth loop on the side of the carrying case. (This may discourage tampering with the infuser during an infusion.) ⓳

CARE OF THE *PARAGON*

The *PARAGON* infuser is durable and is intended to be used for repeated drug deliveries. After each patient use, the exposed surfaces, except the threads, may be wiped clean using isopropyl alcohol or a 10% bleach solution.

NOTE: Do not submerge the *PARAGON* infuser in a bleach solution. After cleaning, if the *PARAGON* is difficult to twist together, place a small drop of lubricating ointment (such as K-Y™ Jelly) on a small section of the threads on the bottom of the infuser. Twist the top of the infuser onto the bottom to spread out the ointment. ⓴

PARAGON HINWEISE FÜR DEN BENUTZER

Gebrauchsanweisung

NOMENKLATUR

1. *PARAGON* Infuser ❶
2. Flüssigkeitsstandanzeige ❷
3. 1,2 Mikron Filter zur Luftentfernung ❸
4. *PARAGON* Injektionssatz ❹
5. Flußratenetikett ❺
6. Luer-Anschluß ❻
7. "Ende der Infusion"-Anzeige ❼

ACHTUNG

1. Benutzen Sie das Verabreichungs-Set nicht wenn der sterile Beutel geöffnet oder beschädigt wurde. Wenn eine der Schutzkappen fehlt oder sich nicht an ihrer Stelle befindet, kann die Sterilität des Verabreichungs-Sets nicht mehr garantiert werden.
2. Nicht für die Zuführung von Blut oder Blutprodukten. Es wird empfohlen, dass die Verabreichungs-Sets alle 24-48 Stunden nach den CDC Richtlinien oder den Vorschriften des Institutes ausgewechselt werden.
3. Das Verabreichungs-Set darf nicht wieder Sterilisiert werden! Die Verabreichungs-Sets sind nur für den Einsatz mit je Einem einzelnen Patienten bestimmt. Der Flüssigkeitspfad ist Steril und nicht-Pyrogenisch

Einleitung

Das *PARAGON*-System ist ein Medikamentenverabreichungssystem, das aus einem wiederverwendbaren mechanischen Infuser und speziell entwickelten Injektionssätzen besteht. Das *PARAGON*-System sorgt für ein exaktes Verabreichung von Medikamenten, die langsame und kontinuierliche Infusionen verlangen, wie z.B. Chemotherapeutika und Analgetika. Das *PARAGON*-System dient auch für Infusionen von Medikamenten, die schneller verabreicht werden müssen, wie z.B. Antibiotika.

DER *PARAGON* INJEKTIONSSATZ

Die Injektionssätze werden aus PVC hergestellt. Jeder Satz ist ca. 127 cm lang und enthält einen 1,2 Mikron Filter zur Luftentfernung. Die Flußrate, mit der das Medikament dem Patienten zugeführt wird, wird von einem am Ende des Satzes angebauten Flußregulator gesteuert. Die Flußraten der einzelnen Sätze sind auf dem Etikett am Filter zur Luftentfernung angegeben. ❸

FÜLLEN DES *PARAGON* IV-BEUTELS - KEIMFREIES VERFAHREN

1. Den IV-Beutel mit dem befestigten Injektionssatz aus der Verpackung nehmen.
2. Die Flußklemme zum Füllventil schieben und schließen. ❹
3. Eine sterile Spritze mit der in den IV-Beutel zu füllenden Lösung füllen.
4. Die Spitze der Spritze an das Füllventil anschließen und die Lösung in den IV Beutel spritzen. ❺ Ggf. die Spritze erneut füllen und den Vorgang wiederholen.
5. Hinweis: Der *PARAGON*-Infuser kann bis zu 100 ml Flüssigkeit aufnehmen. Die maximale Füllmenge beträgt 110 ml. Bei mehr als 110 ml Flüssigkeit kann es schwierig werden, das Gewinde oben und unten am *PARAGON* einzupassen.
6. Die Luft mit Hilfe einer am Füllventil angesetzten Spritze aus dem IV-Beutel absaugen. Ein Drücken auf die Seiten des IV-Beutels, während die Spritze zurückgezogen wird, beschleunigt den Vorgang.
7. Darauf achten, daß die Kappe wieder am Füllventil angebracht wird.
8. Keine Etikette auf den IV-Beutel kleben, sondern um den Injektionssatz wickeln.

EINSETZEN DES IV-BEUTELS IN DEN *PARAGON*-INFUSER

1. Die obere und untere Hälfte des *PARAGON* Infusers auseinanderschrauben. ❻
2. Vor dem Platzieren des IV-Beutels in den *PARAGON* Infuser den schmalen Teil des Injektionssatzes durch den Schlitz im Boden des Infusers schieben. ❼
3. Den Beutel auf die Mitte des Bodens legen und entlang des Beutelrandes drücken, um den Beutel im Unterteil zu sichern. Sicherstellen, daß der Beutel keine Unebenheiten aufweist und ganz glatt liegt. ❽
4. Den dicken Teil des Schlauchs vorsichtig auf volle Länge gradeziehen und auf richtigen Sitz unten am Schlitz prüfen. ❾
5. Das obere und untere Teil des *PARAGON*-Infusers wieder fest zusammenschrauben. ❿

VORFÜLLEN DES INJEKTIONSSATZES

1. Unter Verwendung einer keimfreien Verfahrens die Kappe vom Luer-Anschluß am Ende des Injektionssatzes abnehmen. Die Klemme am IV-Schlauch öffnen. Das Medikament beginnt zum Luer-Anschluß zu fließen.
2. Prüfen, ob sich am Ende des Luer-Anschlusses ein Tropfen bildet, um den Flüssigkeitsstrom zu bestätigen. Beim Vorfüllen des 0.5 ml/h Satzes kann die Tropfenbildung bis zu 10 Minuten dauern. ⓫
3. Die Klemme schließen und die Kappe wieder anbringen.

STARTEN DER INFUSION

1. Den Injektionssatz am IV-Zugang befestigen und den Anschluß sichern. Das Verbindungsstück an der Haut befestigen.
2. Die Infusion durch Öffnen der Klemme am Injektionssatz starten. Die Infusion beginnt sofort.

DIE FLÜSSIGKEITSSTANDANZEIGE

1. Das mit Markierungen versehene Fenster an der Seite des Infusers läßt erkennen, wie weit die Infusion ungefähr fortgeschritten ist. ⓬
2. Wenn der *PARAGON* IV-Beutel mit 100-110 ml voll gefüllt ist, steht die obere Kante der Druckplatte an der oberen runden Markierung. ⓭
3. Mit fortschreitender Infusion bewegt sich die Platte zur unteren Markierung hin, was auf einen fast leeren Beutel hinweist. ⓮

DAS ENDE DER INFUSION

Die Infusion ist komplett, wenn mindestens drei (der sechs) kleine blaue Punkte unten am Boden des *PARAGON*-Infusers zu sehen sind. ⓯

DIE TRAGETASCHE

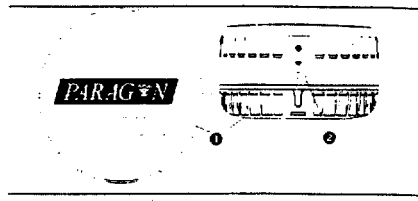
Die Tragetasche kann am Gürtel, über die Schulter oder um die Hüfte getragen werden.

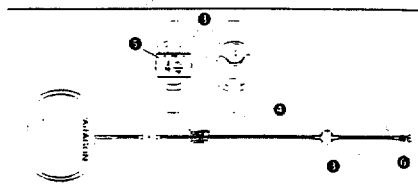
1. Den *PARAGON*-Infuser so in die Tragetasche legen, daß die Unterseite des Infusers durch das durchsichtige Plastikfenster zu sehen ist. ⓰
2. Den Velcro-Verschlußstreifen öffnen und den Injektionssatz so nach unten schieben, daß er durch das Seitenfenster austritt. ⓱ Den Verschlußstreifen schließen. (Wird der Infuser so positioniert, ist die Flüssigkeitsstandsanzeige ersichtlich.)
3. Die vordere Klappe der Tragetasche läßt sich anheben, damit die "Ende der Infusion"-Anzeige durch das durchsichtige Plastikfenster angesehen werden kann. ⓲
4. Bei Bedarf kann ein kleines Schloß durch das größere der zwei Löcher am Reißverschluß und dann durch die Stoffschlaufe an der Seite der Tragetasche geführt werden. (Damit läßt sich eine unzulässige Änderung der Infusereinstellung verhindern.) ⓳

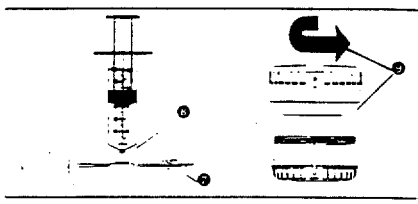
REINIGEN DES *PARAGON*-INFUSERS

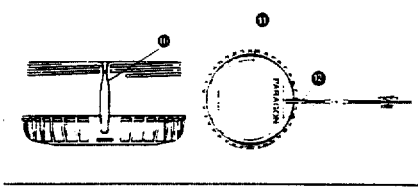
Der *PARAGON*-Infuser ist stabil und zur mehrfachen Verabreichung von Medikamenten vorgesehen. Nach jeder Verwendung an einem Patienten müssen die äußeren Oberflächen, mit Ausnahme der Gewinde, mit Isopropylalkohol oder einer 10%igen Bleichelösung abgewischt werden.

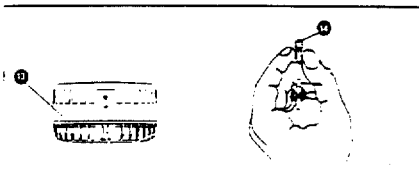
HINWEIS: Den *PARAGON*-Infuser nicht in eine Bleichenlösung eintauchen. Falls der *PARAGON* sich nach dem Reinigen nicht gut zusammenschrauben läßt, einen kleinen Tropfen Schmierpaste (z.B. K-Y™ Gel) auf einen kleinen Teil des Gewindes unten am Infuser auftragen. Das obere Teil des Infusers auf das untere Teil aufschrauben, um die Paste zu verteilen. ⓴

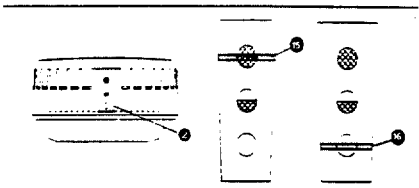


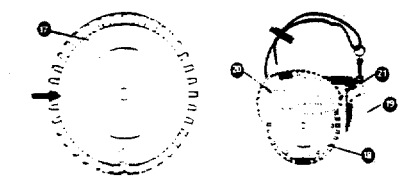


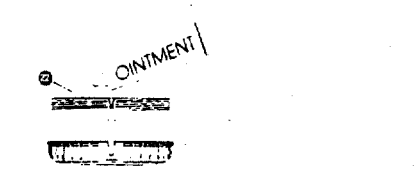












GUÍA DEL USUARIO DE *PARAGON*

Modo de empleo

MODO DE EMPLEO

1 Dispositivo de perfusión *PARAGON* ❶
2 Indicador del nivel del fluido ❷
3 Filtro de aire de 1,2 micrones ❸
4 Tubo de administración *PARAGON* ❹
5 Etiqueta del caudal de flujo ❺
6 Cierre luer ❻
7 Indicador de la finalización de la perfusión ❼

PRECAUCIÓN

No utilice el juego para administrar si la bolsa esterilizada se encuentra abierta o dañada. Si la tapa protectora no está o si no se encuentra colocada en su lugar, la esterilidad del juego para administrar ya no podrá ser garantizada.

No se suministrado para el suministro de sangre o de productos sanguíneos.

Se recomienda que el juego para administrar sea cambiado cada 24 a 48 horas o de acuerdo a las pautas formuladas por el CDC de EE.UU. o de acuerdo a las políticas institucionales.

No vuelva a esterilizar el juego para administrar. Los juegos para administrar han sido fabricados para ser utilizados solamente en un paciente. La vía de administración de líquido se encuentra esterilizada y no es pirogénica.

INTRODUCCIÓN

El sistema de administración de fármacos *PARAGON* consiste en un interruptor de perfusión mecánico reutilizable y de tubos de administración diseñados especialmente para su uso con el mismo. El sistema *PARAGON* aísla la administración de medicamentos que requieran una introducción lenta y continua, tales como quimioterápicos y anestésicos, igualmente se puede utilizar para introducir con rapidez aquellos medicamentos que así lo exijan, tales como antibióticos.

TUBO DE ADMINISTRACIÓN PARAGON

Los tubos de administración están hechos de PVC. Cada tubo tiene aproximadamente 127 cm de largo, y tiene incorporado un filtro de 1,2 micrones para la eliminación de aire. El fármaco fluye hacia el paciente con un caudal de flujo controlado a través de un reductor de flujo que se encuentra al final del tubo. En la etiqueta del filtro se especifican los caudales de flujo empleados para cada tubo. ❺

LLENADO DE LA BOLSA INTRAVENOSA *PARAGON*- USE UNA TÉCNICA ASÉPTICA

1 Saque del paquete la bolsa intravenosa con su tubo de administración acoplado
2 Mueva la pinza de flujo que está al lado de la válvula de llenado y cierre la pinza. ❻
3 Llene una jeringa estéril con la solución a ser introducida en la bolsa intravenosa.
4 Conecte la punta de la jeringa a la válvula de llenado e inyecte la solución en la bolsa intravenosa. ❼ Si es necesario, vuelva a llenar la jeringa y repita el procedimiento.
5 *Nota:* El dispositivo de perfusión *PARAGON* está diseñado para almacenar un total de 100 ml de fluido. El volumen máximo de llenado es de 110 ml; si la cantidad de fluido es mayor de 110 ml, puede ser difícil engranar las ranuras de la parte superior e inferior del *PARAGON*.
6 Saque el aire de la bolsa intravenosa, apretando con una jeringa conectada a la válvula de llenado. Puede ayudarse apretando los lados de la bolsa cuando esté retirando la jeringa.
7 Asegúrese de volver a colocar el sombrerete de la válvula de llenado. No coloque etiquetas en la bolsa intravenosa, es mejor ponerlas alrededor del tubo.

MODO DE CARGA DE LA BOLSA INTRAVENOSA EN EL DISPOSITIVO DE PERFUSIÓN *PARAGON*

1 Retire las mitades superior e inferior del dispositivo de perfusión *PARAGON*. ❽
2 Antes de colocar la bolsa intravenosa en el dispositivo de perfusión *PARAGON*, introduzca la porción dañada del tubo de administración en la ranura que está en la parte inferior del dispositivo de perfusión. ❾
3 Centre la bolsa en el fondo y haga presión alrededor de los bordes de la bolsa, de manera que esta quede totalmente asentada en el fondo. Asegúrese de que no haya arrugas en la bolsa. ❿
4 Con cuidado, tire de la porción gruesa del tubo, de forma que se extienda y se asiente completamente en el fondo de la ranura. ⓫
5 Gire las mitades superior e inferior del dispositivo de perfusión *PARAGON* hasta que se junten. ⓬

CEBADO DEL TUBO DE ADMINISTRACIÓN

1 Usando una técnica aséptica apropiada, retire el sombrerete del cierre luer que está en el extremo del tubo. Abra la pinza de la tubería intravenosa, el fármaco fluirá hacia el extremo del cierre luer.
2 El fluido se está moviendo si se forma una gota del mismo en el extremo del cierre luer. Puede ser necesario esperar 10 minutos para que la gota se forme cuando se este cebando el sistema a 0,5 ml/hr
3 Cierre la pinza y vuelva a colocar el sombrerete. ⓭

INICIO DE LA PERFUSIÓN

1 Acople el tubo de administración al punto de la perfusión intravenosa. Asegure la conexión la piel.
2 Abra la pinza del tubo. El fármaco fluirá automáticamente.

INDICADOR DEL NIVEL DEL FLUIDO

1 La ventanilla con marcas que se encuentra en la parte lateral del dispositivo de perfusión se utiliza para hacer un cálculo aproximado de la progresión de la perfusión. ⓮
2 Cuando la bolsa intravenosa *PARAGON* se llene a su capacidad de 100-110 ml, la parte superior de la placa de presión se alineará con el marcador redondo superior. ⓯
3 A medida que la perfusión progresa, la placa se desplazará al marcador del fondo, indicando que la bolsa está casi vacía. ⓰

FINAL DE LA PERFUSIÓN

La perfusión se ha completado cuando al menos tres (de seis) puntos pequeños azules aparecen en el fondo del dispositivo de perfusión *PARAGON*. ⓱

ESTUCHE PORTÁTIL

El estuche portátil se puede llevar en un cinturón, sobre los hombros o alrededor de la cintura.

1 Coloque el dispositivo de perfusión *PARAGON* en el estuche portátil, de manera que el fondo del dispositivo pueda verse a través de la ventanilla plástica transparente. ⓲
2 Ajuste la banda de Velcro y deslice el tubo de administración hacia abajo, de manera que este salga del estuche a través de la abertura de la ventanilla lateral. ⓳ Cierre la banda; esta manera de colocar el dispositivo de perfusión permite observar el indicador del nivel del fluido.
3 La pieza frontal del estuche portátil se puede alzar para mostrar una ventanilla plástica transparente, lo cual permite observar el extremo del indicador de perfusión. ⓴
4 Si es necesario se puede colocar un candado pequeño, haciéndolo pasar a través del agujero más grande de la cremallera y del lazo de tela que está en la parte lateral del estuche (esto puede disminuir las posibilidades de que se causen daños en el dispositivo de perfusión durante una perfusión). ㉑

CUIDADO DEL PARAGON

El dispositivo de perfusión PARAGON es duradero y está diseñado para usos repetidos de perfusión de fármacos. Después de cada uso con un paciente se pueden limpiar las superficies expuestas (a excepción de las roscas) con alcohol isopropílico o con una solución de hipoclorito de sodio al 10%

NOTA: No sumerja el dispositivo de perfusión *PARAGON* en hipoclorito de sodio. Después de limpiarlo, si es difícil hacer girar las mitades del *PARAGON* para extraerlas, ponga una pequeña gota de pomada lubricante (tal como Jelsema K-Y) en una sección pequeña de las roscas que están al fondo del dispositivo de perfusión. Retire la parte superior del dispositivo de perfusión sobre la inferior para distribuir la pomada. ㉒

GUIDE D'UTILISATION *PARAGON*

Mode d'emploi

MODE D'EMPLOI

1 Dispositif de perfusion *PARAGON* ❶
2 Indicateur de niveau ❷
3 Filtre à bulles d'air de 1,2 micron ❸
4 Tubulure de perfusion *PARAGON* ❹
5 Indicateur de débit ❺
6 Robinet Luer ❻
7 Indicateur de fin de perfusion ❼

PRECAUTIONS

1 Ne pas utiliser le tubulure d'administration si la poche de conditionnement stérile est ouverte ou endommagée. Si l'un des capuchons protecteurs vient à manquer ou n'est pas en place, la stérilité de la tubulure d'administration n'est plus garantie.
2 Ne pas utiliser le système pour les perfusions de sang ou de produits sanguins. Il est recommandé de changer la tubulure d'administration toutes les 24 à 48 heures ou conformément aux recommandations de C.D.C. des Etats-Unis ou des pratiques de l'établissement hospitalier
3 Ne pas restériliser la tubulure d'administration. Les tubulures d'administration sont à usage unique. La voie d'administration du fluide est stérile et apyrogène.

INTRODUCTION

Le *PARAGON* est un système d'administration de médicaments composé d'un dispositif de perfusion mécanique réutilisable et de tubulures de perfusion spécialement conçues. Le *PARAGON* permet une administration précise des médicaments exigeant des infusions lentes et continues, tels que les produits chimiothérapeutiques et les anesthésiques. Le *PARAGON* sert également à infuser les médicaments demandant une administration plus rapide, tels que les antibiotiques.

LA TUBULURE DE PERFUSION *PARAGON*

Les tubulures de perfusion sont en C.P.V. Chaque dispositif fait environ 127 cm de long. Un filtre d'élimination des bulles d'air de 1,2 micron est incorporé à toutes les tubulures de perfusion. Le débit d'écoulement du médicament vers le patient est contrôlé par un système de limitation du débit intégré à une extrémité de l'appareil. Le débit de chaque dispositif est indiqué sur l'étiquette du filtre d'élimination d'air. ❺

REMPLISSAGE DE LA POCHE DE PERFUSION *PARAGON*-UTILISER DES TECHNIQUES ASEPTIQUES

1 Déballer la poche de perfusion munie de sa tubulure de perfusion.
2 Placer le clamp d'écoulement près de la valve de remplissage et fermer le clamp. ❻
3 Remplir une seringue stérile de la solution à injecter dans la poche de perfusion
4 Connecter l'extrémité de la seringue à la valve de remplissage et injecter la solution dans la poche de perfusion. ❼ Remplir à nouveau la seringue et recommencer selon les besoins.
5 Remarque: Le dispositif de perfusion *PARAGON* a été conçu pour accueillir une quantité maximum de 100 ml de liquide. Le volume de remplissage maximum est de 110 ml. Si la quantité de liquide dépasse 110 ml, l'amorce du message en haut et en bas du *PARAGON* risque de se rendre difficile.
6 Evacuer l'air de la poche de perfusion par aspiration à l'aide d'une seringue reliée à la valve de remplissage. Une compression des parois de la poche de perfusion au moment du retrait de la seringue pourra faciliter l'expulsion de l'air.
7 Prendre bien soin de remettre le bouchon en place sur la valve de remplissage.
8 Ne pas placer d'étiquette sur la poche de perfusion. Les étiquettes pourraient s'enrouler autour du dispositif.

CHARGEMENT DE LA POCHE DE PERFUSION DANS LE DISPOSITIF DE PERFUSION *PARAGON*

1 Séparer les deux moitiés du haut et du bas du dispositif de perfusion *PARAGON*. ❽
2 Avant de placer la poche de perfusion dans le dispositif de perfusion *PARAGON*, faire glisser la partie étroite de la tubulure de perfusion dans la fente située dans la partie inférieure du dispositif de perfusion. ❾
3 Centrer la poche dans la partie inférieure et appuyer tout autour de la poche de façon à ce qu'elle soit bien installée dans le dispositif de perfusion. Vérifier qu'il n'y ait aucune pression de la poche. ❿
4 Tirer doucement sur la partie épaisse du tube de sorte à ce qu'il soit complètement détendu et qu'il repose au fond de la fente. ⓫
5 Rassembler ensemble jusqu'à ce qu'elles se touchent les deux moitiés du haut et du bas du dispositif de perfusion *PARAGON*. ⓬

AMORÇAGE DE LA TUBULURE DE PERFUSION

1 En suivant les techniques aseptiques qui conviennent, retirer le bouchon du robinet Luer situé à l'extrémité du dispositif. Ouvrir le clamp sur la tubulure de perfusion. Le médicament devrait s'écouler en direction de l'extrémité du robinet Luer.
2 Confirmer l'écoulement du liquide en observant la formation d'une goutte à l'extrémité du robinet Luer. Avec le débit de 0,5 ml/H, il faut quelquefois attendre jusqu'à 10 minutes pour qu'une goutte se forme après l'amorçage. ⓭
3 Serrer le clamp pour le fermer et remettre le bouchon en place.

DÉMARRAGE DE LA PERFUSION

1 Fixer la tubulure de perfusion au point de ponction. Fixer la connexion contre la peau.
2 Commencer la perfusion en ouvrant le clamp sur la tubulure de perfusion. La perfusion doit démarrer immédiatement.

INDICATEUR DU NIVEAU DE LIQUIDE

1 La fenêtre contenant des indications sur le côté du dispositif de perfusion sert à examiner la progression du déroulement de la perfusion. ⓮
2 Lorsque la poche de perfusion *PARAGON* est remplie dans sa capacité de 100 - 110 ml, le haut de la plaque de pression se trouve dans l'alignement de la marque arrondie du haut. ⓯
3 Au fur et à mesure que la perfusion progresse, la plaque de pression descend vers la marque du bas, indiquant donc que la poche est presque vide. ⓰

FIN DE LA PERFUSION

La perfusion est terminée quand au moins trois (des six) petites parties bleues sont visibles sous la base du dispositif de perfusion *PARAGON*. ⓱

LA POCHE DE RANGEMENT

La poche de rangement peut se porter à la ceinture, sur l'épaule, ou autour de la taille.

1 Placer le dispositif de perfusion *PARAGON* dans sa poche de rangement de sorte que la base du dispositif de perfusion soit visible au travers de la fenêtre en plastique transparent. ⓲
2 Soulever la bande de Velcro et faire glisser le dispositif d'administration vers le bas de sorte qu'il puisse sortir de la poche de rangement par l'ouverture du côté. ⓳ Refermer la bande de Velcro. (Quand le dispositif de perfusion se trouve dans cette position, il est possible de consulter l'indicateur du niveau de liquide.)
3 Le rabat avant de la poche de rangement se soulève sur une fenêtre en plastique transparent qui permet de consulter l'indicateur de fin de la perfusion. ⓴
4 Au besoin, un petit verrou peut être introduit dans le plus gros de deux trous de la fermeture à glissière, puis au travers du passant en tissu sur le côté de la poche de rangement. (Afin de décourager quiconque voudrait toucher à le dispositif de perfusion pendant une infusion.) ㉑

PARAGON. GUIDA PER L'UTILIZZATORE

Istruzioni per l'uso

LEGENDA

1 Infusore *PARAGON* ❶
2 Indicatore di livello del fluido ❷
3 Filtro deboliatore 1,2 u ❸
4 Set di infusione PARAGON ❹
5 Etichetta indicante il flusso del set ❺
6 Connettore Luer Lock ❻
7 Indicatore di fine infusione ❼

AVVERTENZE

1. Non usare il set se la confezione è aperta o danneggiata. Se il cappuccio protettivo manca o non è posizionato, la sterilità non è garantita
2. Non adatto alla somministrazione di sangue. Si raccomanda di sostituire il set ogni 24-48 ore, e secondo le linee guida CDC, o secondo il protocollo dell'ospedale.
3. Non risterilizzare il set. I set si intendono monopaziente. La via di somministrazione è sterile e apirogena.

INTRODUZIONE

PARAGON è un sistema per l'infusione di farmaci costituito da un infusore meccanico riutilizzabile e da un set di somministrazione dedicato. PARAGON consente un accurata somministrazione di soluzioni che richiedono un infusione lenta e continua, quali chemioterapici e anestetici. PARAGON consente anche la somministrazione di farmaci che richiedono alle velocità di infusione come gli antibiotici.

SET DI SOMMINISTRAZIONE PARAGON

I set di somministrazione sono in PVC. Ciascuna linea è lunga circa 127 cm. Nella linea è compreso un filtro deboliatore da 1,2 u. Il flusso è controllato da un riduttore posto all'estremità distale del set. Un etichetta sul filtro indica il flusso del set. ❺

RIEMPIMENTO DELLA SACCA- USARE TECNICA ASETTICA

1. Aprire la confezione
2. Portare la clamp vicino alla valvola di riempimento e chiuderla ❻
3. Riempire una siringa sterile con la soluzione da trasferire nel set
4. Connettere la siringa alla valvola di riempimento e trasferire la soluzione nella sacca ❼. Ripetere nuovamente la siringa e ripetere l'operazione se necessario.

NOTA: la sacca è disegnata per un volume totale massimo di 110 ml. Un eccesso di volume può rendere difficoltosa la chiusura dell'infusore.

5. Rimuovere l'aria dalla sacca aspirando con una siringa dalla valvola di riempimento. La rimozione dell'aria viene facilitata comprimendo delicatamente la sacca al momento di staccare la siringa.
6. Richiudere la valvola di riempimento con un tappino.
7. Non mettere alcuna etichetta sulla sacca, ma eventualmente intorno alla linea.

POSIZIONAMENTO DELLA SACCA NELL'INFUSORE PARAGON

1. Svitare completamente le due parti dell'infusore. ❽
2. Prima di posizionare la sacca nell'infusore, inserire il tubo nella fessura posta nella metà inferiore dell'infusore. ❾
3. Alleggerire la sacca nell'infusore avendo cura di distenderla bene ed assicurandosi che non ci siano pieghe sul contorno. ❿
4. Tirare dolcemente il tubo attraverso la fessura, distendendolo il meglio possibile. ⓫
5. Avvitare la metà superiore dell'infusore a quella inferiore arrivando a fine corsa. ⓬

RIEMPIMENTO DELLA LINEA DI SOMMINISTRAZIONE

1. Usare tecnica asettica,togliere il tappo dall'estremità della linea. Aprire la clamp. La soluzione fluirà attraverso l'estremità luer lock.
2. Confermare il riempimento della linea verificando la formazione di una goccia all'estremità luer lock. Occorrono 10 minuti con un set da 0,5 ml/h. ⓭
3. Chiudere la clamp e posizionare il tappo luer.

INIZIO DELL'INFUSIONE

1. Connettere la linea di somministrazione al paziente. Assicurare la connessione alla cute.
2. Iniziare l'infusione aprendo la clamp della linea di somministrazione L'infusione inizierà immediatamente.

INDICATORE DI LIVELLO DEL FLUIDO

1. La finestra, posta sul lato dell'infusore, con apposti indicatori è usata per stimare la progressione dell'infusione. ⓮
2. Quando la sacca PARAGON è riempita con 100-110 ml, il bordo superiore del piatto di pressione azzurro è allineato con il pallino più alto. ⓯
3. Col processare dell'infusione, il piatto azzurro si muove verso il pallino inferiore indicando che la sacca è quasi vuota. ⓰

FINE INFUSIONE

L'infusione è completa quando sono visibili almeno tre (dei sei) pallini blu sul fondo trasparente dell'infusore PARAGON. ⓱

BORSA PER IL TRASPORTO

Può essere indossata nella cintura, messa a tracolla, o intorno alla vita.

1. Posizionare l'infusore PARAGON nella borsa in modo che il fondo trasparente della stessa sia visibile attraverso la finestra della borsa. ⓲
2. La linea di somministrazione deve fuoriuscire dalla finestra laterale della borsa, previa apertura della strap Velcro. ⓳ Chiudere lo strap. (Posizionare in questo modo l'infusore consente di visualizzare l'indicatore di livello)
3. La parte frontale della borsa ribaltata da un'aletta) è in plastica trasparente, visualizzando così l'indicatori di fine infusione. ⓴
4. Se necessario, la chiusura lampo della borsa può essere chiusa con un piccolo lucchetto (scongiurando chiunque voglia manipolare l'infusore durante l'infusione). ㉑

MANUTENZIONE DEL PARAGON

L'infusore PARAGON è robusto e concepito per essere utilizzato per molteplici infusioni. Dopo ogni paziente, la superfici esposte, tranne la filettatura, possono essere pulite con alcool isopropilico o soluzione di ipoclorito di sodio al 10%

Nota: non immergere l'infusore *PARAGON* nell'ipoclorito di sodio. Se dopo la pulizia le due parti dell'infusore si avvitano con fatica, stendere un po di crema lubrificante (tipo K-Y™ gel) su una piccola sezione della filettatura superiore e distribuirla ravvitando le due parti dell'unisore. ㉒

[redacted]

IMPORTANT

1. Only administration sets distributed by I-Flow Corporation are authorized for use with this product. I-Flow Corporation accepts no responsibility for performance, or the liability for damages, caused by the misuse of this product when used with unauthorized administration sets.
2. This product uses DEHP plasticized PVC. Certain solutions may be incompatible with the PVC material used in the IV administration set. Consult the drug package insert and other available sources of information for a more thorough understanding of possible incompatibility problems.
3. This device contains natural rubber latex. Individuals with known natural rubber latex sensitivities should not use this product.

The *PARAGON* Infuser Specifications

Size: 5.8 cm high; 10.2 cm in diameter

Weight: 260 Gms

Flow Rates: 0.5, 1, 2, 4, and 10 ml/hr

Delivery accuracy: Accuracy is at ±10% at 95% confidence interval.

Priming volume: 1.5 ml

Residual volume: 5 ml or less

NOTES

1. The infusion rates for each administration set are indicated on the administration set label.
2. Actual infusion rates may vary from the specified range due to:
   - viscosity and/or drug concentration.
   - temperatures above or below the operating conditions.
   - the positioning of the *PARAGON* infuser above or below the IV site.
3. The Paragon Drug Delivery System has been calibrated using Normal Saline (NS) as the diluent and skin contact temperature (32°C, 90°F) as the operating environment. When using NS and skin temperature the Paragon System will flow at the specified nominal rate. The use of other diluents or operating temperatures other than the above will affect the nominal flow rate. For example, if 5% Dextrose (D5W) is used as the final diluent, the Paragon System will flow at 10% below the nominal rate due to higher solution viscosity.

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFFESIONAL.

[redacted]

WICHTIG

1. Dieses Produkt darf nur mit Infektionssätzen von I-Flow Corporation verwendet werden. I-Flow Corporation haftet weder für die Lösung noch Schadensersatzansprüche, die auf Mißbrauch dieses Produktes mit nicht zugelassenen Infektionssätzen beruhen.
2. Dieses Produkt benutzt DEHP plastiziertes PVC. Bestimmte Lösungen können möglicherweise mit dem PVC Material, das in den IV Verabreichungs-Sets benutzt wird, unverträglich sein. Wenden Sie sich an die Packungsbeilage und andere erhältliche Informationsquellen für ein besseres Verständnis möglicher Unverträglichkeits-Probleme.
3. Das Infusionsgerät besteht aus unbearbeitetem Gummilatex. Personen, die allergisch auf unbearbeiteten Gummilatex reagieren, wird vom Gebrauch dieses Produktes abgeraten.

Technische Daten des *PARAGON*-Infusers

Abmessungen: 5.8 cm hoch; 10.2 cm Durchmesser

Gewicht: 260 g

Flußrate: 0.5; 1; 2; 4; und 10 ml/h

Verabreichungsgenauigkeit: Die Genauigkeit liegt bei ± 10% bei einem 95%igen Vertrauensniveau.

Vorfüllmenge: 1.5 ml

Rückstandsmenge: Maximal 5 ml

HINWEISE:

1. Die Infusionsraten für jedes Verabreichungs-Set sind auf dem Etikett des Verabreichungs-Sets angegeben.
2. Die echten Infusionsraten können von den angegebenen Spanne aus den folgenden Gründen abweichen:
   - Viskosität und/oder Medikamentkonzentrationen.
   - Temperaturen über oder unter den Betriebsbedingungen.
   - Anbringung des *PARAGON*-Infusers über oder unterhalb des IV-Zugangs.
3. Das Paragon Arznei Verabreichungs-System wurde mit normaler Salzlösung als Verdünnungsmittel geeicht und mit Hautkontakt-Temperatur (32°C, 90°F) als Verabreichungsklima. Beim Einsatz von Physiologischer Kochsalzlösung und der Hauttemperatur fließt das Paragon System zur angegebenen Nennabgeschwindigkeit. Der Gebrauch irgendwelcher anderer Verdünnungsmittel oder Einsätze außer den oben angegebenen beeinflußt die nominale Fließgeschwindigkeit. Wenn zum Beispiel 5% Dextrose (D5W) als abschließendes Verdünnungsmittel benutzt wird, fließt das Paragon System zu 10% unter der Nominalgeschwindigkeit auf Grund der höheren Lösungsviskosität.

Manufactured by
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Lake Forest, CA 92630
Printed in the U.S.A.

U.S. and Foreign Patents Pending

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Borngasse 20, 35619 Braunfels, Germany CE 0123

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IMPORTANTE

1. Utilice unicamente tubos de administracion distribuidos por I-Flow Corporation. I-Flow Corporation no asume responsabilidad alguna por problemas de funcionamiento o por danos causados debido al maltrato de este producto cuando se usa con tubos de administracion no autorizados.
2. Este producto utiliza DEHP de cloruro de polivinilo plastificado. Ciertas soluciones podrian ser incompatibles con el material de cloruro de polivinilo utilizado en el juego para administrar de la intravenosa. Consulte con las indicaciones provistas en la caja de la droga y con otras fuentes de informacion disponibles para entender con mas detalle los posibles problemas de incompatibilidad.
3. Este dispositivo contiene látex de goma natural. Aquellos individuos que sufran de sensibilidad al látex de goma no deberan utilizar este producto.

Especificaciones del dispositivo de perfusion *PARAGON*

Tamano: Altura: 5.8 cm; diametro: 10.2 cm

Peso: 260 gr

Flujo: 0.5; 1; 2; 4; y 10 ml/hr

Precision en la distribucion: La precision es de ±10% a un intervalo de confianza de 95%.

Volumen de cebado: 1.5 ml

Volumen residual: 5 ml o menos

NOTAS:

1. El coeficiente de perfusion para cada juego para administrar se encuentra indicado en la etiqueta del mismo.
2. Los coeficientes de perfusion actuales pueden variar del coeficiente especificado debido a::
   - viscosidad y/o concentracion del farmaco.
   - temperaturas superiores o inferiores a las condiciones de operacion.
   - la colocacion del dispositivo de perfusion *PARAGON* por encima o por debajo del punto de perfusion intravenosa.
3. El Sistema de Suministro de Drogas Paragon ha sido calibrado utilizando Salinidad Normal (SN) como disolvente y la temperatura de contacto de la piel (32°C, 90°F) como el ambiente operativo. Al utilizar la SN y la temperatura de la piel, el Sistema Paragon fluira a una razon nominal especifica. La utilizacion de otros disolventes o temperaturas operativas que no sean las mencionadas anteriormente afectaran la razon nominal de fluido. Por ejemplo, si se utiliza un 5% de Dextrosa como disolvente final, el Sistema Paragon fluira a un 10% por debajo de la razon nominal debido a la viscosidad de la solucion mas alta.

ENTRETIEN DU *PARAGON*

Le dispositif de perfusion *PARAGON* est solide et solide et a été conçu pour être utilisé de façon répétée pour des injections de médicaments. Après chaque patient, il est possible de nettoyer les surfaces visibles, à l'exception du filetage, en les essuyant avec de l'alcool isopropylique ou une solution de 10% d'eau de Javel.

REMARQUE: Ne pas tremper le dispositif de perfusion *PARAGON* dans une solution d'eau de Javel.

Remarque: Ne pas tremper le dispositif de perfusion *PARAGON* dans une solution d'eau de Javel.

Après le nettoyage, si le remontage du *PARAGON* est difficile, placer une petite goutte de pommade lubrifiante (telle que de la vaseline K-Y™) sur une petite section du filetage dans le bas du dispositif de perfusion. Revisser la molde supérieure sur la molde inférieure de manière à bien étaler la pommade. 😊

IMPORTANT

1. Ne sont autorisés avec ce produit que les tubulures de perfusion distribuées par I-Flow Corporation. I-Flow Corporation ne saurait accepter aucune responsabilité pour ce qui est des performances, ni aucune responsabilité pour ce qui est des dommages causés par une utilisation de ce produit avec des tubulures de perfusion non autorisées.
2. Ce produit est fabriqué avec du chlorure de polyvinyle plastifié au DEHP. Certaines solutions médicamenteuses peuvent être incompatibles avec le matériau en CPV utilisé dans la tubulure d'administration. Consulter la notice comprise dans le conditionnement du médicament et toutes les autres sources d'information disponibles pour obtenir le plus de renseignements possibles sur les problèmes d'incompatibilité éventuels.
3. Ce dispositif comprend du caoutchouc naturel au latex. Les personnes diagnostiquées avec une sensibilité naturelle (allergie) au caoutchouc latex doivent s'abstenir d'utiliser ce produit.

Spécifications du dispositif de perfusion *PARAGON*

Dimensions: hauteur 5.8 cm; diametre 10.2 cm

Poids: 260 Gms

Débit d'écoulement: 0.5; 1; 2; 4; et 10 ml/h

Précision de l'administration: La precision est de ±10% dans un intervalle de confiance de 95%.

Volume d'amorçage: 1.5 ml

Volume résiduel: 5 ml ou moins

NOTES

1. Les vitesses de perfusion de chaque dispositif d'administration sont indiquées sur l'étiquette du dispositif.
2. Les vitesses de perfusion réelles peuvent varier par rapport à la gamme spécifiée en raison de:
   - d'une viscosité et (ou) d'une concentration du médicament.
   - de températures supérieures ou inférieures aux conditions d'utilisation.
   - du positionnement du dispositif de perfusion *PARAGON* au-dessus ou au-dessous du point de ponction.
3. Le système d'administration de substances médicamenteuses Paragon a été étalonné à l'aide de serum physiologique salé (SN) comme solvant et de la température de la peau (32°C, 90°F) comme milieu ambiant d'intervention. Avec le solvant SN et la température de la peau, la circulation de fluide s'écoule dans le système Paragon à la vitesse nominale spécifiée. L'emploi de solvants ou de températures d'intervention autres que celles mentionnées ci-dessus affectera la vitesse nominale de circulation. Soit, par exemple, si l'on utilise une solution à 5% de dextrose (D5W) comme solvant final, la circulation dans le système Paragon s'écoulera à une vitesse inférieure de 10% à la vitesse nominale en raison de la viscosité plus forte de la solution.

IMPORTANTE

1. Con *PARAGON* possono essere impiegati solo set di somministrazione prodotti da I-Flow Corporation. I-Flow Corporation declina ogni responsabilità per la prestazione o danni causati dall'impiego non corretto del prodotto con set di somministrazione non autorizzati.
2. Questo prodotto usa PVC plasticizzato con DEHP. Certe soluzioni possono essere incompatibili con il materiale usato nei set di somministrazione. Consultare il foglio istruzioni contenuto nella confezione del farmaco e altre fonti disponibili per la migliore informazione possibile sui possibili problemi di incompatibilità.
3. Questo dispositivo contiene lattice naturale. Soggetti con riconosciuta sensibilità al lattice non dovrebbero usare questo prodotto.

SPECIFICHE DELL'INFUSORE PARAGON

Dimensioni: altezza 5.8 cm; diametro 10.2 cm

Peso: 260 g

Velocità di flusso: 0.5-1-2-4-10 ml/h

Accuratezza: ±10% nell'intervallo di confidenza del 95%

Volume di riempimento: 1.5 ml

Volume residuo: 5 ml max

NOTA:

1. La velocità di flusso di ciascun set di somministrazione è indicata da un etichetta sul set stesso.
2. Le velocità di flusso possono variare da quanto indicato a causa di:
   - viscosità e/o concentrazione del farmaco
   - temperatura sopra o sotto le condizioni operative
   - posizionamento dell'infusore *PARAGON* sopra o sotto il punto di accesso al paziente.
3. Il Sistema di Infusione Farmaci Paragon è stato calibrato usando Soluzione Salina (NS) come solvente e temperatura a contatto della cute (32°C, 90°F) come ambiente operativo. Quando si usano NS e temperatura a contatto della cute, il Sistema Paragon erogherà al flusso nominale specificato. L'impiego di altri solventi a temperature operative diverse da quelle indicate può produrre variazioni del flusso nominale. Ad esempio, se viene usato Destrosio 5% come solvente finale, il Sistema Paragon ha un flusso del 10% al di sotto del valore nominale dovuto alla maggiore viscosità della soluzione.

Patentes Estadounidenses y extranjeras en procesamiento

Fabricado por
I-Flow Corp
Lake Forest, CA 92630
Impreso en EE.UU.

Representante Europeo
MPS Medical Product Service GmbH
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I-FLOW CORPORATION, LAKE FOREST, CA U.S.A.

CONTENTS / INHALT /CONTENU /
CONTENIDO / CONTIENE: 1

REF 5000937

Paragon Administration Set
1 ml/hr (NS, 32°C)

STERILE EO

LOT

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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Manufactured by / Hersteller von /
Fabrique par / Fabricado por / Prodoto Da:
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I-FLOW®

I-FLOW CORPORATION, LAKE FOREST, CA U.S.A.

CONTENTS / INHALT / CONTENU / CONTENIDO / CONTIENE: 12

REF 5000937

Paragon Administration Set

1 ml/hr (NS, 32°C)

STERILE EO

LOT

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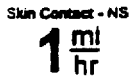

Skin Contact - NS
1 ml/hr

DIRECTIONS FOR USE

Model Numbers
P060020, P065005, P100020, P110005, P125015, P125050, P270010, P270020, P270050(Y), P270100

PainBuster™

INTENDED USE

The PainBuster is intended to provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

CONTRAINDICATIONS

This system is not designed for intravenous, intra-arterial or epidural drug delivery.
Not for blood, blood products, lipids or fat emulsions.

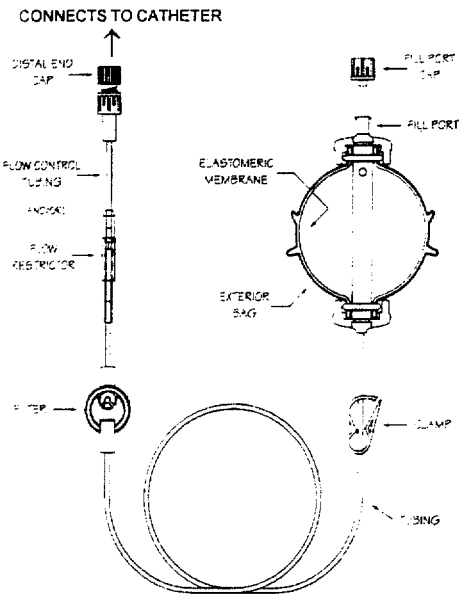
WARNINGS

- Single Use Pump. Do not refill. Discard after use.
- Do not overfill the pump.
- Medications administered with this system should be used in accordance with instructions provided from the drug manufacturer.

DIRECTIONS FOR USE

Use Aseptic Technique

Filling the Elastomeric Pump



1. Close clamp on tubing.
2. Remove protective cap from filling port.
3. Attach filled syringe to the fill port and inject fluid into pump. Repeat if necessary. Do not over fill pump (refer to table for applicable fill volumes). Replace fill port cap.
4. To prime the tubing, open the clamp on the tubing and allow fluid to fill the tubing. Close clamp until ready for use.

Placing the Catheter

1. Insert the introducer needle through the skin (approximately 3-5 cm away from wound site) then push introducer and needle into the surgical wound site.
2. Remove the needle from the introducer.
3. Insert the marked end of the catheter through the hub of the introducer. Advance the catheter approximately 2" into the wound site.
4. Remove the introducer while holding the catheter tightly in place. Assure catheter placement in wound site.
5. Attach the catheter connector to the unmarked end of the catheter. Tighten until catheter cannot be removed.
6. Attach syringe to catheter connector and prime the catheter with medication.
7. Attach the catheter connector to the pump tubing unless using the Y Adapter.
   7.1 If using the Y Adapter for an additional catheter, then attach the Y Adapter to the pump tubing.
   7.2 Attach each catheter connector to the Y Adapter.
8. Tape catheter(s) securely in place.
9. Apply appropriate dressing to catheter site(s).

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Starting the PainBuster System

1. Open the clamp to begin delivering medication.
2. Secure flow restrictor to skin and apply desired dressing.
3. Secure PainBuster Pump to the outer dressing with tape or E-Clip as desired.

Delivery Time Information for the PainBuster

	P060020	P065005	P100020	P110005	P125015	P125050	P270010	P270020	P270050	P270100
Nominal Flow Rate (ml/hr)	2.0	0.5	2.0	0.5	1.5	5.0	1.0	2.0	5.0	10.0
Nominal Delivery Time (days)	1.3	5.4	2.1	9.2	3.5	1.0	11.3	5.6	2.3	1.1
Nominal Volume (ml)	60	65	100	110	125	125	270	270	270	270
Maximum Volume (ml)	65	65	125	110	125	125	335	335	335	335
Retained Volume (ml)	<=3	<=3	<=4	<=4	<=4	<=4	<=9	<=9	<=9	<=9
Approximate Delivery Time	Volume (ml)									
Hours / Days										
6										80
12 / 0.5	38		35			75				160
18	42					100				200
24 / 1	52		65			125				250
30	60									
48 / 2		35	100						250	
60 / 2.5			125							
72 / 3		45			110			175		
96 / 4		55						215		
120 / 5		65					155	250		
6							157	290		
7							195	325		
8							215			
9				110			230			
10							245			
11							265			
12							285			

Delivery accuracy is ±15% (at a 95% confidence interval) of the labeled infusion period when delivering normal saline at 88° F (31°C).

NOTES:

1. The infusion rate for each PainBuster Pump is labeled on the fill port. Flow rates from 0.5 ml/hr to 2 ml/hr are for small wound sites while flow rates from 5 ml/hr to 10 ml/hr are for larger wounds.
2. Actual infusion times may vary due to:
   -viscosity and/or drug concentration.
   -fill volumes.
   -positioning the PainBuster pump above (increase) or below (decrease) the catheter site.
   -temperature: the PainBuster flow restricter (located distal to the filter) should be close to, or in direct contact with, the skin (31°C/88°F). Temperature will affect solution viscosity, resulting in shorter or longer delivery time. If the PainBuster is used with the flow restrictor at room temperature (20°C/68°F), delivery time may increase by approximately 25%.
3. This product uses DEHP plasticized PVC. Certain solutions may be incompatible with the PVC material used in the administration set. Consult the drug package insert and other available sources of information for a more thorough understanding of possible incompatibility problems.

Infusion is complete when the PainBuster Pump is no longer inflated.

CAUTION

Federal (U.S.A.) law restricts this device to sale by or on the order of a healthcare professional.

For Customer Service
Call: 1.800.448.3569
(949) 206.2700

CE 0123

European Representative:
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P270050

PART NO. 5001108

PainBuster™ INFUSION KIT
270 ml Vol x 5 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 270 ml Vol, 5 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P270100

PART NO. 5001109

PainBuster™ INFUSION KIT
270 ml Vol x 10 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 270 ml Vol, 10 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P270010

PART NO. 5001106

PainBuster™ INFUSION KIT
270 ml Vol x 1 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 270 ml Vol, 1 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P270020

PART NO. 5001107

PainBuster™ INFUSION KIT
270 ml Vol x 2 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 270 ml Vol, 2 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P125015

PART NO. 5001104

PainBuster™ INFUSION KIT
125 ml Vol x 1.5 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 125 ml Vol, 1.5 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P125050

PART NO. 5001105

PainBuster™ INFUSION KIT
125 ml Vol x 5 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 125 ml Vol, 5 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

SEE DIRECTIONS FOR USE
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P100020

PART NO. 5001102

PainBuster™ INFUSION KIT

100 ml Vol x 2 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 100 ml Vol, 2 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P110005

PART NO. 5001103

PainBuster™ INFUSION KIT

110 ml Vol x 0.5 ml/hr

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

CONTENTS:
1 each – 110 ml Vol, 0.5 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

LOT

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P060020

PART NO. 5001100

PainBuster™ INFUSION KIT

60 ml Vol x 2 ml/hr

CONTENTS:
1 each – 60 ml Vol, 2 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

LOT

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF P065005

PART NO. 5001101

PainBuster™ INFUSION KIT

65 ml Vol x 0.5 ml/hr

CONTENTS:
1 each – 65 ml Vol, 0.5 ml/hr Pump
1 each – 16GA I.V. Catheter Needle
1 each – 20GA Epidural Catheter Set
1 each – 60cc Syringe
1 each – Transparent Dressing

PACKAGE IS NOT STERILE. INDIVIDUAL COMPONENTS ARE STERILE PACKAGED.

LOT

SEE DIRECTIONS FOR USE
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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P270100

PART NO. 5001109

PainBuster™ INFUSION KIT

270 ml Vol x 10 ml/hr

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P270050

PART NO. 5001108

PainBuster™ INFUSION KIT

270 ml Vol x 5 ml/hr

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P270020

PART NO. 5001107

PainBuster™ INFUSION KIT

270 ml Vol x 2 ml/hr

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P270010

PART NO. 5001106

PainBuster™ INFUSION KIT

270 ml Vol x 1 ml/hr

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P125050

PART NO. 5001105

PainBuster™ INFUSION KIT

125 ml Vol x 5 ml/hr

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P125015

PART NO. 5001104

PainBuster™ INFUSION KIT

125 ml Vol x 1.5 ml/hr

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P110005

PART NO. 5001103

PainBuster™ INFUSION KIT

110 ml Vol x 0.5 ml/hr

LOT

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P100020

PART NO. 5001102

PainBuster™ INFUSION KIT

100 ml Vol x 2 ml/hr

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P065005

PART NO. 5001101

PainBuster™ INFUSION KIT

65 ml Vol x 0.5 ml/hr

LOT

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CONTENTS / INHALT / CONTENU / CONTENIDO: 5

REF P060020

PART NO. 5001100

PainBuster™ INFUSION KIT

60 ml Vol x 2 ml/hr

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL. SEE DIRECTIONS FOR USE.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000688

PainBuster™ PUMP
270 ml Vol x 5 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000689

PainBuster™ PUMP
270 ml Vol x 10 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000686

PainBuster™ PUMP
270 ml Vol x 1 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000687

PainBuster™ PUMP
270 ml Vol x 2 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000684

PainBuster™ PUMP
125 ml Vol x 1.5 ml/hr

STERILE | LOT

SEE DIRECTIONS FOR USE.
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000685

PainBuster™ PUMP
125 ml Vol x 5 ml/hr

STERILE | LOT

SEE DIRECTIONS FOR USE.
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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000682

PainBuster™ PUMP
100 ml Vol x 2 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

Manufactured by / Hersteller von / Fabrique par / Fabricado por:
I-Flow Corporation
Lake Forest, CA 92630 U.S.A.

CE 0123

European Representative / Europaische Vertretung / Représentant pour l'Europe / Representante Europeo:
MPS Medical Product Service GmbH
Borngasse 20, 35619 Braunfels, Germany

1302082A

A PRODUCT OF / EINE PRODUKT VON / UN PRODUIT DE / UN PRODUCTO DE

I-FLOW CORPORATION, LAKE FOREST, CA U.S.A.

CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000683

PainBuster™ PUMP
110 ml Vol x 0.5 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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CE 0123

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MPS Medical Product Service GmbH
Borngasse 20, 35619 Braunfels, Germany

1302083A

118

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I-FLOW CORPORATION, LAKE FOREST, CA U.S.A.

CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000680

PainBuster™ PUMP
60 ml Vol x 2 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

Manufactured by / Hersteller von / Fabrique par / Fabricado por:
I-Flow Corporation
Lake Forest, CA 92630 U.S.A.

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European Representative / Europaische Vertretung / Représentant pour l'Europe / Representante Europeo:
MPS Medical Product Service GmbH
Borngasse 20, 35619 Braunfels, Germany

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

PART NO. 4000681

PainBuster™ PUMP
65 ml Vol x 0.5 ml/hr

STERILE

LOT

SEE DIRECTIONS FOR USE.
CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A HEALTHCARE PROFESSIONAL.

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MPS Medical Product Service GmbH
Borngasse 20, 35619 Braunfels, Germany

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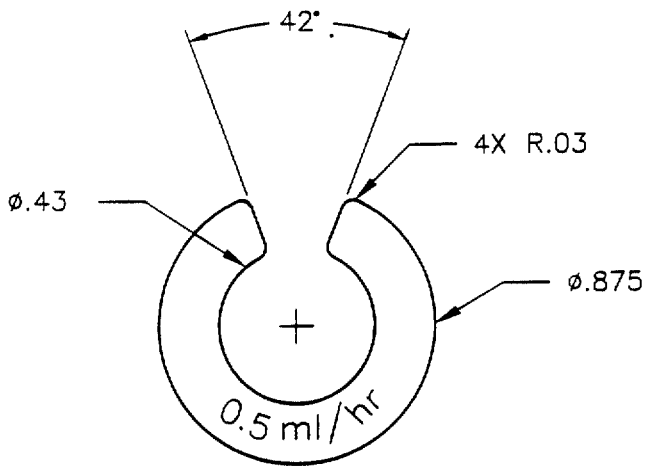
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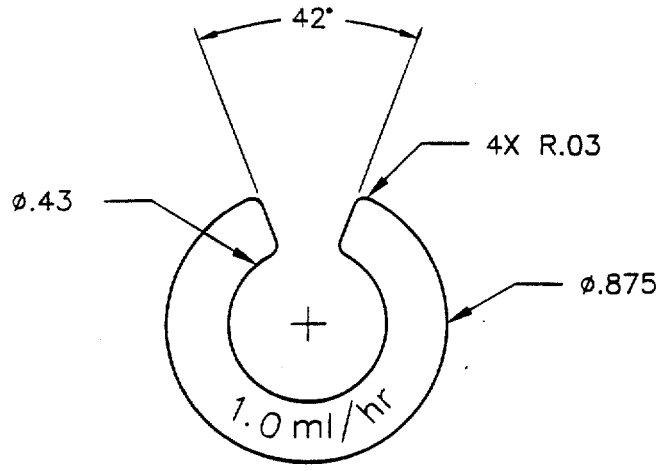
ø.43
ø.875
0.5 ml/hr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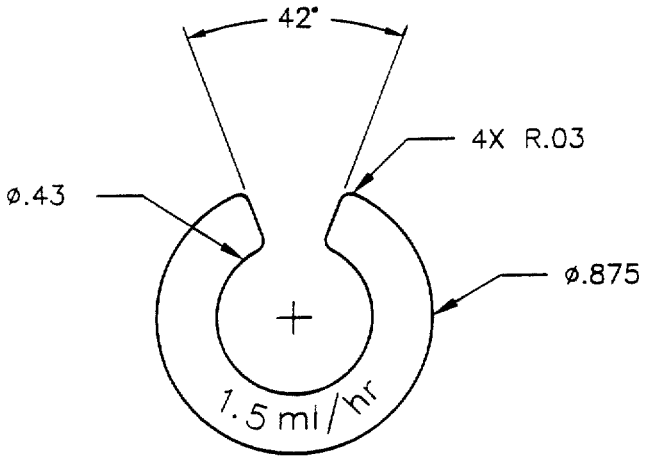
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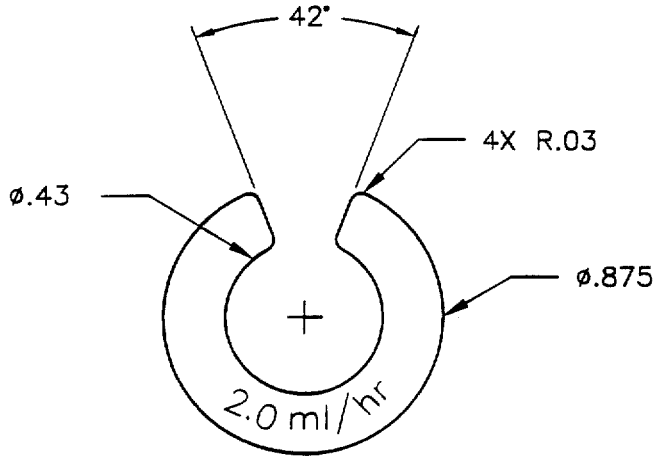
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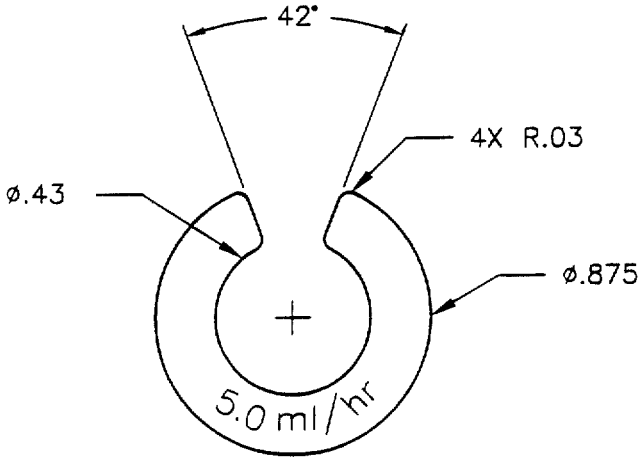
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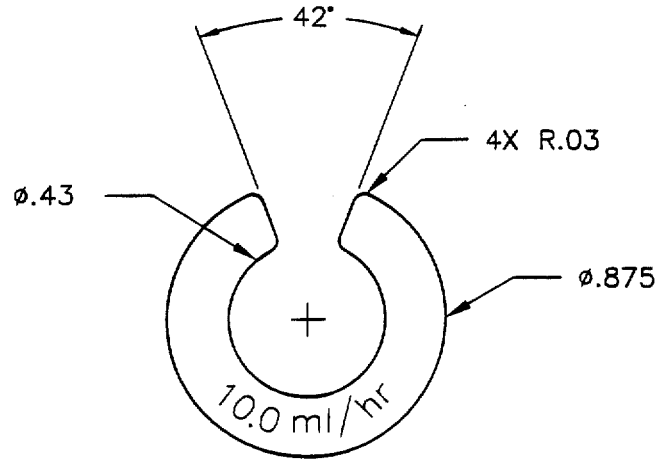
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4X R.03
ø.43
ø.875
10.0 ml/hr

12

Sgarlato Pain Control Infusion Pump Predicate Labeling

The following contains example labeling from the Sgarlato Pain Control Infusion Pump:

- Directions for Use
- Kit Tray Label
- Special Instructions
- Abbrev. Pain Control Infusion Pump Instructions
- Pain Control Infusion Pump Patient Instructions
- Pain Control Infusion Pump Medical Necessity
- Background and Significance of Pain Control Infusion Pump - "PCIP"
- Brochure, "A Significant Improvement in Portable Infusion"
- More background information on Pain Control Infusion Pump
- B. Braun Medical Engineering Memo

Pain Control Infusion Pump

Pain Control System

INDICATIONS
The system is indicated for the relief of pain in patients following surgery, by the continuous administration of medication into the wound site. It is convenient for use by ambulatory patients.

CONTRAINDICATIONS
Not intended for intravenous infusion.

WARNINGS
DISPOSABLE - Destroy after single use. Do not refill or resterilize.
Do not overfill device.
Follow drug manufacturer's instructions for the medication being used.

CAUTION
Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

DIRECTIONS FOR USE:
Use Aseptic Technique.

FILLING RESERVOIR PUMP
1. Close on/off clamp of medication tubing.
2. Remove protective cover from female luer lock filling port and discard.
3. Attach 60 ml syringe without needle to filling port at the top of the Pump Reservoir (refer to figure 1.). Fill reservoir with up to 100 ml of medication.
4. Once filling is complete, remove syringe. Securely attach blue replacement cap to filling port to maintain a sterile filling port.

PRIMING SYSTEM (refer to figure 3a.)
1. Attach clear connector to medication catheter by pushing catheter into connector as deeply as possible. Twist connector as tightly as possible, use **MAXIMUM HAND FORCE** to screw connector components together to assure that the catheter will not pull out. It is almost impossible to constrict the catheter flow by maximum tightening.
2. Hold system reservoir and filter in upright position. Loosen proximal luer connector (green) to allow trapped air to exit.
3. Open on/off clamp (solution will automatically begin to flow into tubing and catheter). (Tighten proximal luer connector when fluid flow without air reaches connector.)
4. Hold the filter vertically and tap filter lightly to remove air bubbles.
5. Keep priming until all air has been purged from tubing, filter and catheter.
6. Allow 10 minutes before placing catheter in patient to see medication drops flow to the end of the medication catheter. If flow is not seen, attempt priming with 60 ml syringe filled with 10 ml or more of medication. Clamp off tubing with pinch clamp. Disconnect proximal luer connector and attach distal connection to syringe. Aspirate air bubbles and then force medication distally until drops of medication are seen at distal end of medication catheter. If flow is not seen, discard unit and repeat above steps with new Pain Control Infusion Pump unit. If flow is seen, reattach proximal connector and release pinch tubing clamp.

PLACING CATHETER (refer to figure 2.)
NOTE: Prime system completely prior to placing catheter.

METHOD A: FROM INSIDE THE WOUND
1. Push introducer needle from the surgical wound site subcutaneously and puncture through skin at a desired location away from the surgical wound site.
2. Thread open end of catheter through the tip of the catheter introducer needle at the puncture site until the catheter is seen in the surgical wound site.
3. Place the end of the catheter in an appropriate location (not in a vessel) within the surgical wound site.
4. Tape catheter to the skin to prevent the catheter from pulling out of the wound site. It is most effective to tape in a linear parallel manner to the catheter (refer to figure 3.)
5. Remove introducer needle from wound site leaving catheter in place and dispose of needle in accordance with institutional protocol.

METHOD B: INSERTION THROUGH SKIN
1. Puncture introducer needle through the skin at a desired location external to the surgical wound site; push the introducer needle subcutaneously into the surgical wound site.
2. The catheter is left free, unattached from the connector. Push catheter into the hub end of the needle and allow catheter to exit at the needle tip into the surgical wound site.
3. Remove introducer needle and tape catheter as described in Method A steps 4 and 5 above.
4. Attach catheter to clear connector per Priming System Procedure Step 1.

DESCRIPTION
The Pain Control Infusion Pump is a complete, lightweight, disposable device which uses a constant internal pressure to infuse medication for control of pain. The system is designed to deliver medication continuously into the surgical wound site over the infusion period.

figure 1.

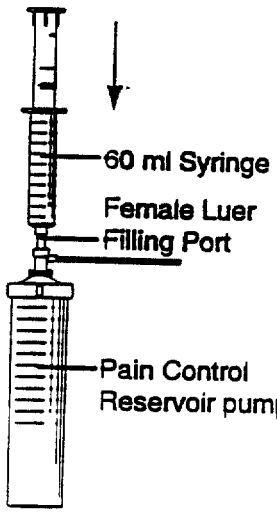


figure 2.

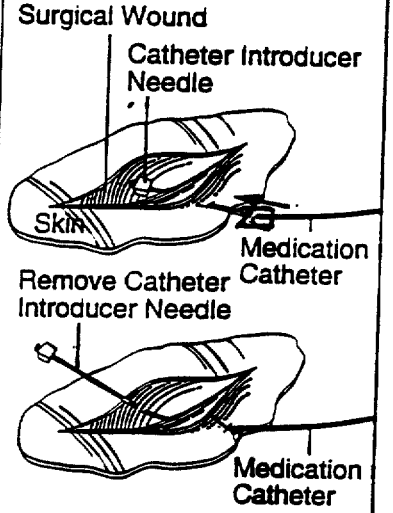
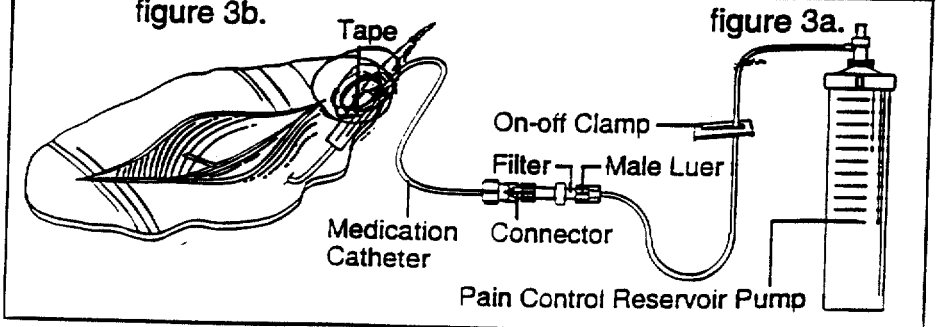


figure 3b.

figure 3a.



Manufactured for:
SGARLATO LABORATORIES, INC.
237 ALMENDRA AVE.
LOS GATOS, CA 95030
Phone 1-800-421-5303
1-408-399-4638
Fax 1-408-354-4922

A4806164 P-2143-3 REV. 1/97

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Pain Control Infusion Pump

Pain Control System

Pain Control System

for continuous delivery of medication for control of pain

RATE: Approximately 2.0 ml/hr

PRODUCT CODE:
PC2000-40

Contents of unopened, undamaged package are:
STERILE • NONPYROGENIC

DISPOSABLE - Destroy after single use.
Do not clean or resterilize.
Store at controlled room temperature.

CAUTION: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician

REFER TO OPERATING INSTRUCTIONS PRIOR TO USE.

U.S. PATENTS 4,997,420 AND 5,078,679 AND OTHER PATENTS PENDING

ONE SYSTEM CONTAINING:

- 100 ml Medication Reservoir Pump
- 34 inch Medication Tubing
- 5 micron Medication Filter and Flow Regulator
- 39-1/2 inch Medication Catheter
- 18 GA. x 2-1/2 in. Catheter Introducer Needle
- 60 ml Syringe
- Catheter Tape
- Replacement Cap
- Carrying Harness

Manufactured for
SGARLATO LABORATORIES, INC.
237 Almendra Avenue
Los Gatos, CA 95030
Phone 1-800-421-5303
1-408-399-4638
Fax 1-408-354-4922

Pain Control Infusion Pump
Pain Control System

LOT NO.: 914420

PEEL TO OPEN

PRODUCT CODE:
PC2000-40

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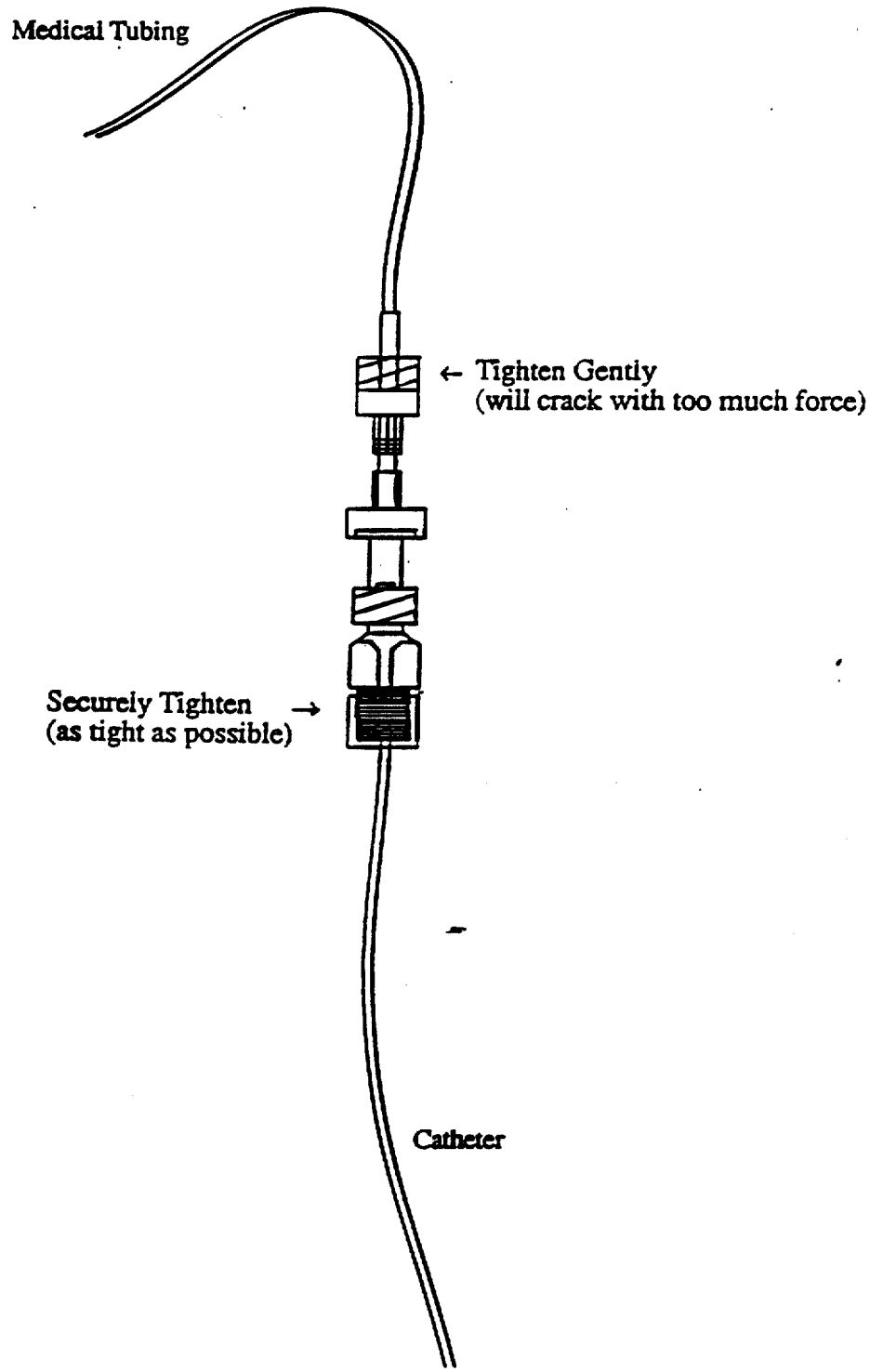
Special Instructions: Please Review



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ABBREV. PAIN CONTROL INFUSION PUMP INSTRUCTIONS

Additional information is provided inside the sterile kit.

IMPORTANT: Use aseptic technique.
RECOMMENDED: Administer prophylactic antibiotic.

FILLING RESERVOIR PUMP:

1. Disconnect flow regulator from tubing at green male luer.
2. Close on/off clamp at the very end of tubing (next to green male luer).
3. Draw medication into 60 ml syringe. Remove air bubbles.
4. Remove and discard protective cap on top of reservoir filling port.
5. Attach 60 ml syringe without needle to reservoir filling port and load up to 100 ml of medication.
6. Remove syringe and attach blue replacement cap to filling port.
7. Prime reservoir and tubing by briefly opening clamp to let air bubbles out.
8. Connect flow filter to tubing. Do not tighten excessively. Open clamp.

PLACEMENT OF CATHETER:

1. Puncture blue introducer needle through the skin external to the surgical wound site. Push needle subcutaneously into the wound cavity.
2. Feed micro catheter through needle and allow catheter to exit at the needle tip into the wound at the desirable surgical plane. IMPORTANT: Do not put catheter in blood vessel.
3. Remove and discard needle, leaving catheter in place.
4. Tape catheter to body very near to the insertion site utilizing the 3-4 loop technique in order to keep catheter securely in place.
5. Insert catheter as deeply as possible (apx. 1/2 inch) into connector. Twist connector as **TIGHTLY AS POSSIBLE** to assure that catheter will not pull out.
6. Tape connector below patient's knee (if procedure is below the knee). RECOMMENDED: Place gauze pad between body and connector for comfort.
7. Attach carrying harness to reservoir. Patients can wear or carry device however they prefer.

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PAIN CONTROL INFUSION PUMP PATIENT INSTRUCTIONS

The PCIP Pain Control System is a portable infusion pump designed to deliver medication directly to the surgical site for management of pain.

How the System Works

PCIP administers local pain medication directly to the pain site via a tiny tube which is placed inside the wound by the physician during surgery. Pain relief is provided directly where it is needed. This is an alternative to other forms of therapy such as pain killers and narcotics taken orally which go throughout the entire body and sometimes cause side effects such as drowsiness, disorientation, nausea or other adverse reactions.

PCIP is comprised of a reservoir with internal spring pressure, tubing and a very precise flow regulator. The device has been filled with medication to flow continuously for a specific period of time. The system should remain completely intact for the duration of the period. Do not remove the blue cap or disconnect the device in any way.

If Complications Arise

If you experience any problems with the PCIP unit such as leakage, the device becoming disconnected, the tube pulling out of the wound site, or if you experience discomfort or excessive pain, call your physician immediately. He/she may prescribe supplemental medication if necessary.

There is a white clamp on the thicker tubing to restrict the fluid flow if necessary. This should be done only upon the direction of your doctor. As a general rule, you do not have to do anything with the unit because it is fully self contained and automatic.

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PAIN CONTROL INFUSION PUMP Medical Necessity

Postoperative pain management is an important concern for anesthesiologists and surgeons. Adequate pain control has been shown to reduce morbidity by improving mobility and decreasing the risk of developing deep venous thrombosis. Patient satisfaction is also increased with control of postoperative pain.

Systematic drugs such as narcotics can provide analgesia but often have side effects such as respiratory depression, excessive sedation nausea and vomiting. Regional anesthesia with local anesthetic reduces the need for systematic medications but requires a pain injection and repeated dosing.

Local infiltration of a surgical incision with a local anesthetic has been shown to provide adequate anesthesia. Techniques used include bathing the incision with local anesthetic prior to closure (provides limited duration of pain relief), repeated injections into wound (painful, increased risk of wound infection and time-consuming and placement of an epidural catheter into the wound to allow repeated boluses of local anesthetic. The last technique still requires additional time from the care given to provide the additional doses.

The Pain Buster infusion pump is a cost effective ambulatory, disposable elastomeric pump designed to continuously deliver a local anesthetic (Bupivacaine 0.25%). It has been developed to produce analgesia for the control of excruciating postoperative pain.

* * *

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Background and Significance of Pain Control Infusion Pump - "PCIP"

Post-operative pain management is an important concern for anesthesiologists and surgeons. Adequate pain control has been shown to reduce morbidity by improving mobility and decreasing the risk of developing deep venous thrombosis. Patient satisfaction is also increased with control of post-operative pain.

Systemic drugs such as narcotics can provide analgesia but often have side effects such as respiratory depression, excessive sedation, nausea and vomiting. Regional anesthesia with local anesthetic reduces the need for systemic medications but requires a painful injection and repeated dosing.

Local infiltration of a surgical incision with a local anesthetic has been shown to provide adequate anesthesia. Techniques used include bathing the incision with local anesthetic prior to closure (provides limited duration of pain relief), repeated injections into the wound (painful, increased risk of wound infection and time-consuming) and placement of an epidural catheter into the wound to allow repeated boluses of local anesthetic. This last technique still requires additional time from the care giver to provide the additional doses.

The PCIP medication infusion pump is a cost effective ambulatory, disposable, spring activated pump designed to continuously deliver a local anesthetic (Bupivacaine 0.25%). It has been developed to produce analgesia for the control of excruciating post-operative pain.

PCIP is assembled aseptically in a Clean Room (Class 100). It consists of simple assembly of components already used in medical devices. A spring is mounted on a syringe plunger and capped by an outer shell. Medical grade PVC tubing is connected to the syringe. A micro-glass cannula is placed in the end of the PVC tubing exiting the connector. A catheter is connected to the end of the PVC tubing. A "Y" connector may be added to add a catheter for more than one delivery site.

When medication is injected into the injection port, it flows into the syringe, pushing the syringe plunger against the spring. As the syringe reservoir is filled, the spring produces more pressure on the plunger, providing pressure on the medication fluid. The medication then flows through the micro-glass cannula which controls the rate of flow (in a fail-safe manner). The fluid exits the system via the epidural catheter. Any break in the system will result in reduced or no drug delivery to the patient.

Clinical experience demonstrates that excruciating post-operative pain decreases over time in most patients. This observation is further demonstrated by the patient's diminishing need for narcotic analgesia to control pain. Continuous infusion of local anesthetic should provide analgesia and reduce the need for systemic medications with little risk to the patient.

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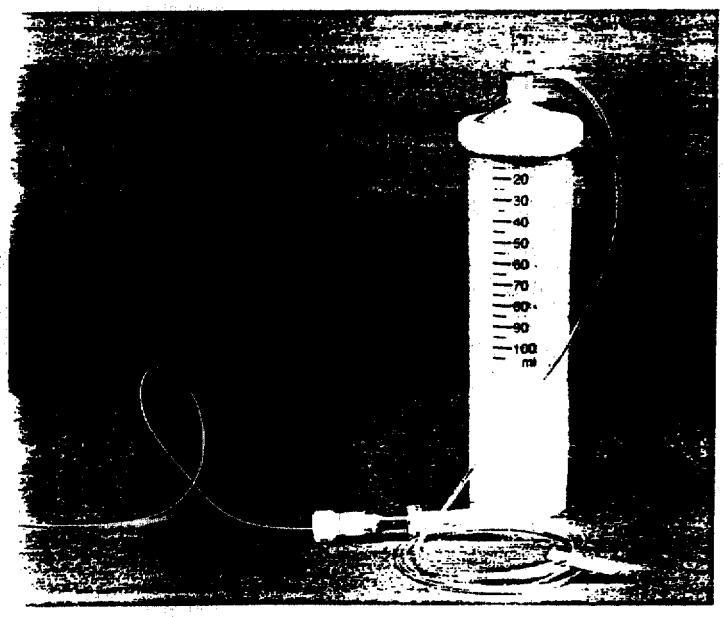
A Significant Improvement in Portable Infusion

Take Aim at the Site of Pain

Now you can provide your patients with safe, reliable, and accurate continuous infusion via Sgariato Lab's SurgiPEACE pump system. SP is suitable for delivery of local anesthetic directly to the pain site. There are many potential applications for pain management.

The SP system is a complete, lightweight disposable device which provides constant internal pressure via a unique precision compression spring and a flow resistor to provide a consistent infusion flow rate throughout the entire course of therapy. The flow rate is selected by the physician and cannot be changed by the patient thus ensuring safety and efficacy. The medication reservoir is constructed of a high quality durable and stable plastic which is suitable for ambulatory use. This simple and practical system is an excellent low cost option for many of your pain treatment needs.



Patent = 5,078,679 Patent = 4,997,420

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Sgariato Laboratories, Inc.

237 Almendra Avenue
Los Gatos, CA 95030
(800) 421-5303
(408) 399-4638
FAX (408)354-4922

Safe and Accurate

- Consistent and reliable flow rate throughout therapy via a precision compression spring.
- Tamper resistant design and unique flow restrictor prevent excess drug delivery and rate manipulation.
- Sterile "closed" system design with integrated tubing reduces risk of contamination.
- Disposable after single use.

Simple and Practical

- No programming, timing setting or electronic [illegible]
- Minimal patient and staff training.
- No cords, outlets, batteries or I.V. poles needed.
- Lightweight and compact design encourages patient compliance.

Flexible

Currently there are three flow rates available.

Model #	Flow Rate	Max Volume	Infusion Time
SP500	0.5 ml/hr	100 ml	8 days
SP1000	1 ml/hr	100 ml	4 days
SP2000	2 ml/hr	100 ml	2 days

Reliable and Durable

- Outer markings on barrel show exactly how much fluid is in the reservoir at any point in time.
- Durable hard plastic pump design minimizes possibility of pump being damaged or crushed, especially for long term use.
- All polypropylene housing provides for greater drug stability and less sensitivities compared to elastomeric pumps. Drug stability information is available.

Cost Effective

- Low Cost
- Reduces or eliminates potentially expensive clinician intervention time.
- Low cost alternative to other more costly forms of pain treatment.

Indications and Usage: For patients requiring slow continuous administration of medication. It is convenient for ambulation use for inpatients, outpatients or home care.

Contraindications: Not designed for rapid infusion of medications.

Kit Options: Carrying harness, catheter, needle, catheter connector, "Y" adapter for multiple catheters.

Sgarlato Laboratories, Inc.

237 Almendra Avenue
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(800) 421-5303
(408) 399-4638
FAX (408)354-4922

(b)(4) (b)(4) LABORATORIES, INC.

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123

B. BRAUN MEDICAL ENGINEERING MEMO	TO: File	FROM: Bill Reiser BR	DATE: 7-18-93 8-25-93 BR
	DISTRIBUTION: (b)(4) (b)(4)		
	SUBJECT: Sgarlato Pump - Flow Rate Testing		

(b)(4)

(b)(4)

Procedure:

1. (b)(4)
2. (b)(4)
3. (b)(4)
4. (b)(4)

Results:

(b)(4)

(b)(4)

Summary:

(b)(4)

(b)(4)

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BURRON MEDICAL ENGINEERING MEMO	TO: File	FROM: Bill Reiser BR	DATE: 5-5-92
	DISTRIBUTION:		
	SUBJECT: (b)(4) (b)(4)		

(b)(4)

(b)(4)

Procedure:

(b)(4)

(b)(4)

Results:

(b)(4)

(b)(4)

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Homepump C-Series Predicate Labeling

The following contents are example labeling from the Homepump C-Series 65ml Volume, 0.5 ml/hr flow rate model:

- P/N 111111 - Directions for Use
- P/N 1301712 - Flow Rate Label
- P/N 111112 - Pouch Insert
- P/N 1301758 - Pouch Label
- P/N 1301757 - Inner Box Label
- P/N 1301759 - Shipper Box Label

HOMEPUMP®

DISPOSABLE ELASTOMERIC INFUSION SYSTEM

DIRECTIONS FOR USE

C-SERIES MODELS: C060020, C065005, C100020 C125050, C270010, C270020, C270100

The Homepump Disposable Elastomeric Infusion System is designed for use by ambulatory patients.

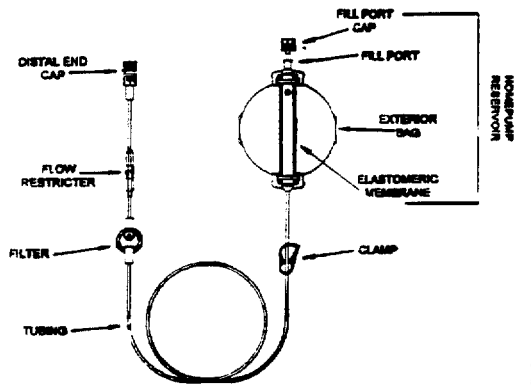
- The Homepump is indicated for continuous delivery of medications through intravenous, intra-arterial, subcutaneous or epidural routes.
- The Homepump is not intended for the delivery of blood, blood products or TPN.
- The Homepump tubing is made of DEHP plasticized PVC.
- **Epidural Administration:** Epidural infusion of analgesics is limited to use of indwelling catheters specifically designed for epidural delivery. To prevent infusion of drugs not indicated for epidural use, do not use IV set with additive ports. It is strongly recommended that devices used for administration of medication via epidural routes be clearly differentiated from all other infusion devices.

  Warning: Epidural administration of drugs other than those indicated for epidural use could result in serious injury to the patient.
- It is the responsibility of the pharmacist to assure, that the medication is prepared and administered in accordance with the drug manufacturer's package insert. It is the responsibility of the healthcare provider to assure the patient is educated on the proper use of this product.
- Refer to Center for Disease Control *Guideline for Prevention of Intravenous Therapy-related Infections* for specific recommendations regarding the usage of IV administration sets.

- Do not use while showering, bathing, or swimming.
- Do not microwave or submerge in water.
- Do not reuse.

Use aseptic technique.

1. Remove filled Homepump from protective plastic bag and verify that the clamp on the tubing is closed.
2. Remove distal end cap from tubing. Open clamp. Fluid will fill the tubing set. When all air has been expelled from the tubing set, close clamp.
3. Attach the Homepump tubing to the appropriate access site, as instructed by your healthcare provider.
4. Begin infusion by opening the clamp.
5. When the elastomeric membrane is no longer extended, infusion is complete; disconnect and dispose of the Homepump as instructed by your healthcare provider.



Effects of Environmental Factors (such as storage time, temperature, solution viscosity, backpressure, and/or fill volume) on Infusion Delivery Times

The information below will assist the healthcare provider in understanding these factors:

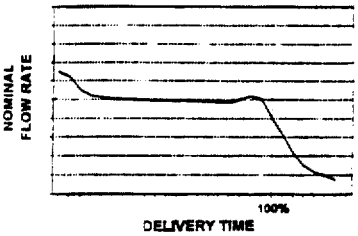
1. C-Series Homepump delivery should be started immediately after filling. Storage of a filled Homepump unit for more than 8 hours prior to starting infusion may result in a 10% longer delivery time.
2. If a filled Homepump unit needs to be stored in the refrigerator or freezer, for any reason, allow the unit to warm to room temperature before using: If refrigerated, allow 4 hours for C060020, C065005, C100020, C125050; allow 12 hours for C270010, C270020, C270100. If frozen, allow 8 hours for C060020, C065005, C100020, C125050; allow 24 hours for C270010, C270020, C270100.

   Note: Delivery time can increase significantly as a result of extended storage time.
3. The C-Series Homepump System is designed for the infusion tubing to be worn under the clothing, while the Homepump reservoir can be worn in the manner most comfortable to the patient. The Homepump flow restricter (located distal to the filter) should be close to, or in direct contact with, the skin (31°C/88°F).

   Temperature will affect solution viscosity, resulting in shorter or longer delivery time. If the Homepump is used with the flow restricter at room temperature (20°C/68°F), delivery time will increase by 25%.
4. Homepump delivery times are based on normal saline. Addition of any drug or use of another diluent may change viscosity and result in longer or shorter delivery time; use of D5W will result in a 10% longer delivery time.
5. When administering through a central intravenous, arterial, or epidural catheter, follow the instructions provided by the catheter manufacturer. The length, diameter, and position (pressure at catheter tip) may affect delivery time.
6. A Homepump filled with more than the nominal volume will infuse at a lower than nominal flow rate.

   A Homepump filled with less than the nominal volume will infuse at a higher than nominal flow rate.

Typical Flow Curve for a Homepump



Delivery Time Information for C-Series Homepumps

	C060020	C065005	C100020	C125050	C270010	C270020	C270100
NOMINAL FLOW RATE (ml/h)	2	0.5	2	5	1	2	10
NOMINAL VOLUME (ml)	60	65	100	125	270	270	270
MAXIMUM VOLUME (ml)	65	65	125	125	335	335	335
RETAINED VOLUME (ml)	2	2	3	3	6	6	8
APPROX. DELIVERY TIME	VOLUME (ml)						
6 h							60
12 h	35		33	75			100
16 h	42			100			200
24 h / 1 d	52		65	125			250
36 h	60						
48 h / 2 d		35	100				
60 h							
72 h / 3 d		45				175	
96 h / 4 d		55				215	
120 h / 5 d		65			165	255	
6 d					175	285	
7 d					195	325	
8 d					215		
9 d					230		
10 d					245		
11 d					255		
12 d					265		

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REVISIONS			
REV	DESCRIPTION	DATE	APPROVED
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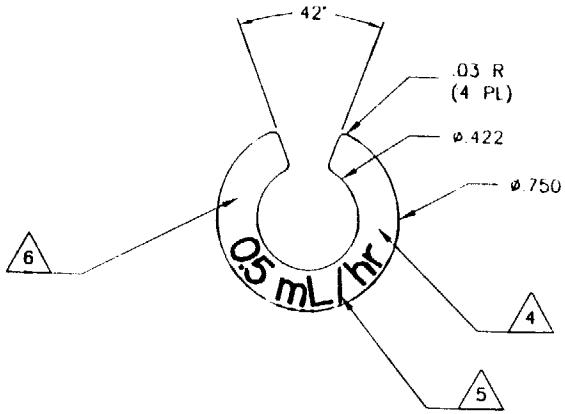

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FINISH	APPROVALS / DATE	TITLE: FLOWRATE LABEL, SNAP CAP, 0.5 ml/hr	
UNLESS OTHERWISE NOTED ALL DIMENSIONS ARE IN: INCHES TOLERANCES: LINEAR: .XX± .01 CONCENTRICITY. ± .XXX± .005 FLATNESS: ± ANGLES ± 0.5° ROUNDNESS: ±	(b)(4)	SIZE: B	DRAWING NO.: 1301712 REV.: A
DO NOT SCALE DRAWING	SCALE: 2:1	CAD FILENAME: 1301712A	SHEET: 2 OF: 3

(4 7/8")

HOMEPUMP®

DISPOSABLE ELASTOMERIC INFUSION SYSTEM

FOR SINGLE USE ONLY
- **Fluid pathway and areas under undisturbed protective caps are sterile and nonpyrogenic.**
- Do not remove from package until ready for use.
- Do not use if previously opened or damaged.
- See Directions for Use in the dispenser box.
- Storage: 10°-40°C, 10-90% relative humidity.

INFUSIONSGERÄT ZUR EINMALIGEN VERWENDUNG
- **Auf Sterilität und Pyrogenfreiheit geprüft.**
- **Nicht verwenden, wenn Schutzkappen abgefallen oder gelockert sind oder wenn Packung beschädigt ist.**
- Bitte Gebrauchsanweisung in der Sammelpackung beachten.
- Lagerung: 10°-40°C, 10-90% Luftfeuchtigkeit.

(6 1/2")

DIFFUSEUR PORTABLE À USAGE UNIQUE
- **Stérile, apyrogène.**
- Vérifier l'intégrité du protecteur individuel avant usage.
- Se référer au mode d'emploi dans l'emballage de protection.
- Conserver à 10°-40°C, 10-90% humidité.

BOMBA DE INFUSION PARA UN SOLO USO
- **Estéril, apirógena.**
- No utilizar si el envase unitario no esta integro.
- Consultar el modo de empleo en la caja dispensadora.
- Conservar a 10°-40°C, 10-90% humedad.

STERILE | EO

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USA

CAUTION: Federal (U.S.A.) Law restricts this device to sale by or on order of a physician.

U.S. Pat. Nos. D324,911; 5,080,652; 5,105,983; and Foreign Pat. Pend.

Assembled in Mexico 111112, Rev. B

TITLE:	C-Series pouch insert		
DRWG NO:	111112	REV:	B
SHT	3 OF 4	PRINTED AT	100 %

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(4 7/8")

DIRECTIONS FOR FILLING - Use Aseptic Technique.

1. Remove the cap from the fill port and retain for later use.
2. The HOMEPUMP can be filled with a syringe or other filling device. Remove all air from the filling device and attach it securely to the fill port.
3. Close the clamp and fill the HOMEPUMP with no more than the recommended maximum fill volume.
4. Remove filling device from the fill port.
5. Securely attach the cap to the fill port.
6. Label with the appropriate pharmaceutical and patient information.
7. Put HOMEPUMP into protective plastic bag for shipping and handling.

ANLEITUNG ZUM FÜLLEN - Auf aseptische Arbeitsweise achten.

1. Die Schutzkappe vom Füllport entfernen und zur Seite legen.
2. Die HOMEPUMP kann mit einer Spritze oder einer anderen Füllvorrichtung gefüllt werden. Die gesamte Luft aus der Füllvorrichtung entfernen. Füllvorrichtung sicher mit dem Füllport verbinden.
3. Die Klemme schliessen und die HOMEPUMP mit höchstens dem empfohlenen maximalen Füllvolumen füllen.
4. Die Füllvorrichtung vom Füllport entfernen.
5. Die Schutzkappe wieder aufsetzen.
6. Mit den entsprechenden pharmazeutischen und Patienteninformationen bezeichnen.
7. Für den Versand, Transport und kurzfristige Lagerung vorgesehene HOMEPUMP in den Kunststoff-Schutzbeutel verpacken.

(6 1/2")

INSTRUCTIONS POUR LE REMPLISSAGE - Utiliser une technique aseptique.

1. Retirer le bouchon protecteur du site de remplissage et le mettre de côté.
2. La HOMEPUMP peut être remplie avec une seringue ou un autre appareil de remplissage. Expulser tout l'air de l'appareil de remplissage et raccorder le de façon sûre au site de remplissage.
3. Fermer le clamp et remplir la HOMEPUMP sans dépasser le volume de remplissage maximum.
4. Retirer l'appareil de remplissage du site de remplissage.
5. Raccorder le bouchon protecteur sur le site de remplissage.
6. Etiqueter avec les renseignements pharmaceutiques et informations pour le patient appropriés.
7. Mettre la HOMEPUMP dans le sac protecteur en plastique pour l'expedition et la manutention.

INSTRUCCIONES PARA LLENAR - Use una técnica aséptica.

1. Remueva la tapa del orificio superior y reténgala.
2. El HOMEPUMP se puede llenar con una jeringa u otro sistema de llenado. Elimine todo el aire del sistema de llenado y conéctelo firmemente al orificio superior.
3. Cierre la pinza y llene el HOMEPUMP sin sobrepasar el máximo volumen recomendado.
4. Remueva el sistema de llenado del orificio superior.
5. Vuelva a conectar la tapa en el orificio superior asegurándola firmemente.
6. Márque el HOMEPUMP con la correspondiente información farmacéutica y del paciente.
7. Ponga el HOMEPUMP en la bolsa de plástico protectora para envio y manejo.

TITLE: C-Series pouch insert		
DRWG NO: 111112	REV: B	
SHT 4 OF 4	PRINTED AT 100 %	

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CONTENTS / INHALT / CONTENU / CONTENIDO: 1

REF C065005

PART NO. 5001013

Homepump ECLIPSE® C-Series 65 ml Volume, 0.5 ml/hr

Assembled in Mexico

STERILE EO

LOT

CAUTION: FEDERAL LAW (U.S.A.) RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN. SEE DIRECTIONS FOR USE.

Manufactured by / Hersteller von / Fabrique par / Fabricado por:
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European Representative / Europaische Vertretung / Représentant pour l'Europe / Representante Europeo:
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Borngasse 20, 35619 Braunfels, Germany

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CONTENTS / INHALT / CONTENU / CONTENIDO: 6

MODEL NO.: C065005

PART NO.: 5001013

Homepump ECLIPSE® C-Series
65 ml Volume, 0.5 ml/hr

Printed in U.S.A.

Assembled in Mexico



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CONTENTS / INHALT / CONTENU / CONTENIDO: 24

REF C065005

PART NO. 5001013

Homepump ECLIPSE® C-Series
65 ml Volume, 0.5 ml/hr

Assembled in Mexico

STERILE EO

LOT

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Appendix E
References

Br. J. Anaesth. (1986), 58, 790–800

LOCAL ANAESTHETIC TECHNIQUES FOR PREVENTION OF POSTOPERATIVE PAIN

E. N. ARMITAGE

HISTORY

The potential benefits of local anaesthetic techniques in the postoperative period have long been recognized. In a review of early work, Simpson and Parkhouse (1961) pointed out that, in 1935, Capelle irrigated abdominal wounds with local anaesthetic injected through large, curved, hollow needles. These were inserted at the end of the operation and left in place in a manner similar to deep tension sutures. The method was apparently effective, but was not adopted widely because of fear of wound infection and delayed healing. Gerwig, Thompson and Blades (1951) used the same principle when they inserted polyethylene tubes deep to the anterior rectus sheath for wound irrigation, and they noted that patients so treated required only a quarter of the usual amount of morphine.

Gius (1940) described the use of paravertebral block with procaine for the treatment of post-operative atelectasis, and Cleland (1949) used "continuous" caudal and extradural analgesia for over 100 abdominal and ano-rectal cases. He claimed that this resulted in normal postoperative respiration and early, painless ambulation. Bonica (1953) used intermittent injections through an indwelling extradural catheter to produce segmental analgesia, and found that this gave complete pain relief and allowed effective ventilation and coughing. Dawkins (1956) preferred to give extradural lignocaine as an infusion. He found that this technique was capable of providing truly continuous analgesia, and pointed out that the use of the word "continuous" is a misnomer when applied to intermittent injections or top-ups of local anaesthetic.

These pioneer workers had demonstrated that local anaesthetics produce excellent postoperative analgesia, but they had also encountered the drawbacks. Infusion systems were open to the criticism that the extent of block might be difficult to control and that any sudden, unsuspected hypotension could be dangerous to a patient in the sitting position (Bonica, 1957). Regarding intermittent top-ups, Simpson and colleagues (1961) summarized the situation as follows: "The exacting nature of the technique, the necessity for scrupulous asepsis, and the large numbers of injections required, make continuous postoperative analgesia by means of intermittent, mid-thoracic extradural block unsuitable for routine use except where the special facilities of an intensive therapy unit are available."

These early observations provide guidelines for the "ideal" local anaesthetic technique for use in the postoperative period. It should be effective over the whole of the painful area, but its extent should not be difficult to control. It should not readily produce toxic effects and should not be unduly labour-intensive. Side effects should be minimal.

EXTRADURAL BLOCK

This is particularly useful because it can provide analgesia after surgery of the thorax, abdomen, pelvis and lower limb.

Factors affecting the catheter

Position. The catheter must be placed so that local anaesthetic solution injected through it produces analgesia at the site of operation. The mode of spread of solution depends on the method of administration. Injected solution emerges from the catheter under pressure and spreads equally up and down the extradural space. The catheter tip should therefore lie at the segment innervating the middle of the required area of analgesia. For upper abdominal operations, this should be between T6 and T8. An infused solution enters the extradural space under minimal pressure and its spread is

E. N. ARMITAGE, M.B., B.S., F.F.A.R.C.S., Brighton General Hospital, Brighton, W. Sussex.

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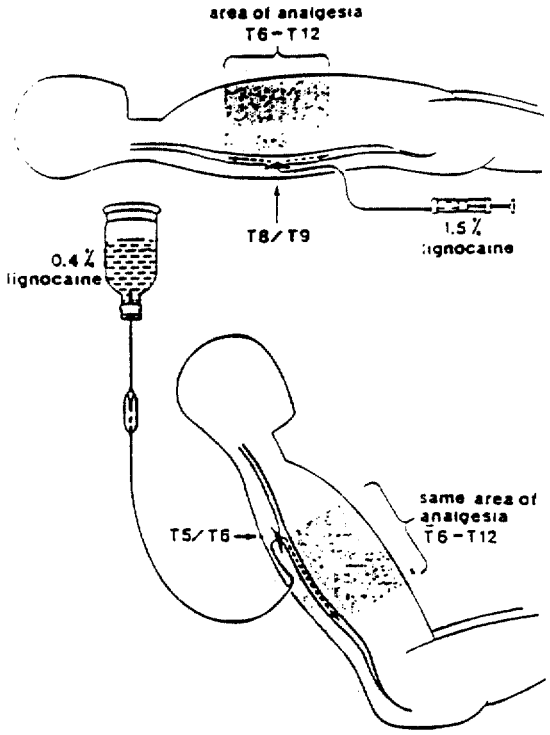

FIG. 1. The original illustration by Green and Dawkins (1966). The lower diagram shows the catheter tip placed at the upper end of the required area of block when the patient is in the 45° sitting position and the local anaesthetic is infused. The upper diagram shows the same area of analgesia obtained with the patient supine and the solution administered as a bolus.

mostly influenced by gravity. Since the patient is likely to be sitting up when the postoperative infusion is in progress, the catheter tip should be at the segmental level innervating the upper end of the surgical incision (fig. 1) (Green and Dawkins, 1966).

Insertion. When an extradural block is used only for the duration of surgery, it is customary to insert a short length of catheter (2–3 cm) to the extradural space. Looping and knotting cannot occur and the risk of venous and dural puncture is minimized. Although this is satisfactory during and immediately after the operation, the catheter tends to become extruded as the patient mobilizes and as infusions are continued or repeated injections given. At least 5 cm of catheter should therefore be inserted to the extradural space if long-term analgesia is planned.

Duration. The pain of major surgery is at its most severe and debilitating in the first 2 or 3 days and extradural analgesia is of most benefit during this time. Thereafter, the intensity of pain diminishes and it can usually be controlled adequately with i.m. opioids or oral preparations.

Infection is unlikely to occur when catheters are removed after 2 days and patients have been reported in whom they have been left in place for between 7 and 25 days (Dawkins, 1966; Lloyd and Rucklidge, 1969; Spoerel, Thomas and Gerula, 1970). However, skin infection was noted after 3 days at the entry site of the catheter in one instance. Infection of the extradural space is very rare (Baker et al., 1975), but it is serious when it occurs (Saady, 1976) and injections and infusions should be delivered through a system which includes a bacterial filter. Indwelling catheters can migrate and the tip can enter a blood vessel or puncture the dura. The length of time for which a catheter is left in place represents a compromise between these possible hazards and the benefits resulting from the analgesia. Two to three days would seem to be the optimal time.

Choice of drug

It is important that a local anaesthetic, given by intermittent bolus injection or by infusion, should not produce systemic toxicity. Reynolds (1971) found bupivacaine to have a wider safety margin than lignocaine or mepivacaine when given by intermittent injection during surgery. Tucker and Mather (1975) used a computer model to predict the pattern of drug concentrations in the extradural and plasma compartments, and concluded that longer-acting agents such as etidocaine accumulate rapidly in the extradural space, but slowly in the plasma (fig. 2). Systemic toxicity and tachyphylaxis were observed when lignocaine was administered as a continuous extradural infusion (Sjogren and Wright, 1972). Bromage (1975) found that, in low concentration, bupivacaine produced less motor block, for any given degree of sensory block, than did etidocaine, amethocaine and lignocaine. The evidence suggests that bupivacaine is the agent of choice for postoperative use.

It may be thought that the addition of adrenaline to the local anaesthetic could be beneficial on the grounds that the risk of systemic toxicity would be reduced, but in fact plasma concentrations are not significantly decreased (Wahba, Don and Craig, 1975). Hypotension is more marked when the local anaesthetic solution

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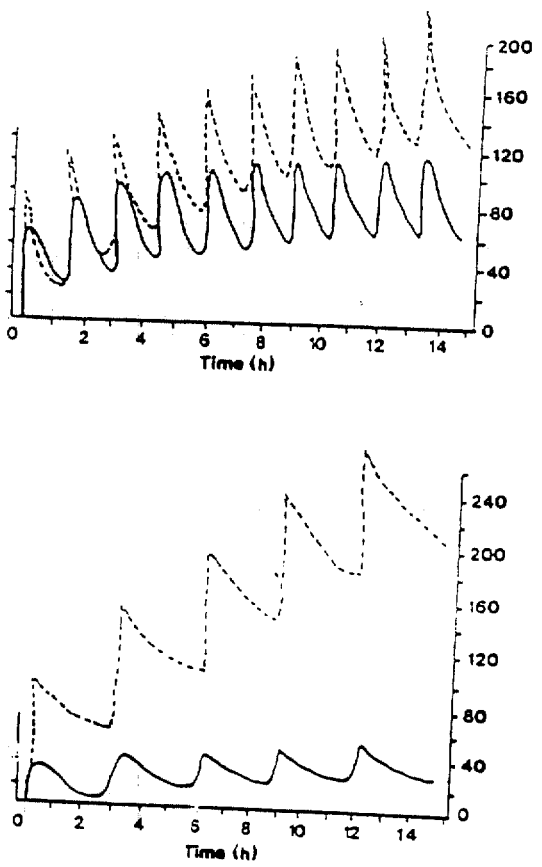

FIG. 2. Predicted local and systemic accumulation of lignocaine during multiple extradural injections at 1.5-h intervals (upper graph), and of etidocaine at 3-h intervals (lower graph). Continuous line: arterial plasma concentration. Broken line: amount unabsorbed (percentage of the initial dose). (From Tucker and Mather (1975).)

contains adrenaline (Kennedy, 1966) and in view of the possibility that the prolonged infusion of adrenaline might cause ischaemic nerve damage, its use should be avoided.

Anticoagulation

The extradural space is vascular and since the insertion of a catheter is a "blind" procedure, occasional damage to blood vessels is inevitable. Haemorrhage from such damage cannot be controlled directly and although this is of little clinical consequence in the presence of normal clotting mechanisms, it does have implications for patients receiving anticoagulants. Some will be receiving oral anticoagulants for pre-existing cardiovascular disease. Others may require heparinization during arterial procedures, and the administration of low-dose heparin for prophylaxis against deep vein thrombosis after major surgery is now widely practised.

There has been understandable reluctance to insert extradural catheters to patients in any of these categories, but there is evidence that the procedure may be safe in certain circumstances. Rao and El-Etr (1981) reported 3164 patients who received continuous extradural anaesthesia before the administration of heparin during operation. The activated clotting time was approximately twice the preoperative value, but the authors found no evidence of extradural haematoma. Odoom and Sih (1983) reported 950 patients who received intraoperative heparin after insertion of the catheter, but these patients had also received oral anticoagulants before operation and their clotting mechanisms were abnormal at the time of catheter insertion (mean thrombotest: 19%; normal range: 70–130%). None developed neurological complications.

Although these studies appear to demonstrate the relative safety of heparinization after insertion of an extradural catheter, the authors stress the importance of controlling the degree of heparinization through the activated clotting time, and they regard thrombocytopaenia, prior heparinization, long-term aspirin therapy and a thrombotest below 10% as contraindications. The management of the individual case depends on the balance between factors contributing to the thrombosis risk and the benefits likley to be conferred by the extradural. For major abdominal operations, the present author inserts the catheter before surgery and does not institute low-dose heparin therapy until 6–8 h after operation.

Bolus Injection

Intermittent injection, or topping-up, is the traditional method of prolonging analgesia into the postoperative period. It is satisfactory if the increments are given on a regular, timed basis with the objective of preventing pain. It is much less satisfactory if given on demand, since this implies that the presence of pain is the indication for a top-up. If the top-ups are to be given by nursing or medical staff, the patient nursed in an intensive therapy unit or a high dependency area stands a better chance of receiving prompt attention, and the method is therefore inappropriate for the majority of patients who return to a general

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surgical ward. Early attempts were made to overcome this difficulty by the use of a mechanical injection device which delivered a predetermined dose of lignocaine or mepivacaine at regular intervals (Cox and Spoerel, 1964). More recently, Scott, Schweitzer and Thorn (1982) used a specially designed roller pump to deliver 6–10-ml doses of 0.5% bupivacaine 2 hourly. They found this provided good analgesia over 24 h. In the same study, another group of patients received 0.5% bupivacaine 4–5 ml given every 1–2 h by nurses. It was not possible to continue this regimen overnight and, even over the 8 h for which data were available, good analgesia was obtained in less than half the patients, because the nurses could not give the injections frequently enough. Schweitzer (personal communication) subsequently found that when 2-ml doses of 0.5% bupivacaine were delivered hourly through the pump, good analgesia was obtained.

Continuous Infusion

It was soon appreciated that it should be possible to maintain a constant state of analgesia by administering local anaesthetic by infusion. The method has the advantage that syringe drivers and variable rate infusion pumps are standard equipment and readily available, and the maintenance and monitoring is not labour-intensive.

Low volume/high concentration. Early workers (Spoerel, Thomas and Gerula, 1970) used standard concentrations of drug, 1 or 2% lignocaine or mepivacaine, at a rate of 5–12 ml h^{-1} after thoracic and abdominal surgery. They continued the infusion for an average of 3 days and claimed good results in 77% of cases. Pflug and colleagues 1974) achieved excellent analgesia after upper abdominal surgery, infusing 0.5% bupivacaine at a rate of 3–5 ml h^{-1}. They reduced the concentration to 0.25% on the 3rd day, but kept the rate constant. It would seem that further reduction of the rate results in variable blocks. This is because an infused solution, unlike a bolus injection, has minimal injection pressure to propel it away from the catheter tip, and an increase in drug concentration is insufficient to compensate for this lack of physical spread. Renck and colleagues (1976) gave 1% bupicavacaine at a rate of 0.75 ml h^{-1} after thoracic surgery and failed to achieve reliable analgesia.

High volume/low concentration. In the author's opinion, this is the method of choice. It involves the infusion of 0.1–0.125% bupivacaine 16–24 ml h^{-1}. Assuming that the catheter tip is appropriately placed, there is rarely any difficulty in achieving adequate spread of analgesia, motor block is less intense and drowsiness, a systemic side effect of bupivacaine, is less common than with the 0.25% solution (Griffiths, Diamond and Cameron, 1975). The accidental administration of excessive volume is likely to result in less severe toxic effects if a solution of low concentration is used. Hypotension is less common with an infusion than with a bolus technique (Scott, Schweitzer and Thorn, 1982), and infusions have been used safely on general surgical wards after abdominal and thoracic surgery (Ross, Clarke and Armitage, 1980). Unfortunately, local anaesthetics are not yet commercially available in low concentration and large volume, and suitable solutions have therefore to be specially prepared.

Practical aspects of management

Filters. Extradural filters are designed to prevent the passage of bacteria and are capable of excluding particles as small as 0.22 μm. When fluid is infused at a rate of, for example, 20 ml h^{-1}, particles accumulate rapidly on the filter and its resistance increases. The resulting increase in pressure between the filter and the pump may cause separation of the infusion line at a junction point. This problem can be overcome by changing the filter every 12 h, but it is the author's practice to insert a blood filter between the pack of local anaesthetic solution and the administration set. This removes the larger particles, and the bacterial filter usually lasts for the duration of the infusion.

The pump. Resistance in an infusion line is high, since fluid has to pass not only through the filter, but also along the narrow 90-cm long extradural catheter. The pump must therefore be powerful. It should also be quiet and accurate and give warning when solution is flowing faster or slower than the selected rate. Nursing staff should have easy access to an illustrated chart showing the common causes of, and remedies for, pump malfunction.

Bolus during an infusion. Although an infusion of 0.1% bupivacaine 20 ml h^{-1} will often give satisfactory analgesia for 2–3 days without the need for adjustment, the block will sometimes regress. Setting the pump at a higher rate will not correct a regressing block unless a bolus is first

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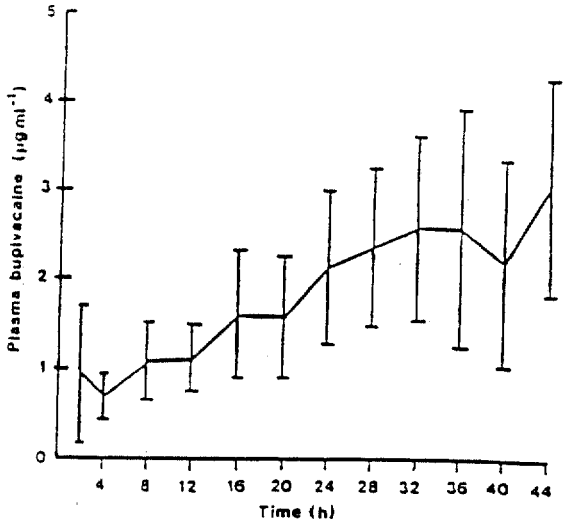

FIG. 3. Mean plasma bupivacaine concentrations (+SD) in nine patients kept free of pain with extradural infusions of 0.125% bupivacaine after abdominal or thoraco-abdominal surgery.

given to re-establish the required area of analgesia. A "bolus" can be given without breaching the infusion line by running the pump at 90 drops min^{-1}. A standard administration set delivers 4.5 ml during 1 min at this rate, and volumes of 4.5–9 ml are usually required. Griffiths, Diamond and Cameron (1975) infused 0.125% or 0.25% bupivacaine at 15 ml h^{-1} after thoracic surgery and achieved satisfactory analgesia in five of seven patients. However, in spite of this generous rate, a mean of five bolus doses (5–8 ml of 0.25% bupivacaine) was required during the 48-h period studied.

A regressing block may not be the only reason for a bolus being required. Gjessing and Tomlin (1979) have suggested that the intensity of postoperative pain is not constant, but cyclical. They identified four peaks (occurring at 4, 10, 14 and 18 h) during an 18-h period in women undergoing total hip replacement, and two peaks (at 6–8 and 12–16 h) in men having the same operation. They also suggested that patterns of pain may be different after different types of surgery.

Motor block. Weakness or paralysis of the lower limb muscles is not usually produced when nerves are subjected to intermittent bolus injections of local anaesthetic, but it is quite common, even with dilute solutions, during the course of an infusion. This is presumably because the large, resistant motor fibres eventually become affected after they have been bathed constantly for several hours. The patient should be warned of this possibility at the preoperative visit and assured that recovery of function occurs within 2 or 3 h after reduction of the infusion rate. Similarly, surgeons should be aware that symptoms do not necessarily betoken a neurological or vascular disaster.

Additional sedation. Since postoperative extradural block is performed to provide better pain control at the operation site than conventional opioid analgesia, it is sometimes felt that *any* discomfort indicates a failure of the block and that *no* opioid should be necessary. This attitude fails to take into account the fact that there are some sources of discomfort which the extradural is intrinsically incapable of relieving, or which lie outside its range. These include anxiety about the recent operation, sleeplessness as a result of noise and the need for frequent postoperative observations, and shoulder tip pain which is thought to result from pneumoperitoneum. The administration of occasional, small doses of opioid under these circumstances, far from devaluing the block, greatly enhances it and gives excellent overall results.

Plasma concentrations. The extradural infusion of a local anaesthetic drug over a long period may lead to potentially toxic plasma concentrations. Ross, Clarke and Armitage (1980) followed intraoperative boluses of 0.25% bupivacaine with the postoperative infusion of 0.125%, and measured venous plasma concentrations at 4-h intervals for 44 h. The infusion rate was adjusted so that patients were pain-free and side effects were minimal, and it varied between 12 and 36 ml h^{-1} with an average of 20 ml h^{-1}. This regimen produced mean venous bupivacaine concentrations of 3 μg ml^{-1} (range 1.3–4.9 μg ml^{-1}) after 44 h (fig. 3). Patients were assessed clinically when the blood samples were taken and no signs of cerebral toxicity were detected, although one patient became euphoric. Reynolds (1971) has stated that even mild toxic symptoms are unlikely to appear at plasma concentrations less than 1.6 μg ml^{-1}. Unfortunately, this figure has sometimes subsequently been taken to represent "the toxic level" for bupivacaine and this is

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clearly an incorrect interpretation of the original statement.

The appearance of toxic symptoms depends on factors other than the plasma concentration. Scott (1975) administered i.v. bupivacaine at different rates to conscious volunteers and found that symptoms appeared at low plasma concentrations when the infusion rate was high. The rate of increase in concentration tends to be very slow when dilute bupivacaine is given by extradural infusion (fig. 3) and this may explain why no toxic effects were observed in Ross's patients. A further explanation may lie in the fact that α-globulin, the protein to which bupivacaine binds, increases after surgery and may match the increase in plasma bupivacaine concentration. The unbound fraction of the drug may remain virtually constant under these circumstances.

Although venous plasma concentrations are often measured, it is the arterial concentration which is more closely related to the development of toxic symptoms. Griffiths, Diamond and Cameron (1975) followed intraoperative injections of 0.5% bupivacaine (with adrenaline) 6–8 ml with a postoperative infusion of 0.125% bupivacaine at a mean rate of 13 ml h^{-1} and they supplemented this, as required, with boluses of 0.25% bupivacaine 5–8 ml. They took arterial samples and found a mean value of 2 μg ml^{-1} (range 0.93–3.76 μg ml^{-1}).

Effects on the cardiovascular system

Some degree of hypotension almost invariably accompanies extradural block and it is fear of its consequences and, perhaps, uncertainty about its significance which deters many from prolonging the block after operation.

The normal patient. The sympathetic denervation caused by extradural block results in peripheral arterial and venous dilatation. The latter gives rise to decreased venous return and, if the affected veins are below the level of the right atrium, cardiac output may be reduced. Mean arterial pressure decreases in proportion to the decrease in cardiac output and peripheral vascular resistance. As a consequence, coronary blood flow is reduced, but fortunately this is accompanied by a similar reduction in the myocardial oxygen requirement.

Sympathetic block below T4 results in dilatation of the splanchnic, pelvic and lower limb vessels, and various mechanisms come into play to compensate for this. Vasoconstriction above the level of the block occurs, mediated by unblocked sympathetic vasoconstrictor fibres (T1–4), and release of catecholamines may be mediated by any unblocked fibres to the adrenal medulla. Unblocked cardiac sympathetic fibres mediate an increase in myocardial contractility and heart rate. In addition, vascular tone below the level of the block may return because of autoregulation of flow by precapillary sphincters (Granger and Guyton, 1969) and it has been suggested that low plasma concentrations of local anaesthetic drug cause cardiovascular stimulation (Bonica, Berges and Morikawa, 1970).

Sympathetic block above T4 reduces or abolishes compensatory vasoconstriction in the head, neck and upper limb as well as the ability of the cardiac sympathetic fibres to stimulate the heart. It is therefore surprising that the cardiovascular changes noted with upper thoracic blocks have been relatively modest. McLean and colleagues (1967) found a 15–20% reduction in cardiac output and an increase in central venous pressure (CVP). Bonica and colleagues (1971, 1972) also demonstrated an increase in CVP and found that mean arterial pressure and peripheral resistance decreased by about 20%, but they observed no change in cardiac output or heart rate.

Relation of sympathetic to sensory block. There is disagreement as to whether or not a sympathetic block extends higher or lower than a somatic block. Bonica, Berges and Morikawa (1970) were unable to demonstrate any sympathetic block in two of eight patients, even though all had skin hypoalgesia. On the other hand, Horner's syndrome is occasionally seen following an extradural where the analgesia is confined to the lower thoracic segments. Wugmeister and Hehre (1967) concluded that sympathetic and somatic block extended to the same level because loss of pin prick and cold sensation affected the same area. The above evidence suggests that there is wide variation between patients. The practical consequence is that the incidence and severity of hypotension are also likely to vary.

Patients in pain. The effect of extradural block on the cardiovascular system of the postoperative patient was studied by Sjogren and Wright (1972). They maintained analgesia with 0.4% lignocaine infused overnight at a rate of 30–45 ml h^{-1} and took cardiovascular measurements before discontinuing the infusion. The measurements were repeated when the block had worn off and the

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patients were in pain, and again when the infusion had been re-commenced and the patients were pain free. The measurements taken when patients were in pain showed an increase in cardiac output, heart rate and mean arterial pressure and a decrease in stroke volume and skin blood flow—changes which indicated a strong sympathetic stimulation of the circulation. Re-establishment of analgesia was followed by a return to the values obtained before pain had been allowed to occur. Holmdahl and colleagues (1972) gave continuous extradural analgesia after cholecystectomy and found that hypotension was less of a problem when the catheter was placed in the thoracic rather than the lumbar region.

Effects on the respiratory system

Patients who have undergone major thoracic and abdominal surgery are prone to respiratory infection because pain prevents them from breathing deeply and coughing effectively. The abolition of pain by continuous extradural block might be expected to improve pulmonary function, and various aspects of the subject have been investigated.

The normal patient. Extradural block has very little effect on respiratory parameters in the normal patient. A block to the level of T4 had no significant effect on functional residual capacity (FRC), expiratory reserve volume (ERV) or inspiratory capacity. However, a block extending higher than T4 caused a decrease in ERV of 12–36% (Freund et al., 1967; Sjogren and Wright, 1972; Takasaki and Takahashi, 1980). Arterial blood-gas tensions showed little change (Ward et al., 1965). Extradural block should theoretically allow unopposed vagal tone to cause bronchoconstriction, but no such change was found, even in the presence of high blocks, in three separate studies (Sjogren and Wright, 1972; Wahba et al., 1972; Takasaki and Takahashi, 1980) and Bromage (1978) quoted patients in whom extradural block has actually proved therapeutic in status asthmaticus.

The ability to cough effectively requires co-ordinated, powerful contraction of the diaphragm and muscles of the abdominal wall. Motor block to the latter occurs during upper thoracic spinal anaesthesia (Egbert, Tamersoy and Deas, 1961), but extradural block has minimal effect, perhaps because motor block cannot be shown to extend as high as sensory block (Freund et al., 1967).

Patients in pain. The effects of extradural block are not as dramatic as might be expected. There is sometimes improvement in lung volume measurements such as FRC and vital capacity (VC), but results are inconsistent and improvement is limited to reduction of deterioration rather than restoration of preoperative values (Simpson et al., 1961; Wahba, Don and Craig, 1975). However, the greatest benefit is seen in patients with chronic obstructive airways disease after upper abdominal surgery. Extradural block improved the VC from 37% of the preoperative value to 90% in these patients (Simpson et al., 1961). The effect on arterial blood-gas tensions is even less impressive. Patients are relatively hypoxaemic on the 1st day after upper abdominal surgery, whether they have received extradural analgesia or not (Muneyuki et al., 1968; Spence, Smith and Harris, 1968; Sjogren and Wright, 1972; Pflug et al., 1974; Spence and Logan, 1975), and when pain is relieved by extradural block, no improvement in Pa_{O_2} is seen (Muneyuki et al., 1968; Drummond and Littlewood, 1977).

There is, however, a marked improvement in the ability to cough. Sjogren and Wright (1972) studied patients receiving thoracic and lumbar extradural analgesia after gall bladder surgery and found that the peak expiratory flow rate increased by 64% and 90%, although these improved values were still only approximately one-half those obtained before operation.

It is not easy to find clear-cut evidence that extradural block causes significant improvement in respiratory function or reduces the incidence of postoperative chest infection in normal patients. However, since extradural analgesia improves the ability to cough, and increases VC to a greater extent in patients with chronic obstructive airways disease, it probably conveys most benefit to this group of patients, who most need it.

Other effects

Lower limb blood flow. Extradural block increases blood flow to the lower limb (Bonica, Berges and Morikawa, 1970), the skin receiving most of the increase (Cousins and Wright, 1971). Therefore flow must increase through the long and short saphenous veins, which drain the skin, and also through the femoral and iliac veins. Since thrombi in the latter vessels are most likely to result in pulmonary embolism (PE) (Modig et al., 1983), extradural block may be expected to play an

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important part in the prevention of deep vein thrombosis (DVT) and PE.

Total hip replacement carries a high incidence of DVT, and PE is the commonest cause of immediate postoperative death after this procedure. Modig and colleagues (1983) studied patients in two groups, one of which received extradural anaesthesia for the operation and extradural analgesia after operation, and the other in which general anaesthesia was followed by postoperative opioid analgesia. The incidence of DVT was reduced significantly in the extradural patients. Lung scans were used to detect PE, which was found in 33% of the general anaesthesia/opioid group, but in only 10% of the extradural group.

Gastric emptying and intestinal motility. Opioids delay gastric emptying and reduce intestinal motility (Nimmo et al., 1978). Extradural block, by eliminating or greatly reducing the need for opioids, avoids these problems, but it also has a direct effect on the bowel, mediated by the sympathetic system. Increased sympathetic activity inhibits bowel contractility and predisposes to distension. This in turn increases tension, and hence the likelihood of rupture, at sites of anastomosis. Extradural block, by reducing sympathetic activity, reverses these trends; paralytic ileus is minimized and the nasogastric tube, which contributes to inefficient coughing and expectoration, can be removed early. Peristalsis is sometimes very active and diarrhoea occasionally persists into the postoperative period. The author has in one instance had to discontinue an infusion for this reason. However, the overall benefits are considerable (Aitkenhead, 1984).

Monitoring

It is important, whether the patient is nursed in an intensive therapy unit, a high-dependency area or a general ward, that the nursing and medical staff are familiar with the behaviour and management of patients receiving extradural analgesia, and the ways in which they differ from those receiving opioids. Systolic arterial pressure remains low for the first 12–24 h, but usually increases without specific therapy on the 1st day after operation. Ephedrine is occasionally required. Fears that the relative hypotension and complete analgesia may mask abdominal signs, causing delay in diagnosis of surgical complications, are groundless. Patients suffering from haemorrhage or an anastomotic leak look and feel unwell, in marked contrast to those running a normal postoperative course with extradural analgesia.

It is possible to check the infusion rate and the integrity of the line without disturbing the patient, and this should be done hourly. The adequacy of the block should be assessed every 4 h during the day. The patient should not only be free from pain at rest, but should be able to lift his head off the pillow from the 45° sitting position, take a deep breath, and cough, without pain. If any of these tests cause discomfort, a bolus should be given and the tests repeated after 15 min. The patient should be able to move both lower limbs. If a patient has a stable and easily controlled block, it is unnecessary to disturb him for assessments during the night. However, an early assessment is essential the following morning so that any adjustments can be effective before the arrival of the physiotherapist.

OTHER BLOCKS

It is not always necessary or desirable for a block to extend over a wide area, involve the sympathetic system or act bilaterally. Many blocks are capable of providing excellent analgesia, with minimal systemic effect, over a limited field, but although they have been used satisfactorily as single-shot techniques, they have not gained widespread acceptance for prolonged postoperative analgesia because it has been assumed that they must be repeated every few hours. This assumption is not necessarily correct, because it has been found that a catheter can be inserted through the fascial sheaths which surround neurovascular compartments. The sheaths extend peripherally and invest individual nerves, and Winnie, Ramamurthy and Durrani (1973) have shown that local anaesthetic solution injected through the sheath of, for example, the femoral nerve can be made to track centrally in the neurovascular compartment so that it affects the obturator nerve and lateral cutaneous nerve of the thigh in addition.

Paravertebral

Eason and Wyatt (1979) used continuous paravertebral block for analgesia after thoracotomy. They located the paravertebral space by loss of resistance to injection of air, and passed an end-hole extradural catheter into the space through a Tuohy needle. They found that at least four segments were affected by a single, 15-ml injection of 0.375% bupivacaine. The advantages

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claimed for the technique are that it can be performed comparatively easily in patients with kyphoscoliosis and other distortions of the bony spine, and hypotension is minimal since sympathetic block is unilateral.

Intercostal

Murphy (1983) inserted an extradural catheter through a Tuohy needle to an intercostal space in 25 patients who had undergone cholecystectomy through a Kocher incision. Only two patients required any supplementary opioid on the 1st day after operation, but on the 2nd this figure had increased to six. Peak flow measurements were made on the 2nd day before and after an injection of bupivacaine. A mean improvement of 37% was recorded 30–40 min after the top-up.

Inguinal paravascular (three-in-one)

Rosenblatt (1980) used this technique for postoperative analgesia after knee surgery in a 13-yr-old patient suffering from cystic fibrosis. An 18-gauge, 5-cm Teflon catheter was threaded over a 22-gauge, 8.75-cm spinal needle. When the needle had entered the fascial sheath surrounding the femoral nerve, local anaesthetic was injected to distend the sheath and facilitate passage of the catheter. On the 1st day after operation, 0.75% bupivacaine 15 ml was injected every 6 h. On the 2nd day, 0.5% bupivacaine was infused at 4 ml h^{-1} and continued for 24 h.

Sciatic

Smith, Fischer and Scott (1984) described a technique for continuous sciatic nerve block which they used first to relieve the pain of an ischaemic foot and later, with an inguinal paravascular block, for postoperative analgesia following below-knee amputation. They located the sciatic nerve with a 16-gauge Medicut cannula connected to a nerve stimulator. After the injection of 2% lignocaine 8 ml to open up the neurovascular space, a 16-gauge extradural catheter was passed easily into it. Bupivacaine 0.5% was infused at a rate of 6 ml h^{-1} through both the femoral and sciatic catheters for 48 h, and the patient was completely free of pain.

Axillary

Although the brachial plexus can be blocked at various points along its course, the axillary approach is the most suitable for insertion of a cannula. A 20- or 22-gauge i.v. cannula is recommended and it is less likely to be dislodged during an injection if an extension set is interposed between it and the syringe or pump (Hughes and Desgrand, 1986). Rosenblatt, Pepitone-Rockwell and McKillop (1979) performed an axillary block for the repair of injured tendons in the hand of a 15-yr-old boy. They infused 0.25% bupivacaine at a rate of 10 ml h^{-1} for 2 days and the patient required no narcotic agents. Rosenblatt recommends that cannulae should be sutured in position if they are to be used for postoperative analgesia. The application of an occlusive, transparent, adhesive drape probably immobilizes the cannula just as well and has the advantage that the puncture site and surrounding skin can be inspected easily for signs of infection.

CONCLUSION

"Slapping the patient on the face and telling him or her that 'it's all over' is a complete inversion of the truth. As far as the patient is concerned, it is just the beginning" (Berry, 1979).

There is irrefutable evidence that patients suffer considerable pain after operation (Donald, 1976; Foott, 1978). Suitable drugs, equipment and techniques are available. The problem is essentially the practical one of how to provide analgesia safely, simply and continuously for 2–3 days. The solution depends as much on organization and attitudes as on techniques. One reason for the inadequacy of conventional opioid analgesia is that it is prescribed by members of one profession and administered by members of another. The result is that neither doctors nor nurses take full responsibility for it. Analgesia should be the responsibility of a small number of designated individuals and its effectiveness should be their main concern. A second, related, requirement is that the experience and availability of staff must be taken into account when the method of local anaesthesia is being selected, so that it can be easily and safely managed. This factor may determine whether analgesia is best administered by intermittent injections or by infusion. Last, there is little prospect of patients enjoying complete, continuous analgesia as long as their attendant staff think and talk in terms of pain relief. Analgesia should be given with the intention of preventing pain rather than relieving it.

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BUPIVACAINE INFUSION FOR ILIAC CREST DONOR SITES

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Pain is common after a bone graft has been taken from the iliac crest (Kurz, Garfin and Booth 1989). Local wound infiltration with bupivacaine at closure is effective, but relief lasts for only four hours (Todd and Reed 1991). We report a method of infusing bupivacaine which gives effective and lasting analgesia.

Patients and methods. Patients requiring iliac crest grafts were randomly selected to receive either bupivacaine infiltration at wound closure or bupivacaine infusion postoperatively.

For the infusion group, a fine-bore catheter was tunnelled into the wound between muscle and fat and used to infiltrate 0.5% bupivacaine solution at a rate of 5 ml/hour for 48 hours by a syringe driver. A drain was also used; drain and catheter were removed after two days.

For the infiltration group 10 ml of 0.5% bupivacaine solution was injected into the soft tissues by needle and syringe immediately before skin closure. A drain was used.

At 24 hours postoperatively, patients graded their pain on a visual analogue scale (Banos et al 1989; Campbell and Lewis 1990), taking zero as no pain and 10 as worst imaginable pain.

There were nine patients in the infusion group and seven in the infiltration group. The results were analysed by Student's *t*-test.

Results. All patients could distinguish iliac crest pain from that of other operation sites. The average pain score in the infusion group was 2.2 while that in the control group was 5.4 ($p < 0.01$).

Discussion. We have confirmed that infusion is a more effective method of pain relief than single infiltration. The technique is simple, but we recommend that the catheter is placed subcutaneously to reduce intraosseous absorption and the risk of toxicity (Gilman et al 1990).

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Chemical Stability of Meropenem in Portable Infusion Pumps

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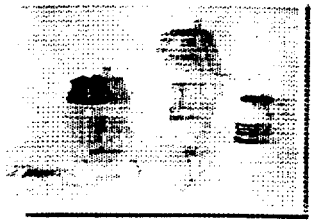
OBJECTIVES

The purpose of this study was to obtain documentation on the stability and compatibility of meropenem solutions prepared with sodium chloride 0.9% (NS) in two different portable infusion pumps, Intermate® and Home Pump® Eclipse.

STUDY DESIGN

Solutions containing 5, 10 and 20 mg/mL of meropenem were prepared by constituting 1.0 g vials of Meronem® with 20 ml of WFI and further diluting with NS. The solutions were then filled in Intermate®, 105 mL and Home Pump® Eclipse, 100 mL pumps which were stored at 4°C and 25°C. Analyses were carried out initially and after 6, 24 and 48 h storage at 25°C and after 24, 48, 72 and 96 h at 4°C.



ANALYTICAL METHOD

Samples were inspected visually and the pH was recorded. The content of meropenem was determined by a reversed phase HPLC-method. The stability indicating ability of the method is shown in Fig. 1. The method precision was ≤ 0.5%.

Column:	Hichrom HiRPB, 5um particles, 3.2 x 150 mm
Mobile phase:	Acetonitrile : Methanol : Water : 0.1 M TBAH in methanol, (30 : 20 : 170 : 3), pH adjusted to 7.5 with 0.1 M H_3PO_4
Flow rate:	0.65 mL/min
Detection:	UV at 300 nm

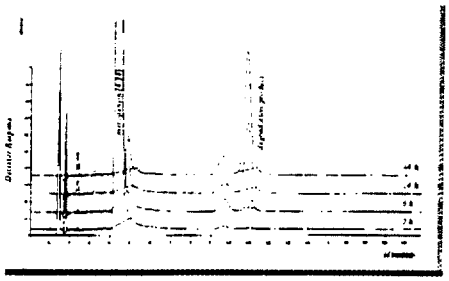


Fig. 1. Chromatograms of meropenem 20 mg/mL solution stored at 25°C.

RESULTS

The stability of meropenem in NS was found to be strongly dependent on both storage temperature and drug concentration. See Table 1 and Fig. 2.
Only minor changes in pH were noted, but the colour of the solutions changed gradually from almost colourless to strongly yellow depending on potency and storage temperature.
No significant difference in stability for solutions stored in the different reservoirs could be seen.

Table 1. Chemical stability

Conc.	$t_{90\%}^{4°C}$	$t_{90\%}^{25°C}$
5 mg/mL	>96 h	26 h
10 mg/mL	96 h	20 h
20 mg/mL	72 h	14 h

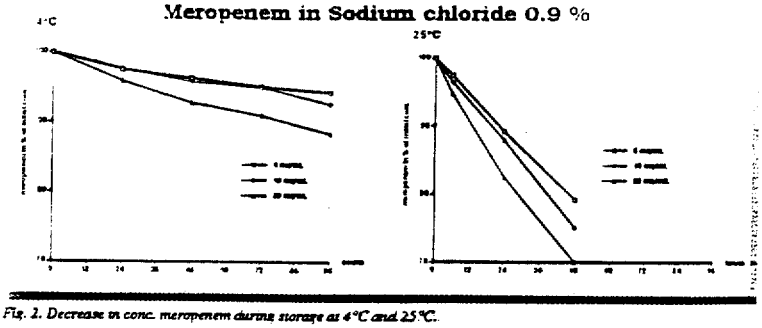


Fig. 2. Decrease in conc. meropenem during storage at 4°C and 25°C.

CONCLUSION

At the estimation of the utility time the warming-up period of 4 - 6 h required to achieve the nominal flow-rate of the pump devices must be considered. Estimated utility times, if a maximum of 10% degradation is accepted, are given in Table 2. When doses of 2 g are needed the use of larger volume pumps that allows concentrations of ≤10 mg/mL are recommended to obtain a better stability. Administration time exceeding 1 hour is to be avoided for therapeutic reasons.

In conclusion, despite relatively short stability, meropenem can be stored and administrated in portable infusion pump systems. Especially for patients suffering from e.g. cystic fibrosis this offers the advantages of home i.v. antibiotic therapy.

Table 2. Utility time

Conc.	Refrig. (+ 4°C)	RT (+ 25°C)	Utility time
5 mg/mL	96 h	6 h	102 h
10 mg/mL	72 h	6 h	78 h
20 mg/mL	24 h	6 h	30 h

REGIONAL ANESTHESIA AND PAIN MANAGEMENT
SECTION EDITOR
DENISE J. WEDEL

BRIEF COMMUNICATION

Postoperative Patient-Controlled Local Anesthetic Administration at Home

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For most day-surgery patients, postoperative pain can be managed adequately at home with conventional oral analgesics, such as paracetamol, nonsteroidal antiinflammatory drugs (NSAIDs), and weak opioids (codeine, dextropropoxyphene). However, for moderate to severe pain, this treatment may be inadequate (1–4). Our recent study of 1035 patients undergoing a variety of day-surgical procedures (5) showed that approximately 30% of patients experienced moderate to severe pain at home. Severe pain was experienced by many patients who underwent the following surgeries: orthopedic (knee, shoulder, iliac bone graft, maxillofacial, halux valgus), breast augmentation, inguinal hernia, and varicose veins. We describe a technique using an elastometric balloon pump, which allows the patient to self-administer local anesthetic analgesia at home. This study was undertaken to evaluate the safety and applicability of the technique in a wide range of surgical procedures.

Methods

Ethics committee approval was obtained for this preliminary prospective study of 70 patients undergoing a variety of day-surgical procedures (Table 1). Informed consent was obtained from each patient at the time of preoperative evaluation. The technique involves the placement of a multihole, thin (22-gauge) epidural catheter (B. Braun, Melsungen, Germany) subcutaneously into the surgical wound, subacromially, intraarticularly, or in the axillary brachial plexus sheath (Table 1). The catheter was tunneled 4–5 cm subcutaneously by the surgeon and firmly secured on the skin by using sterile tape (Proxi-Strip®; Johnson & Johnson, New Brunswick, NJ). Axillary brachial plexus catheters were placed and secured in position by anesthesiologists. The catheters were introduced 3–5 cm within the sheath and secured to the skin by using transparent dressing and tape.

These catheters were used for surgery and postoperative analgesia. They could be secured in less than 5 min. Using aseptic technique, the catheters were connected to a 50- or 100-mL elastometric (balloon) pump (Fig. 1) with the appropriate concentration and volume of local anesthetic drug (Home pump®; I-Flow Corporation, Lake Forest, CA). The balloon pump was filled with a volume of local anesthetic to provide 10 doses for postoperative pain management. The Home pump® is designed and approved to deliver intravenous antibiotics and cytostatic drugs and costs approximately $15–$20. Postoperatively, when the patient feels pain, the local anesthetic infusion is started by opening the clamp (Fig. 2a). The patient stops the infusion by closing the clamp after the prescribed time (usually 6 min) or earlier if pain relief is adequate (Fig. 2b). When the patient no longer requires analgesia, he or she removes the tape, pulls out the catheter, and discards the pump. In most cases, the patient self-administers the first dose in the postanesthesia care unit (PACU).

Bupivacaine 0.125% was used in brachial plexus catheters; in all other catheters, a 0.25% concentration was used. The 0.125% solution was used to reduce or avoid the risk of possible injury due to excessive motor block. The maximal volume of local anesthetic allowed for each administration was 2.5 mL for maxillofacial surgery, 5–10 mL for surgical wounds, and 10 mL for the remaining procedures. An appropriate pump (50 or 100 mL) filled with local anesthetic to provide 10 doses at home was given to the patient before discharge. The patient was instructed to avoid using the pump more than once every hour.

Before using the technique at home, it was evaluated in 35 inpatients. These patients were given instructions, which were later provided in similar form

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Table 1. Use of Patient-Controlled Regional Analgesia After Various Surgical Operations

Diagnosis	No. of patients	Treatment at hospital / home		Site of catheter placement
Hand surgery				
Arthroplasty	8	7	1	Brachial plexus sheath
Arthrodesis	2	2	—	Surgical wound
Arthroscopy	6	2	4	Brachial plexus sheath
Soft tissue injury	13	5	8	Surgical wound (n = 7) Plexus sheath (n = 6)
Tendon surgery	10	5	5	Surgical wound (n = 6) Plexus sheath (n = 4)
Radius fracture	2	1	1	Surgical wound
Orthopedic surgery				
Arthroscopic subacromial decompression	14	4	10	Subacromial
Shoulder arthroscopy (Bankart)	3	—	3	Intraarticular
Knee surgery	1	1	—	Surgical wound
Plastic surgery				
Breast augmentation	2	—	2	Surgical wound.
Bone graft (iliac crest)	4	4	—	Near iliac crest (supraperiosteal)
Lymph node removal	2	2	—	Surgical wound
Maxillofacial/oral surgery				
Mandibular reconstruction	1	1	—	Supraperiosteal
Multiple teeth extraction	1	1	—	Subalveolar
Arthroplasty (temporomandibular joint)	1	—	1	Supraperiosteal
Total	70	35	35	

In plexus catheters, 0.125% bupivacaine was administered; in all other catheters, the concentration was 0.25%. The volumes of bupivacaine were as follows: maxillofacial surgery 2.5 mL, wound infiltration 5–10 mL, shoulder and knee surgery 10 mL.

Figure 1. Use of the pump (arrow) in the patient's home.

to the home patients. The written instructions to the patients included information about: a) symptoms of local anesthetic overdosage; b) protection of the catheter and pump system during washing, showering, etc.; c) catheter removal before discarding the pump; and d) how to contact nurses and anesthesiologists.

Additionally, the patient was given a form on which to record the following: pain intensity on a verbal scale (severe, moderate, mild, none) after each treatment, the clock time of each administration, the total number of times a local anesthetic was self-administered, use of "rescue" analgesic tablets (NSAIDs, acetaminophen/codeine, or acetaminophen/dextropropoxyphene), technical problems with the pump, and overall satisfaction/dissatisfaction (excellent, adequate, poor) with analgesia. Onset of analgesia was assessed from first administration of local anesthetic in the PACU and from patient comments. The duration of analgesia was evaluated from the clock time at each administration. The patient was given a stamped, self-addressed envelope in which to return the completed questionnaire within 2–3 days after surgery. A nurse made a follow-up call the day after surgery and inquired about the patient's general condition, pump function, satisfaction/dissatisfaction with analgesia, and suggestions for improving technique.

Results

Seventy patients received analgesia by self-administration of local anesthetic solution on demand. All patients (100%) returned the completed questionnaire. The results are based on data from inpatients, PACU, and patient comments from the questionnaire. None of the patients had any problems using the pump. The onset of analgesia was usually within 5 min but was longer (up to 15 min) in patients with brachial plexus and subacromial catheters. The duration of analgesia after each administration of local anesthetic varied from 2 to 8 h. Most patients required two to four administrations.

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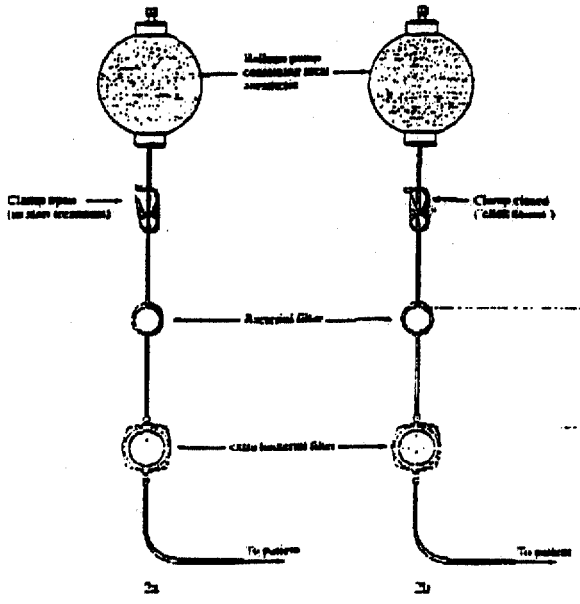

Figure 2. Self-administration of the local anesthetic solution by a patient. On opening the clamp (a), the solution starts running into the catheter. After the prescribed time (usually 6 min), the patient closes the clamp (confirmed by a clicking sound) to stop the infusion (b). The patient is encouraged to use a timer as a reminder to close the clamp.

Six patients did not use the pump at home because the first dose of local anesthetic in the hospital provided prolonged pain relief; these patients were not included in the data analysis. Pain relief was considered good to excellent by 57 (89%) patients, adequate by 4 (6%) patients, and poor by 3 (5%) patients. However, 4 patients complained that the total amount of medication was insufficient (all had received a 50-mL pump). Except for the above-mentioned 3 patients with poor analgesia and 4 patients who received an insufficient dose of local anesthetic, none required analgesic tablets. Follow-up calls confirmed that the technique was generally perceived as simple and effective. No technical problems were encountered. None of the patients reported any symptoms of local anesthetic toxicity. One patient commented that the act of removing the catheter was unpleasant. One patient with opioid dependency required unusually large doses (three doses of 20 mL 0.25% bupivacaine subacromially during a period of 1.5 h). Although this patient was asymptomatic, a bupivacaine level was drawn approximately 2 h after the first dose and was found to be 1.15 μmol/L, which is well below toxic levels.

Discussion

Effective management of pain may make the difference between surgery being performed on an inpatient or day-care basis. Although NSAIDs, paracetamol, and weak opioids, such as codeine and dextropropoxyphene, are adequate for mild to moderate pain, these drugs may be ineffective in patients with moderate to severe pain. Local anesthetic infiltration in a wound or close to peripheral nerves is not common; in several studies, it has been demonstrated as a highly effective analgesic technique (6–10). Infiltration with local anesthetics modulates pain at the peripheral level by inhibiting the transmission of nociceptive impulses from the site of injury. The technique is generally considered to be simple, safe, and inexpensive. The main limitation to its widespread use is the need for repeated administration because of the short analgesic effect (usually two to six hours) of a single dose. Intermittent injections or continuous infusions through indwelling catheters in the wound area have been described for inpatients (6–10,11). Our preliminary data show that this technique can also be used at home. This study demonstrates the safety, efficacy, and applicability of the technique in a wide range of surgical procedures. Although nearly all patients had adequate to excellent pain relief, the efficacy of this technique was not compared with that of oral analgesics.

The major concern with this pump system is that the entire volume of local anesthetic will be delivered if the patient fails to close the clamp. To avoid this complication, the following steps were taken: a) oral and written information was given to the patient and the escort, b) the use of a timer was encouraged, c) the patient was informed that a clicking sound is heard when the clamp is closed, and d) the patient was instructed to close the clamp and contact an anesthesiologist if there was numbness of the tongue or tinnitus. The "worst-case scenario" is that all 50 mL of 0.125% or 0.25% bupivacaine is delivered (100 mL is used only for shoulder surgery), and although technically possible, this should not lead to any serious problems because the local anesthetic is delivered to peripheral tissue, the drug is delivered over a period of 1 h, and the total dose of bupivacaine is large but not excessive. The doses we used are far smaller than some reported in the literature. Single infiltration by 50 mL 0.25% bupivacaine after cholecystectomy (12,13) and repeated administration of 10 mL 0.25% bupivacaine every 4 hours for 48 hours (7,14) have been reported. Doses up to 40 mL 0.25% bupivacaine every 4 hours for 48 hours have been administered subcutaneously to treat pain after abdominal aortic surgery, and no signs of systemic toxicity were observed in any of these studies (16). However, it may not be valid to compare the intermittent administration of large doses of local anesthetics and accidental

administration of 50–100 mL of 0.125% or 0.25% bupivacaine within one hour.

Other concerns may be the risk of delayed wound healing and infection. The latter may be particularly important for intraarticular technique. The literature does not support these concerns. Indeed, local anesthetic drugs have bacteriostatic and antimicrobial effects (17–19). The surgeon tunnels the catheter under the skin so that it exits 3–5 cm from the wound. This procedure reduces the risk of infection and catheter dislodgment. The closed pump system described herein avoids repeated injections and handling of the catheter, thereby further reducing the risk of infection. A bacterial filter is included in the pump system (Fig. 2), and an additional bacterial filter was used in this study. Nevertheless, the risk of infection at home needs to be studied in more detail.

Although there were no complications in any of our 70 patients, we emphasize that our results are preliminary. Controlled trials are necessary to compare this technique with traditional methods and to evaluate the optimal concentration and volume of local anesthetic. The role of opioids and nonopioids, such as NSAIDs and clonidine, as adjuvants to local anesthetic drugs also needs to be studied.

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Pleural Anesthetics Given Through an Epidural Catheter Secured Inside a Chest Tube

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Pain management after thoracic surgical procedures is a difficult clinical problem. A variety of pain management methods are used with variable efficacy. This paper presents an effective method of pleural anesthetic administration using a pleural catheter inserted through a chest tube.

(Ann Thorac Surg 1991;51:133–4)

Analgesia after thoracotomy, tube thoracostomy, or thoracic trauma may pose a difficult problem for the surgeon and the patient. A variety of analgesic methods are currently available including narcotic agents, patient-controlled analgesics, intercostal nerve blocks, and pleural anesthetic agents. Moderate- to long-acting local anesthetics (eg, bupivacaine) administered into the pleural space provide a safe and effective method of pain control in thoracic surgical patients [1, 2] as well as in abdominal surgical patients [3, 4]. This type of anesthetic administration may decrease narcotic requirements and, therefore, decrease narcotic side effects such as respiratory depression and paralytic ileus [3]. Pleural anesthetics do not require the multiple percutaneous injections with t risk of intravascular injection of anesthetic or of pne mothorax during the administration of intercostal ner blocks. Pleural anesthetics can be administered eith through an indwelling pleural catheter or through a che tube. Pleural catheters maintain a closed sterile syste preventing contamination and avoiding other mechanic problems associated with injections directly into che tubes such as pneumothorax. Pleural catheters may placed percutaneously during thoracotomy but can difficult to position optimally. Likewise, placement durir tube thoracostomy may be difficult owing to the sm caliber and flexibility of the catheters. This paper d scribes a method of percutaneous placement of a pleur catheter through a chest tube, enabling safe, easy, an accurate catheter placement during thoracotomy or tul thoracostomy.

Technique

We use a standard epidural catheter insertion set and standard chest tube. The epidural introducer needle

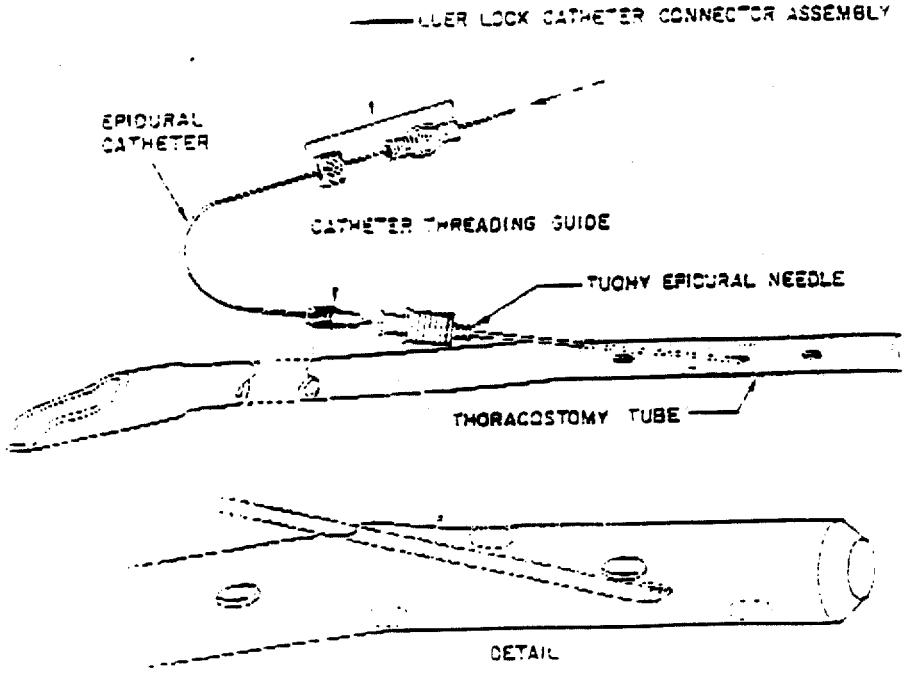

Fig 1. The catheter is advanced through the introducer needle, which is inserted through the side of the chest tube near the hole closest to the chest cortex. The tip of the catheter is positioned approximately 1 cm from the tip of the chest tube, then the introducer needle is removed. The Luer lock adaptor is then attached to the proximal end of the pleural catheter.

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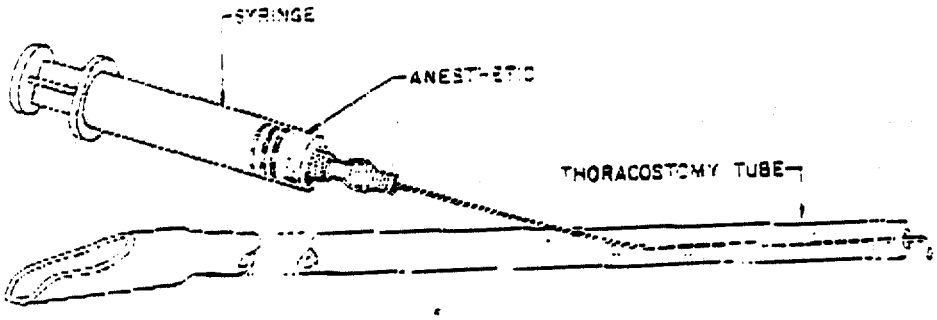

Fig 1. The assembly is placed directly during thoracotomy or percutaneously using standard tube thoracostomy techniques. The tip of the catheter is positioned posteriorly and at the apex. The catheter is firmly attached to the external portion of the chest tube with tape.

inserted through the side of the chest tube near the hole closest to the chest bottle. The epidural catheter is then inserted through the needle and advanced until its tip protrudes about 1 cm through the distal end of the chest tube (Fig 1). The combined assembly is then inserted percutaneously using standard tube thoracostomy techniques. If placed during an intrathoracic procedure, the catheter is inserted into the chest tube after the tube has been pulled through the chest wall. The entry site of the catheter into the chest tube should be positioned within the pleural space to prevent potential air leak. Ideally, the assembly should be positioned posteriorly within the pleural space.

After insertion, the pleural catheter can be secured to the chest tube with ½-inch tape but not tied with the chest tube stitch. The pleural catheter is then fitted with a Luer cap that will allow injections directly through the rubber diaphragm (Fig 2). Local anesthetics are administered through the pleural catheter as needed. We use preservative-free 0.25% bupivacaine with epinephrine at 0.3 mL/kg every 6 hours as needed for pain. However, continuous infusion of local anesthetic agents may also be used [1]. The maximum safe dose of 0.25% bupivacaine with epinephrine is up to 1 mL/kg of body weight every 6 hours.

Comment

Pleural administration of local anesthetics is an effective method of pain management in patients undergoing thoracic surgical procedures including percutaneous tube thoracostomy [1, 2]. Administration requires either an indwelling pleural catheter or a chest tube. The former provides a closed system with maintenance of sterility and avoidance of mechanical problems associated with repeated injections directly into the chest tube. Pleural catheters can be placed directly during thoracotomy. Blind percutaneous placement may be difficult owing to the flexibility and the small caliber of these catheters. In addition, blind percutaneous placement carries a small risk of pneumothorax or lung injury [4]. The combination of pleural catheter and chest tube facilitates percutaneous placement and enables the surgeon to use pleural anesthetics in any patient requiring a chest tube. This system ensures good positioning of the catheter posteriorly and at the apex of the pleural space. It also prevents kinking or coiling of the pleural catheter, which may be a problem even with catheters placed during open thoracotomy. A closed sterile system without air leak is maintained. The catheter can also be securely attached to the chest tube, which helps avoid inadvertent removal. In our experience, efficacy is excellent and redosing is easy with use of a Luer lock adapter. We have used this technique in more than 25 patients undergoing either thoracotomy or thoracostomy tube placement. Specific surgical procedures include posterolateral thoracotomy for pulmonary resections, tube thoracostomy for pneumothorax, and tube thoracostomy after transhiatal esophagectomy.

In our experience, there have been no complications attributable to the pleural catheter nor have there been any instances of cardiac or central nervous system problems caused by the anesthetics. We have observed that when this technique is used, the patients rarely require parenteral narcotics during the 4 to 6 hours after administration of the anesthetics.

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Maternal hypotension has resulted from regional anesthesia. Elevating the patient's legs and positioning her on her left side may help prevent hypotension. Fetal heart rate should be monitored continuously, especially during paracervical block, and electronic fetal monitoring is advisable.

Epidural, spinal, paracervical, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Use of obstetric anesthesia may increase the need for forceps assistance during delivery.

Administration of local anesthetics by paracervical nerve block during labor has been associated with a high incidence of fetal acidosis and bradycardia and has occasionally resulted in perinatal death. Fetal bradycardia may occur in 20–30% of patients receiving paracervical block anesthesia with the amide-type local anesthetics and may be associated with fetal acidosis. The risk of fetal bradycardia appears to be increased with prematurity, toxemia of pregnancy, and fetal distress. Changes in fetal heart rate and blood pH have been reported following epidural anesthesia. Some clinicians have advised against the use of continuous paracervical block for anesthesia during labor and against use of amide-type local anesthetics for paracervical block produced by a single injection. If paracervical block anesthesia is undertaken, the possible risk to the fetus must be considered, particularly when fetal distress is anticipated or in the presence of predisposing factors such as toxemia of pregnancy, prematurity, or diabetes mellitus.

Possible inadvertent intracranial injection of local anesthetic solution into the fetus has reportedly occurred following attempted paracervical and/or pudendal block. Such inadvertent injection has resulted in unexplained neonatal depression at birth which was associated with high serum concentration of the anesthetic; seizures usually occurred within 6 hours after birth. Prompt use of supportive measures and forced urinary excretion of the local anesthetic has reportedly been effective for managing this complication.

Systemic absorption of some local anesthetics during paracervical block in early pregnancy (anesthesia for elective abortion) may be rapid, since maternal seizures and cardiovascular collapse have occurred under these conditions. Therefore, the recommended maximum dose of the drug should not be exceeded and injection should be made slowly and with frequent aspiration, allowing a 5-minute interval between sides.

In obstetrics, low spinal (saddle block) and caudal anesthesia are contraindicated in psychologically unsuited patients and in those with pelvic disproportion, abruptio placentae, unengaged or floating fetal head and placenta praevia, unless cesarean section is contemplated after induction of caudal anesthesia. In addition, these anesthetic procedures should not be used when intrauterine manipulations are required.

Safe use of local anesthetics during pregnancy prior to labor has not been established with respect to adverse effects on fetal development. Careful consideration should be given to this fact before administering these drugs in pregnant women.

Dosage and Administration

■ Administration

Parenteral local anesthetics may be administered by infiltration or by epidural (including caudal), spinal (subarachnoid, intrathecal), or peripheral or sympathetic block techniques. The drugs may be given by single injection or continuous block techniques in which repeat injections are given through a catheter inserted into the area being anesthetized. Local anesthetic solutions containing preservatives should *not* be used for spinal or epidural (including caudal) anesthesia. Partially used bottles of solutions which do not contain preservatives should be discarded. In spinal anesthesia, the outside of the ampuls should be sterilized, preferably by autoclaving. (See Cautions: Other Adverse Effects.) Prior to use, syringes and needles should be rinsed with acidified, distilled water to remove traces of alkaline salts and small particles.

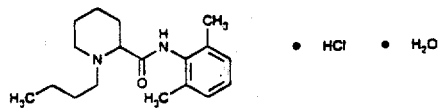
The patient's blood pressure should be monitored during spinal anesthesia. Resuscitative equipment and drugs which may be required for treatment of adverse reactions should be immediately available when local anesthetics are used. (See Cautions: Precautions and Contraindications.) Proper positioning of the patient is extremely important in spinal anesthesia. For specific procedures and techniques of administration, specialized references should be consulted.

■ Dosage

Generally, lower concentrations of local anesthetics are used for infiltration and peripheral or sympathetic nerve block anesthesia than for epidural anesthesia; highest concentrations (but small doses) are used in spinal anesthesia. Dosage varies with the anesthetic procedure, the degree of anesthesia required, and individual patient response. The smallest dose and concentration required to produce the desired effect should be used, especially in obstetrics. Reduced dosage is indicated in debilitated or acutely ill patients, in very young children or geriatric patients, and in patients with liver disease, arteriosclerosis, or occlusive arterial disease. In pregnant women at term, local anesthetic dosage for epidural and spinal procedures should generally be reduced to one-half to two-thirds of the usual average adult dose.

For specific dosages and additional information on chemistry and stability, pharmacokinetics, uses, and cautions of the parenteral local anesthetics, see the individual monographs in 72:00.

Bupivacaine Hydrochloride



Chemistry and Stability

■ Chemistry

Bupivacaine hydrochloride is a local anesthetic of the amide type with a long duration of action. Bupivacaine hydrochloride differs structurally from mepivacaine hydrochloride only in the substitution of a butyl group for the *N*-methyl group. Bupivacaine hydrochloride occurs as a white, odorless, crystalline powder and is freely soluble in water and in alcohol. The pK_a of bupivacaine hydrochloride is 8.1.

Bupivacaine hydrochloride injection is a sterile solution of the drug in water for injection. Commercially available solutions of bupivacaine hydrochloride have a pH of 4–6.5. Bupivacaine and epinephrine injection is a sterile solution of bupivacaine hydrochloride and epinephrine or epinephrine bitartrate in water for injection; the injection contains 0.001% (1:100,000) or less epinephrine. Bupivacaine hydrochloride solutions that contain epinephrine bitartrate have a pH of 3.3–5.5. Bupivacaine hydrochloride solutions, with or without epinephrine, in multiple-dose vials may contain methylparaben 0.1% as a preservative. A hyperbaric solution for spinal anesthesia is commercially available and contains 0.75% bupivacaine hydrochloride in 8.25% dextrose. The hyperbaric solution has a pH of 4–6.5 and a specific gravity of 1.030–1.035 at 25°C and 1.03 at 37°C.

■ Stability

Bupivacaine hydrochloride solutions should be stored between 15–30°C and freezing should be avoided; solutions containing epinephrine should be protected from light. Bupivacaine hydrochloride solutions should not be used if their color is pinkish or darker than slightly yellow or if a precipitate is present.

Bupivacaine hydrochloride solutions that do not contain epinephrine may be autoclaved at 15 PSI at 121°C for 15 minutes; solutions containing epinephrine should not be autoclaved.

Pharmacokinetics

■ Absorption

Bupivacaine hydrochloride has a long duration of action. Onset of anesthesia following administration of 0.5% solutions of bupivacaine hydrochloride for dental anesthesia occurs in about 2–10 minutes and duration of action is up to 7 hours in many patients. Onset of anesthesia following administration of 0.25 or 0.5% solutions of bupivacaine hydrochloride in epidural, including caudal block, and peripheral or sympathetic nerve block occurs in about 4–17 minutes and duration of action ranges from 3–7 hours. In epidural block, 0.75% solutions of bupivacaine hydrochloride produce a slightly shorter onset of action; duration of action may be from 6–9 hours. Although 0.25 and 0.5% solutions provide adequate sensory blockade in single doses, they do not produce complete muscle relaxation. If given by the continuous block method, however, repeat doses will increase the degree of motor block. The first repeat dose of 0.5% bupivacaine hydrochloride may give complete motor block. Single-dose epidural block with usual doses of 0.75% bupivacaine hydrochloride or single-dose intercostal nerve block with usual doses of a 0.25% solution may produce complete motor blockade which is necessary for abdominal surgery. In spinal anesthesia, a 0.75% solution in 8.25% dextrose has an onset of sensory blockade within 1 minute and motor blockade and dermatome level are usually maximal within 15 minutes; the duration of sensory blockade averages 2 hours and complete return of motor ability averages 3.5 hours following a 12-mg dose. Epinephrine may prolong the duration of action of bupivacaine.

After epidural or caudal administration of 125 or 150 mg of bupivacaine hydrochloride, peak plasma concentrations of 0.45–1.25 µg/mL have been demonstrated. After administration of bupivacaine hydrochloride for caudal, epidural, or peripheral nerve block, peak blood bupivacaine concentrations

occur within 30–45 minutes. Cumulation of the drug occurs with multiple doses; however, the long duration of bupivacaine hydrochloride anesthesia reduces the need for repeated doses.

■ Distribution

After absorption into the blood, bupivacaine hydrochloride is more highly bound to plasma proteins than are any other local anesthetics; bupivacaine is reportedly 82–96% bound. Bupivacaine hydrochloride has the lowest degree of placental transmission of parenteral local anesthetics and may cause the least fetal depression.

■ Elimination

The elimination half-life of bupivacaine hydrochloride is 1.5–5.5 hours in adults and 8.1 hours in neonates. Bupivacaine hydrochloride is principally metabolized to pipecolylxylidine (PPX) by *N*-dealkylation, probably in the liver. Bupivacaine is excreted in urine as small amounts of PPX, unchanged drug (5%), and other metabolites as yet unidentified.

Uses

Bupivacaine hydrochloride is used for infiltration anesthesia and for peripheral, sympathetic nerve, and epidural (including caudal) block anesthesia. A 0.75% solution of the drug in 8.25% dextrose is used for spinal anesthesia. Bupivacaine is *not* used for obstetric paracervical block or topical anesthesia.

Bupivacaine hydrochloride has been used for IV regional anesthesia† in various orthopedic and general surgical procedures; however, high plasma concentrations of the drug may occur following tourniquet release, and cardiac arrest and death have resulted. Bupivacaine therefore should *not* be used for IV regional anesthesia.

Cautions

■ Precautions

Bupivacaine hydrochloride shares the toxic potentials of the local anesthetics, and the usual precautions of local anesthetic therapy should be observed. (See Cautions in the Local Anesthetics, Parenteral, General Statement 72:00.)

The 0.75% solution of bupivacaine hydrochloride is no longer recommended for obstetric anesthesia, since use of this concentration for epidural anesthesia in obstetric patients has been associated with cardiac arrest with difficult resuscitation or death. Cardiac arrest has occurred after seizures resulting from systemic toxicity, apparently following inadvertent intravascular injection.

Some commercially available formulations of bupivacaine hydrochloride contain sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals. The overall prevalence of sulfite sensitivity in the general population is unknown but probably low; such sensitivity appears to occur more frequently in asthmatic than in nonasthmatic individuals.

■ Pediatric Precautions

Pending accumulation of further data on the use of the drug in pediatric patients, bupivacaine hydrochloride solutions should not be used in children younger than 12 years of age and the solution for spinal anesthesia should not be used in children younger than 18 years of age.

Dosage and Administration

■ Administration

Bupivacaine hydrochloride may be administered by infiltration, and by epidural (including caudal) block, or by peripheral or sympathetic nerve block. Bupivacaine hydrochloride solutions containing preservatives should *not* be used for epidural or caudal block. For spinal anesthesia, the bupivacaine hydrochloride solution in dextrose is administered by subarachnoid injection. Partially used solutions that do not contain preservatives should be discarded.

Resuscitative equipment and drugs that may be required for treatment of adverse reactions should be immediately available when bupivacaine is administered. For specific procedures and techniques of administration, specialized references should be consulted.

■ Dosage

Dosage of bupivacaine hydrochloride varies with the anesthetic procedure, the degree of anesthesia required, and individual patient response. The usual dosages should generally be reduced in young, geriatric, or debilitated patients and in patients with cardiac and/or hepatic disease. The smallest dose and lowest concentration required to produce the desired effect should be used.

Most experience to date is with single doses up to 175 mg of bupivacaine hydrochloride without epinephrine or 225 mg of the drug with epinephrine 1:200,000, but individual patients and procedures may require more or less of the drug. Doses should not be repeated more frequently than every 3 hours and dosage should not exceed 400 mg daily, since clinical experience with higher dosage is lacking.

For infiltration anesthesia, 0.25% bupivacaine hydrochloride may be used. Solutions of 0.25 or 0.5% bupivacaine hydrochloride with or without epinephrine and *containing no preservatives* are used for single dose or continuous epidural or caudal anesthesia. For caudal block, the usual dose of bupivacaine hydrochloride is 15–30 mL of 0.25 or 0.5% solution (37.5–150 mg). For epidural block (other than caudal block), the usual dose of bupivacaine hydrochloride is 10–20 mL of 0.25 or 0.5% solution (25–100 mg); in obstetrics, incremental doses of 3–5 mL of the 0.5% solution, not exceeding 50–100 mg at any dosing interval, are recommended. Repeat doses should be preceded by a test dose containing epinephrine if the vasoconstrictor is not contraindicated. Solutions of 0.75% bupivacaine hydrochloride with or without epinephrine should be used only for single dose epidural (but not caudal) anesthesia and may be given in a dose of 10–20 mL (75–150 mg); the 0.75% solution should *not* be used for obstetric anesthesia (see Cautions) and should be reserved for surgical procedures in which a high degree of muscle relaxation and prolonged effect are necessary. During epidural administration, the 0.5 and 0.75% solutions should be administered in incremental doses of 3–5 mL, with sufficient time between doses to detect toxic manifestations of inadvertent intravascular or intrathecal injection.

For peripheral nerve block, bupivacaine hydrochloride 0.25 or 0.5% with or without epinephrine may be given in a dose of 5 mL (12.5–25 mg) up to a maximum of 400 mg daily. For sympathetic nerve block, the dose of bupivacaine hydrochloride is 20–50 mL of a 0.25% solution (50–125 mg).

For retrobulbar anesthesia, the usual dose of bupivacaine hydrochloride is 2–4 mL of a 0.75% solution (15–30 mg).

For anesthesia in the maxillary and mandibular area when a longer duration of local anesthesia is desired (e.g., for oral surgery procedures generally associated with substantial postoperative pain), the usual dose of bupivacaine hydrochloride with epinephrine is 1.8 mL of a 0.5% solution (9 mg) per injection site; occasionally, a second dose of 1.8 mL (9 mg) per injection site may be necessary. Injections should be made slowly with frequent aspirations. The total dose of 0.5% bupivacaine hydrochloride solution for all injection sites spread out over a single dental sitting should usually not exceed 18 mL (90 mg) in healthy adults.

A solution of 0.75% bupivacaine hydrochloride in 8.25% dextrose is used for spinal anesthesia. For spinal anesthesia in lower extremity and perineal procedures, a dose of 1 mL (7.5 mg) is generally sufficient. For lower abdominal procedures, a dose of 1.6 mL (12 mg) may be used. For obstetrical spinal anesthesia in a normal vaginal delivery, doses as low as 0.8 mL (6 mg) have been used. For spinal anesthesia in cesarean section, doses of 1–1.4 mL (7.5–10.5 mg) have been used.

For further information on chemistry and stability, pharmacology, pharmacokinetics, uses, cautions, and dosage and administration of bupivacaine hydrochloride, see the Local Anesthetics, Parenteral, General Statement 72:00.

Preparations

Bupivacaine Hydrochloride

Parenteral Injection	0.25%	**Bupivacaine Hydrochloride Injection** (preservative-free in ampuls, single-dose vials and syringes, or with methylparaben in multiple-dose vials), Abbott
		Marcaine® Hydrochloride (preservative-free in ampuls and single-dose vials or with methylparaben in multiple-dose vials), Sanofi
		Sensorcaine® (preservative-free in ampuls and single-dose vials or with methylparaben in multiple-dose vials), Astra
	0.5%	**Bupivacaine Hydrochloride Injection** (preservative-free in ampuls, single-dose vials and syringes, or with methylparaben in multiple-dose vials), Abbott
		Marcaine Hydrochloride (preservative-free in ampuls and single-dose vials or with methylparaben in multiple-dose vials), Sanofi
		Sensorcaine® (preservative-free in ampuls and single-dose vials or with methylparaben in multiple-dose vials), Astra
	0.75%	**Bupivacaine Hydrochloride Injection** (preservative-free), Abbott

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Parenteral *cont'd*		**Marcaine‡ Hydrochloride** (preservative-free). Sanofi
		Sensorcaine‡ (preservative-free). Astra

Bupivacaine Hydrochloride in Dextrose

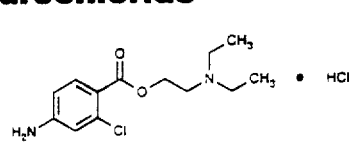
Parenteral		
Injection	0.75% in 8.25% Dextrose	**Bupivacaine Spinal** (preservative-free). Abbott
		Marcaine‡ Spinal (preservative-free). Sanofi
		Sensorcaine‡ Spinal (preservative-free). Astra

Bupivacaine Hydrochloride Combinations

Parenteral		
Injection	0.25% with Epinephrine Bitartrate 1:200,000 (of epinephrine)	**Bupivacaine Hydrochloride & Epinephrine** (with sodium metabisulfite in ampuls and single-dose vials or with methylparaben and sodium metabisulfite in multiple-dose vials. Abbott
		Marcaine‡ Hydrochloride with Epinephrine (with sodium metabisulfite in ampuls and single-dose vials or with methylparaben and sodium metabisulfite in multiple-dose vials). Sanofi
	0.5% with Epinephrine Bitartrate 1:200,000 (of epinephrine)	**Bupivacaine Hydrochloride & Epinephrine** (with sodium metabisulfite in ampuls and single-dose vials or with methylparaben and sodium metabisulfite in multiple-dose vials). Abbott
		Marcaine‡ Hydrochloride with Epinephrine (with sodium metabisulfite in ampuls and single-dose vials or with methylparaben and sodium metabisulfite in multiple-dose vials). Sanofi
		Sensorcaine‡ with Epinephrine (with sodium metabisulfite in ampuls and single-dose vials or with methylparaben and sodium metabisulfite in multiple-dose vials). Astra
	0.75% with Epinephrine Bitartrate 1:200,000 (of epinephrine)	**Bupivacaine Hydrochloride & Epinephrine** (with sodium metabisulfite). Abbott
		Marcaine‡ Hydrochloride with Epinephrine (with sodium metabisulfite). Sanofi
		Sensorcaine‡ with Epinephrine (with sodium metabisulfite). Astra

‡Use is not currently included in the labeling approved by the US Food and Drug Administration.

Chloroprocaine Hydrochloride



Chemistry and Stability

■ Chemistry

Chloroprocaine hydrochloride is a local anesthetic of the ester type with a short duration of action. The drug differs structurally from procaine hydrochloride only in the presence of a chlorine atom on the benzene ring. Chloroprocaine hydrochloride occurs as a white, crystalline powder and is soluble in water and slightly soluble in alcohol. Commercially available solutions of chloroprocaine hydrochloride have a pH of 4.5.

■ Stability

Chloroprocaine hydrochloride injections should be stored at a temperature less than 40°C, preferably between 15–30°C; freezing should be avoided. If chloroprocaine hydrochloride injection is stored at low temperatures, crystallization may occur; crystals will redissolve when the solution reaches room temperature. Solutions containing undissolved material should not be used.

Although commercially available chloroprocaine hydrochloride solutions are sterile, the vials can be autoclaved for terminal sterilization without substantial loss in potency. Sterilization with ethylene oxide is not recommended, since absorption of ethylene oxide through the vial closure may occur. Solutions of chloroprocaine hydrochloride may become discolored after prolonged exposure to light and should be protected from direct sunlight. Discolored solutions should never be administered.

Chloroprocaine hydrochloride is incompatible with alkali hydroxides and their carbonates, soaps, silver salts, iodine, and iodides.

Pharmacokinetics

The onset and duration of action of chloroprocaine are somewhat shorter than those of procaine. Depending on the dose and site of injection, 1 or 2% chloroprocaine hydrochloride solutions without epinephrine produce anesthesia in 6–12 minutes and duration of action is 30–60 minutes. Addition of epinephrine 1:200,000 prolongs duration of action to 60–90 minutes.

Chloroprocaine is hydrolyzed by plasma pseudocholinesterases more rapidly than is procaine. The drug is excreted by the kidneys, chiefly as diethylaminoethanol and 2-chloro-4-aminobenzoic acid.

Uses

Chloroprocaine hydrochloride is used for infiltration anesthesia, and for peripheral, sympathetic, and epidural (including caudal) block anesthesia. Chloroprocaine hydrochloride solutions containing a preservative should *not* be used for caudal or epidural anesthesia. The drug is *not* used for spinal anesthesia. Chloroprocaine hydrochloride is not effective as a topical anesthetic.

Cautions

Chloroprocaine hydrochloride shares the toxic potentials of local anesthetics, and the usual precautions of local anesthetic therapy should be observed. (See Cautions in the Local Anesthetics, Parenteral, General Statement 72:00.)

Dosage and Administration

Chloroprocaine hydrochloride may be administered by infiltration and by epidural (including caudal) block or by peripheral or sympathetic nerve block. Chloroprocaine hydrochloride solutions containing preservatives should *not* be used for epidural or caudal block. Partially used bottles of solutions which do not contain preservatives should be discarded. Dosage of chloroprocaine hydrochloride varies with the anesthetic procedure, the degree of anesthesia required, and individual patient response. The smallest dose and lowest concentration required to produce the desired effect should be used. Resuscitative equipment and drugs which may be required for treatment of adverse reactions should be immediately available when chloroprocaine is administered. For specific procedures and techniques of administration, specialized references should be consulted.

Single adult doses of chloroprocaine hydrochloride (without epinephrine) should not exceed 800 mg. When administered with epinephrine (1:200,000), chloroprocaine hydrochloride doses should not exceed 1 g. A 1:200,000 epinephrine/chloroprocaine hydrochloride solution may be prepared by adding 0.15 mL of 1:1000 epinephrine hydrochloride injection to 30 mL of a 2 or 3% chloroprocaine hydrochloride solution that does not contain a preservative. Solutions containing epinephrine should *not* be used for interdigital block.

Solutions of 2 or 3% chloroprocaine hydrochloride with or without epinephrine and *containing no preservatives* are used for epidural or caudal anesthesia. To prevent intravascular or subarachnoid injection of a large epidural dose of anesthetic solution, a test dose (approximately 3 mL of a 3% solution or 5 mL of a 2% solution) should be injected prior to administering the total dose; motor paralysis and extensive sensory anesthesia indicate subarachnoid injection. The test dose should be repeated if the patient is moved such that the epidural catheter may have been displaced. At least 5 minutes should elapse after each test dose before proceeding further. Injection of a large, single dose through a catheter should be avoided; instead, the drug should be administered in fractional doses. If a large volume of the drug is inadvertently injected into the subarachnoid space, an appropriate volume (e.g., 10 mL) of cerebrospinal fluid should be withdrawn through the catheter or by separate lumbar puncture. For epidural anesthesia in the cervical or

Y-Site Injection Compatibility (1:1 Mixture) (Cont.)

Bumetanide

Drug	Mfr	Conc	Mfr	Conc	Remarks	Ref	CII
Piperacillin sodium–tazobactam sodium	LE	40 mg/ml[b]	RC	0.04 mg/ml[b]	Physically compatible with no change in measured turbidity or increase in particle content in 4 hr at 22 °C under fluorescent light	1688	C
Vinorelbine tartrate	BW	1 mg/ml[a]	RC	0.04 mg/ml[a]	Physically compatible with no change in measured turbidity or increase in particle content in 4 hr at 22 °C under fluorescent light	1558	C

[a]*Tested in sodium chloride 0.9%.*
[b]*Tested in dextrose 5% in water.*

Additional Compatibility Information

Vehicles— Bumetanide is stated to be physically and chemically compatible in glass or PVC containers of dextrose 5% in water, sodium chloride 0.9%, and Ringer's injection, lactated, for at least 24 hours (2; 4).

Milrinone— Bumetanide may precipitate if mixed with milrinone lactate infusions (1442).

BUPIVACAINE HCL
AHFS 72:00

Marcaine — **Sanofi Winthrop**

Products— Bupivacaine HCl (Sanofi Winthrop) is available in concentrations of 0.25, 0.5, and 0.75% (2.5, 5, and 7.5 mg/ml, respectively) in 10- and 30-ml single-dose vials. It also is available in 30-ml (0.5 and 0.75%) and 50-ml (0.25%) single-dose ampuls. The 0.25 and 0.5% concentrations also come in 30-ml multiple-dose vials with methylparaben 1 mg/ml as a preservative. Sodium hydroxide or hydrochloric acid is used to adjust the pH (2).

Bupivacaine HCl (Sanofi Winthrop) is also available in concentrations of 0.25, 0.5, and 0.75% with epinephrine 1:200,000 as the bitartrate. In addition to bupivacaine HCl, each milliliter contains epinephrine bitartrate 0.0091 mg, sodium metabisulfite 0.5 mg, monothioglycerol 0.001 ml, ascorbic acid 2 mg, edetate calcium disodium 0.1 mg, and sodium lactate buffer. Multiple-dose vials contain methylparaben 1 mg/ml as a preservative. Sodium hydroxide or hydrochloric acid is used to adjust the pH (2).

A hyperbaric solution of bupivacaine HCl (Sanofi Winthrop) is available in 2-ml ampuls. Each milliliter contains bupivacaine HCl 7.5 mg and dextrose 82.5 mg (8.25%) with sodium hydroxide or hydrochloric acid to adjust the pH (2).

pH— Bupivacaine HCl injection and the hyperbaric solution have a pH of 4 to 6.5. Bupivacaine HCl with epinephrine 1:200,000 has a pH of 3.4 to 4.5 (2).

Specific Gravity— Bupivacaine HCl 0.5% with epinephrine 1:200,000 has a specific gravity of 1.008 at 25 and 37 °C. The hyperbaric solution has a specific gravity of 1.030 to 1.035 at 25 °C and 1.03 at 37 °C (2).

Dosage— Bupivacaine HCl may be administered intradermally, subcutaneously, submucosally, epidurally, or intrathecally as a single injection or repeat injections made through a catheter into the area being anesthetized. Injections should be made slowly, with frequent aspirations, to guard against intravascular injection (2; 4).

Dosage varies with the anesthetic procedure, degree of anesthesia required, and patient response. Most experience has been with single doses, up to 225 mg with epinephrine 1:200,000 or 175 mg without epinephrine. These doses should not be repeated more frequently than every three hours and should not exceed 400 mg daily. Incremental doses should be used when feasible (2; 4).

For infiltration anesthesia, 0.25% bupivacaine HCl solution may be used. Solutions of 0.25 or 0.5% bupivacaine HCl, with or without epinephrine and containing no preservatives, are used for single or continuous epidural or caudal anesthesia. For epidural or caudal block, the usual doses of bupivacaine HCl range from 25 to 150 mg. In obstetrics, incremental doses of 3 to 5 ml (15 to 25 mg) of the 0.5% solution, not exceeding 50 to 100 mg at any dosing interval, are recommended. A test dose, containing epinephrine if not contraindicated, of 10 to 15 mg (2; 4) or 20% of the total dose, whichever is less (4), should be injected at least five minutes prior to the total dose and any repeat doses. The 0.75% solution should not be used in caudal or obstetric anesthesia. This solution, with or without epinephrine, should be used only for single-dose epidural anesthesia; it may be given in a dose of 75 to 150 mg. For retrobulbar anesthesia, the usual dose is 15 to 30 mg (2 to 4 ml) of the 0.75% solution. In oral surgery, the usual dose of bupivacaine HCl with epinephrine 1:200,000 is 9 mg per injection, given as 1.8 ml of a

0.5% solution. A second dose may be necessary. The total dose in a dental sitting should not exceed 90 mg (18 ml) in healthy adults (2; 4).

A solution of bupivacaine HCl 0.75% in dextrose 8.25% is used for spinal anesthesia. A 7.5-mg dose is usually sufficient for anesthesia of the lower extremity and perineal procedures. For lower abdominal procedures, the dose may be 12 mg. Doses of 6 to 10.5 mg have been used for obstetrical spinal anesthesia (2; 4).

Bupivacaine HCl should not be used in children younger than 12 years, and the solution for spinal anesthesia should not be used in children younger than 18 years (2; 4). For pregnant women at term, the usual average adult dose should be reduced by one-half to two-thirds (4). Usual dosages should be reduced in young, geriatric, or debilitated patients and in patients with cardiac or hepatic disease (2; 4).

Stability— Bupivacaine HCl injections should be stored at 15 to 30 °C; freezing should be avoided (2; 4). Products containing epinephrine should be protected from light during storage (4).

Bupivacaine HCl without epinephrine and the hyperbaric solution may be autoclaved at 121 °C and 15 psi for 15 minutes. Products containing epinephrine should not be autoclaved (2; 4).

Bupivacaine HCl with epinephrine should not be used if a pinkish color, a color darker than "slightly" yellow, or a precipitate develops (2).

Compatibility Information

Additive Compatibility

Bupivacaine HCl

Drug	*Mfr*	*Conc/L*	*Mfr*	*Conc/L*	*Test Soln*	*Remarks*	*Ref*	*CII*
Fentanyl citrate	JN	20 mg	WI	1.25 mg	NS[a]	Physically compatible with little or no loss of either drug in 30 days at 3 and 23 °C	1396	C

[a]Tested in PVC containers.

Drugs in Syringe Compatibility

Bupivacaine HCl

Drug (in syringe)	*Mfr*	*Amt*	*Mfr*	*Amt*	*Remarks*	*Ref*	*C*
Hydromorphone HCl	KN	65 mg/ml	AST	7.5 mg/ml	Visually compatible for 30 days at 25 °C	1660	C
Iohexol		1 ml	AST	0.25 and 0.125%[a]/4 ml	Visually compatible with no bupivacaine loss by HPLC in 24 hr at room temperature. Iohexol not tested	1611	C
Morphine sulfate	MA	129 mg/ml	AST	7.5 mg/ml	Visually compatible for 30 days at 25 °C	1660	C

[a]Diluted 1:1 in sodium chloride 0.9%.

Additional Compatibility Information

Epinephrine and Fentanyl— A solution composed of bupivacaine HCl (Winthrop) 0.44 mg/ml, fentanyl citrate (Janssen) 1.25 µg/ml, and epinephrine HCl (Abbott) 0.69 µg/ml was stored in 100-ml portable infusion pump reservoirs (Pharmacia Deltec) for 30 days at 3 and 23 °C. The samples were then delivered through the infusion pumps over 48 hours at near-body temperature (30 °C). The samples were visually compatible throughout, and bupivacaine HCl and fentanyl citrate exhibited no loss by HPLC analysis. Epinephrine HCl sustained about a 5 to 6% loss by HPLC analysis after 20 days of storage at both temperatures and about a 9 to 10% loss after 30 days of storage and subsequent pump delivery. The authors recommended restricting storage before administration to only 20 days (1627).

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Regional Anesthesia 22(4):351–356, 1997

Local Anesthetic Infusion Through Nerve Sheath Catheters for Analgesia Following Upper Extremity Amputation

Clinical Report

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Background and Objectives. Reports about the efficacy of local anesthetic perfusion of nerve stumps following lower extremity amputation are conflicting. We report our experience with this technique following amputation of the upper extremity. *Methods.* Six consecutive patients undergoing proximal upper extremity amputations (four forequarter amputations and two shoulder disarticulations) for malignancy were prospectively observed. In all patients, catheters were placed within the amputated nerve sheaths at the conclusion of the procedure. Bupivacaine, 0.25%, was administered through each catheter as a bolus and then as a continuous infusion for at least 72 hours after surgery. Narcotic usage, level of pain as reported verbally, and presence of phantom limb pain during the infusion were recorded. For at least 1 year after operation, data were gathered on the presence of phantom limb pain and its intensity during each follow-up visit. *Results.* Complete analgesia was achieved in all patients by postoperative day 2. Narcotic usage was low. Three of the six patients reported phantom limb pain during follow-up evaluation. *Conclusions.* Continuous local anesthetic perfusion of amputated nerves via a catheter placed under direct vision provided excellent postoperative analgesia. The incidence of phantom limb pain for cancer patients did not differ from that previously reported but was easily managed pharmacologically. The technique may also be efficacious for traumatic amputations. *Reg Anesth 1997; 22: 351–356.*

Key words: amputation, postoperative analgesia, nerve sheath catheters, phantom limb.

Phantom limb pain is a devastating complication of amputation. It occurs in 83% of patients within the first 4 days of amputation. Patients describe classic neuropathic pain as "knifelike," "sticking," "shooting," "burning" (1). In a retrospective chart review of upper extremity amputations in our institution from 1978 to 1992, 50% of patients had phantom limb pain requiring narcotic analgesics during follow-up evaluations. All these patients received general endotracheal anesthesia and intravenous narcotics postoperatively for pain control; all patients were followed for at least 1 year. Because the review was retrospective and the patients were not specifically asked about

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phantom pain, the number of patients who experience phantom pain is probably greater than 50%, as phantom limb pain is frequently underreported by patients and underdocumented by care givers (1,2).

The role of preemptive analgesia and its timing in the prevention of phantom limb pain are unknown. Examination of the literature reveals the lack of rigorous, well controlled studies of this difficult problem. Bach et al. (3) reported on a small series of patients undergoing lower extremity amputations who had epidural analgesia initiated 72 hours before surgery; these patients received either narcotics, local anesthetics, or both before surgery in this nonblinded study. Their postoperative pain was treated with intravenous narcotics and nonsteroidal antiinflammatory medications. The incidence of phantom limb pain in this study was 27% during the first week, 0 at 6 months, and 0 at 1 year; in the control group of 14 patients, the incidence of phantom limb pain was 64%, 38%, and 27%, respectively. Another study by Fisher and Meller (4) on 11 patients, who received no preoperative interventions for lower extremity amputations but who did receive postoperative nerve sheath infusions of local anesthetics up to 1 year postoperatively, reported a total absence of phantom limb pain in these patients; however, two patients had nonpainful paresthesias, similar to those found in our study. This, too, was a nonblinded study and the length of follow-up evaluation was not specified.

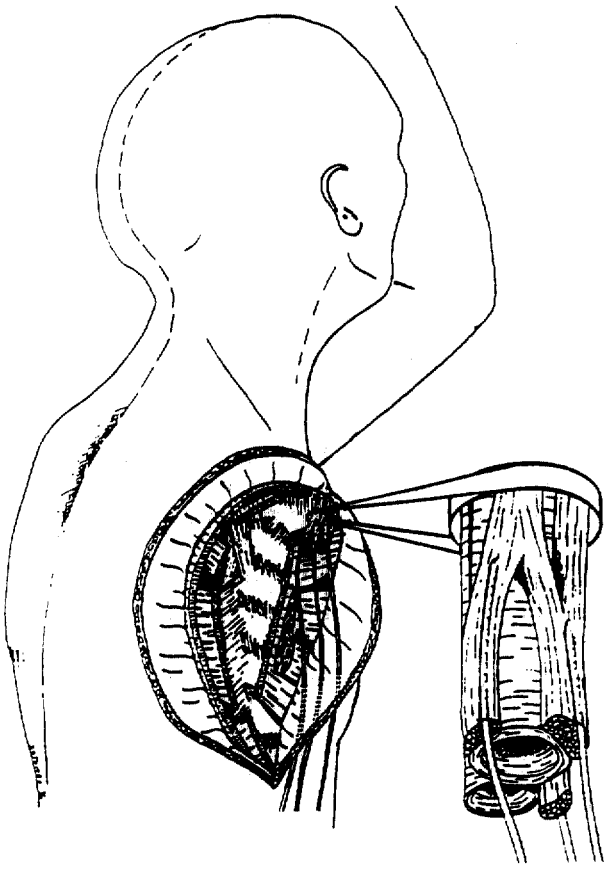
Woolf and Chong (5), in their review of preemptive analgesia, point out that in 22 of 24 studies comparing a preemptive intervention with no intervention, an analgesic effect could be demonstrated in the patients who received preemptive intervention. However, in studies comparing interventions made before versus after surgery, a preemptive effect could only be demonstrated in half the cases. There is no clear evidence as to when preemptive intervention of phantom limb pain should be initiated.

Initial reports of continuous nerve sheath infusion of local anesthetic described excellent pain control and decreased risk of phantom limb pain following lower extremity amputation (4,6). In a more recent report, however, analgesic use and the incidence of phantom limb pain did not differ between patients undergoing lower extremity amputation followed by continuous bupivacaine nerve sheath infusions and control patients (7). To our knowledge, no other investigators have applied this strategy to upper extremity amputation, a much rarer operation. This report describes the use of this technique for postoperative analgesia in six patients undergoing upper extremity amputation. The efficacy of analgesia and the incidence of phantom limb pain were examined.

Materials and Methods

With institutional review board approval, data were gathered prospectively in consecutive patients undergoing upper extremity amputation for malignancy at our institution between 1992 and 1995. All patients underwent general inhalational anesthesia with fentanyl, up to 5 μg/kg. With the forequarter amputations, the nerves were transected at the cord level and either two or three catheters were placed. The shoulder disarticulations were at the terminal branch level, and the catheters were placed in the median, ulnar, and radial nerve branches. In each case, the nerves were sharply transected proximal to the level of amputation. No clips or sutures were used on the nerve ends, and the nerves were cut at 5–10 cm proximal to the wound edges. After amputation, 20-gauge polyamide closed-tip catheters (Burron Medical, Bethlehem, PA were threaded between the epineurium and the severed nerve under direct visualization by the surgeon (Fig. 1). The technique for catheter placement involves transection of the nerves, identification of the epineurium, and placement of the catheter between the epineurium and the nerve. The catheter was typically threaded as far as it could be easily introduced, 2–5 cm proximal to the transection level. Two or three catheters were placed for each patient because at least two catheters enabled a greater volume of local anesthetic to be delivered if necessary. This strategy resulted from our experience with a patient who was not included in the study group because of extensive chest wall excision. Only one catheter was placed in this patient, and she complained of persistent pressure paresthesia when the rate of analgesic infusion was increased from 6 to 8 mL/h.

The catheters were secured with a suture to the epineurium and brought out at a site distant from the wound closure. After the catheters were secured, bupivacaine, 0.25%, was administered through each catheter, first as 10-mL boluses and then, when the patient reached the recovery room, as continuous infusions beginning at 4 mL/h by means of infusion pumps (Bard MedSystems, North Reading, MA). The rate of the infusions through all the catheters was adjusted to a combined maximum of 0.5 mg/kg/h as needed to achieve analgesia, and the infusions were main-



ig. 1. Schematic drawing of nerve sheath catheters threaded between the epineurium and the nerve following shoulder disarticulation. All catheters are brought out to the skin and secured with a suture.

tained for a minimum of 72 hours. Morphine sulfate, [illegible]g every 6 minutes maximum, was available to patients as needed by means of a patient-controlled device. The analgesic regimen was switched after the first postoperative day to oral narcotics, to be given at the patient's request.

Twice daily during infusions, patients were questioned about the following symptoms of local anesthetic toxicity: tinnitus, perioral numbness, metallic taste, and sedation. The amount and type of supplemental analgesics (morphine sulfate equivalents) used postoperatively were recorded. Pain and phantom limb sensation were assessed as follows. Before and twice daily for 3 days after amputation, patients were asked to assess the degree of pain in the affected upper extremity by means of a verbal scale ranging from 0 (no pain) to 10 (worst pain). At all postoperative follow-up visits, patients were asked whether they had any sensations in the phantom limb. These follow-up visits were scheduled at 2 weeks, at 1 month, and every 3 months for the first year and then every 6 months thereafter. Data are reported as mean ± SD.

Results

Six patients were studied (Table 1), three women and three men with a mean age of 59.5 years (range, 20–84). Their mean pain score preoperatively was 4.5 ± 3.8. Complete analgesia was achieved in all patients by postoperative day 2, the mean pain scores on postoperative days 0 to 3 being 3.8 ± 4.1, 1.8 ± 1.6, 0 ± 0, and 0 ± 0 respectively. After 24 hours of patient-controlled morphine, most patients received oral narcotics on request. The amount of morphine sulfate equivalent administered during the entire hospitalization averaged 20 mg, and for postoperative days 0 to 3, it was 10.4 ± 11.0 mg, 3.1 ± 4.2 mg, 1.1 ± 1.7 mg, and 4.9 ± 7.7 mg, respectively. For three patients who rated pain as 3 or higher and had an initial dose of bupivacaine of 4 mL/h, the infusion rate

Table 1. Demographic Data and Diagnoses for Patients Who Underwent Upper Extremity Amputation for Malignancy at One Institution in 1992–1995

Patie...	Sex	Age (y)	Diagnosis	Area of Amputation	Follow-up Period (months)	Outcome
1	M	45	Recurrent osteosarcoma of the proximal humerus	Forequarter	15	Dead of disease
2	M	20	Osteogenic sarcoma of the proximal humerus	Shoulder disarticulation	41	Alive, no evidence of disease
3	F	82	Malignant fibrous histiocytoma of the proximal humerus	Forequarter	21	Alive, no evidence of disease
4	F	61	Angiosarcoma of the arm	Forequarter	22	Alive, no evidence of disease
5	F	65	Malignant fibrous histiocytoma of the proximal humerus	Shoulder disarticulation	27	Alive with disease
6	M	84	Metastatic adenocarcinoma with a humeral nonunion	Shoulder disarticulation	26	Alive, no evidence of disease

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was increased by 2 mL/h. The average rate of bupivacaine administration was 6 mL/h per catheter, with a range of 4–8 mL/h per catheter. Only one patient, a 90-kg, 20-year-old, received the maximum infusion rate, for a total of 45 mg/h over 80 hours. No patient exhibited any symptoms of local anesthetic toxicity.

During the infusion period and at subsequent follow-up visits throughout the study, all six patients reported nonpainful phantom sensations. Three patients reported phantom limb pain. In one of these patients, the infusion of bupivacaine was delayed by 90 minutes, and pain was rated as 10 on emergence from anesthesia. The patient was given additional boluses of 0.25% bupivacaine, and his infusion rates were increased to the maximum. He was also given morphine sulfate and ketorolac intravenously. His pain decreased to 4 on postoperative day 1 and to 0 by postoperative day 2. Phantom limb pain developed 2 weeks after amputation, which he described as "exactly what it felt like when I woke up." He received oxycodone, amitriptyline, and mexiletine for 10 weeks and has subsequently been free from phantom limb pain for 28 months. In a second patient, numbness in the phantom extremity was rated as 2 out of 10, but she took no medication 15 months after the amputation. In a third patient, pain was rated as 10 before the amputation and as 0 immediately afterward. At 1 month following surgery, intermittent phantom limb pain developed and gradually worsened. This patient has refused all pharmacologic interventions, and he rated pain as 8 out of 10 at 16 months after the amputation.

Discussion

All patients in this study underwent amputation of an upper extremity for malignancy. This analgesic technique may also be applicable to amputations for other indications, although this study did not examine other patient populations.

Although continuous infusion of local anesthetics via catheters placed percutaneously into nerve sheaths has provided effective analgesia following many types of extremity surgery (8–11), this is the first clinical report of analgesia following amputation of the upper extremity that was obtained by infusing local anesthetic through nerve sheath catheters. Our data suggest that (1) peripheral nerve sheath catheters can be used to infuse local anesthetic directly onto nerves of amputated limbs and (2) this technique can be used to obtain successful analgesia following upper extremity amputation. Although the number of patients we studied was small, our results are clinically valuable because of the limitations imposed by any study of upper extremity amputation: it is a rare operation, and phantom limb pain is such a devastating complication, both physically and emotionally, that studies using intravenous narcotic analgesia, with its known lack of efficacy, would be difficult to justify.

Local anesthetic block of peripheral nerves may reduce the nociceptive impulses from the periphery to the spinal cord and thus may prevent spinal cord hyperexcitability, which can lead to chronic phantom limb pain. Other techniques that would provide afferent block of impulses to the central nervous system should be equally efficacious in providing analgesia and possibly preventing phantom limb pain. To our knowledge, no other investigators have reported the use of continuous cervical epidural or interscalene block for analgesia following upper extremity amputation. The possible advantages of this technique over percutaneously placed catheters are that (1) catheters are known to be correctly placed, because they are placed under direct vision, and (2) these catheters cannot be pulled out or dislodged during surgery. The obvious disadvantage is that catheters are placed following surgery, when spinal cord hyperexcitability may have already occurred.

In one study, patients undergoing lower extremity limb salvage or amputation who received bupivacaine through a nerve sheath catheter placed during surgery under direct vision had substantially decreased postoperative narcotic analgesic requirements (6). No catheter-related complications or side effects secondary to the bupivacaine were reported. The incidence of phantom limb pain was not specified by Malawer et al.; however, none of the 12 amputees has since developed phantom limb pain (personal communication, 1994).

Other studies of the incidence and severity of phantom limb pain following lower extremity amputation have so far been conflicting. In one study (4) postoperative narcotic usage by a prospective, nonblinded series of 11 patients who underwent lower extremity amputation and received a continuous infusion of local anesthetic through a catheter placed directly into the amputated stump of the sciatic or posterior tibial nerve, was compared with that by a retrospective control group who underwent a similar procedure. Mean narcotic use differed significantly between the groups. Also, phantom limb pain was totally absent at 1 year in the nine surviving patients who received a continuous local anesthetic infusion. In

trast with those positive results, no difference narcotic usage was reported in a retrospective review of patients undergoing lower extremity amputation bupivacaine-treated patients and control patients (7). When 9 of the bupivacaine-treated patients and 12 control patients were subsequently interviewed to assess their phantom limb pain, seven of the 9 bupivacaine-treated patients (77%) and half of the control patients reported this complication. A number of factors may influenced the different outcomes of the two comparable studies: for example, patient selection was dissimilar. All the patients in the positive study had peripheral vascular disease, compared with 0% in the negative study. The total mass of bupivacaine administered and the way it was administered also differed between the two studies: 25 mg/h by continuous infusion in the positive study, compared with 75 mg/h with intermittent boluses in the negative study.

Our technique more closely resembled that used in the positive study namely, continuous infusion of local anesthetic at a much larger volume (up to 5 mg/h). We followed the recommendations of Malawer et al. (6), who used a maximum infusion rate of 0.5 mg/kg/h and the same technique in their study. The reported serum bupivacaine levels ranged from undetectable to 1.1 μg/mL. In our study, only one patient received the maximum infusion rate of bupivacaine. In patients with hepatic or renal disease, the maximum infusion rate of bupivacaine should be reduced because bupivacaine clearance may be impaired.

The patients in both the positive and negative study differed from ours, all of whom had cancer. The incidence of phantom limb pain in patients undergoing amputation for cancer has been reported to be as high as 90% within the first year (2). Factors that place a patient at risk for developing phantom limb pain include preoperative pain level and coping strategy used (12,13). In oncology patients, pain is the most common presenting symptom. The combination of pain with the psychologic traumatization of the patient given a devastating diagnosis of cancer may lead to a higher incidence of phantom pain in oncology patients than in trauma patients. Krane and Heller (2) and Smith and Thompson (14) reported phantom limb pain to be more common in pediatric oncology patients than in pediatric trauma patients. In our series, phantom limb pain occurred during the first year in only three of the six patients, and only one patient, who refused further treatment, had significant pain at 1 year follow-up evaluation. On the basis of our experience with local anesthetic infusion through nerve sheath catheters following upper extremity amputation, we recommend the following:

- Two or more nerve sheath catheters should be placed within the amputated brachial plexus during surgery if at all possible.
- Bupivacaine should be administered through each catheter as a bolus followed by an infusion of at least 20 mg/h to the brachial plexus (based on the minimum effective infusions in our study and the positive experimental study [4]).
- A strategy for pain-free emergence from anesthesia should be developed, including timely delivery of local anesthetic and addition of other analgesic modalities as needed. Phantom pain should be treated aggressively if it develops.

Although this report is not conclusive, it suggests that continuous infusion of local anesthetic via nerve sheath catheters provides excellent postoperative analgesia following upper extremity amputation. The incidence of phantom limb pain did not differ from the retrospectively reviewed histories of other patients undergoing this procedure without this intervention. Combining this technique with preoperative nerve block may improve the immediate postoperative analgesia and may reduce the incidence of phantom limb pain. However further studies are needed to delineate the role of analgesia, whether preemptive or postoperative, in preventing phantom limb pain.

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The effects of incisional bupivacaine on postoperative narcotic requirements, oxygen saturation and length of stay in the post-anesthesia care unit

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We compared postoperative pain and narcotic requirements, oxygen saturation (Sao_2) and length of stay in the post-anesthesia care unit (PACU) in patients who received 30 ml of either 0.25% bupivacaine (B) or saline placebo (S) infiltrated into the operative incision. Twenty ASA I–III patients undergoing abdominal surgery were studied in a double-blinded randomized prospective trial. Study and control groups were not different in patient age, procedure, intra-operative narcotics administered or preoperative Sao_2. In the PACU, patients receiving B had significantly lower analog pain scores (6.0 vs 8.3, $P=0.02$). They had lower respiratory rates (15.6 b/min vs 19.1, $P=0.02$), required significantly less narcotic (4.5 mg morphine sulphate vs 11.0, $P=0.03$) and were discharged from the PACU almost an hour sooner than patients receiving S ($P=0.02$). Patients receiving B had significantly higher minimum Sao_2 than those receiving S (93.3 % vs 89.9, $P=0.04$). Discharge pain scores, Sao_2 and respiratory rates were not significantly different between B and S groups. Finally, mean requirements for narcotics for the first 24 h were reduced by approximately 30% (from 406.9 mg meperidine to 255.5 mg, $P=0.006$). This study demonstrates that infiltration of a long-acting local anesthetic lowers initial pain scores and requirement for narcotics in the PACU. The effect can be seen for at least the first 24 h. A lower requirement for postoperative narcotics is accompanished by faster wake-up, more alert patients, and, most importantly, higher Sao_2 and shorter PACU stay. This may have a significant effect on pulmonary morbidity following abdominal operations.

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Postoperative pain is frequently undertreated (1, 2). Inadequately treated incisional pain, however, may lead to splinting, loss of sighing and reduction of vital capacity (3, 4). These, in turn, may contribute to postoperative pulmonary morbidity. Thus upper abdominal operations, in particular, are associated with a high incidence of postoperative pulmonary complications. Several approaches for the treatment of postoperative pain have been advocated, including epidural and intrathecal narcotics (5), intrapleural anesthetics (6, 7) and patient-controlled analgesia (PCA) (2, 5, 8). The most commonly employed method of postoperative pain control, however, remains intramuscular or intravenous injection of narcotics.

Considerable attention has been focused upon the respiratory depression induced by narcotic analgesics. In the immediate postoperative period, narcotic administration may be particularly dangerous, since narcotics depress the ventilatory response to carbon dioxide and may impair consciousness and protection of the airway at a time when residual anesthetics are still present (8–10). An alternative may be to employ local anesthetics to provide immediate postoperative analgesia (11–13). First suggested in the 1950s, incisional infiltration of local anesthetic has experienced renewed popularity with the development of long-acting local anesthetics such as bupivacaine hydrochloride.

Previous studies have not examined the immediate postoperative period, nor have they controlled for intraoperative narcotic administration (11–13). The purpose of this study was to compare postoperative pain and narcotic requirements, oxygen saturation (Sao_2 = oxygen saturation measured by pulse oximetry) and length of stay in the post-anesthesia care unit (PACU) in patients receiving either 0.25% bupivacaine or saline placebo infiltrated into the operative incision.

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Table 1
Criteria for PACU nurse assessment of patients.

Nausea: 0 = none, 1 = mild, 2 = moderate, 3 = severe, with emesis
Alertness: 0 = unresponsive, 1 = responds to pain, 2 = responds to voice, 3 = follows commands, 4 = spontaneous speech
Hypertension: defined as systolic bp > 160, diastolic bp > 100 or either value greater than 20% greater than pre-op.

MATERIAL AND METHODS

After Human Subjects Committee approval and informed consent, 20 ASA I–III patients aged 30–70 years were enrolled in the study. The subject population was selected from patients scheduled to undergo abdominal surgery (cholecystectomy, ventral herniorraphy, staging laparotomy, or colostomy closure) under general anesthesia. Most patients had a history of smoking, but none was receiving medications for respiratory disease. Patients were introduced to a visual analog pain scale ranging from zero (no pain) to ten (maximum pain imaginable) the night before surgery and informed that they would receive as much pain medicine as they needed postoperatively. Patients received no premedication. Induction was accomplished with thiopental (4–6 mg/kg) plus succinylcholine (1.5 mg/kg) or vecuronium (0.1 mg/kg) for intubation. Maintenance was with a balanced anesthetic of isoflurane, oxygen, nitrous oxide and i.v. fentanyl. In order to approximate most closely the usual anesthetic practice, administration of the anesthetic was left to the individual anesthesiologist in charge of each case but did not include any intrathecal or epidural medications. Intraoperative narcotics were administered as considered appropriate by the anesthesiologists, but none were given in the last 20 min of the procedure. Ten minutes before the end of the procedure, just prior to skin closure, 30 ml of either 0.25% bupivacaine or non-preservative normal saline were infiltrated into the subcutaneous tissue, muscle and fascia of the surgical incision. Choice of medication or control was assigned randomly by the pharmacist preparing the medication, based upon a random table created in advance. The patient, surgeons, anesthesiologists and PACU personnel were all blinded as to the identity of the injected solution.

All study patients were cared for by one of two PACU nurses. In the PACU, as soon as a patient was capable of responding, he was asked to gauge his pain on the visual analog pain scale. If he reported any pain, morphine sulphate (MS) was injected i.v. in 2–4 mg increments at 5–10-min intervals until he was comfortable. The decision whether or not to medicate was left to the two PACU nurses, who followed their normal criteria for postoperative medication. Discharge criteria from the PACU followed standard protocol for the hospital, and required patients to be alert and pain-free, and for 30 min to have elapsed since any i.v. medication. Prior to discharge from the PACU, the patient was asked to gauge his pain on the visual analog scale once more. Total narcotic administered intraoperatively and in the PACU, analog pain scores, time spent in the PACU and the length of time before the patient was able to respond to the visual analog scale were recorded. PACU nurses made a subjective assessment on a five-point scale of the patient's degree of alertness on arrival and discharge from the PACU (Table 1). Similarly, nausea and vomiting were recorded on a four-point scale (Table 1). Because postoperative hypertension sometimes results from inadequate pain control, hypertension, defined as systolic or diastolic pressure greater than 120% of preoperative values or systolic pressures greater than 160 mmHg (21.3 kPa) was recorded if present.

Sao_2 was measured preoperatively, and continuously both during the operation and in the PACU. It is the practice in our institution to provide supplemental oxygen (Fio_2 35% by mask) to all patients in the PACU. Room air saturation was measured in study patients by removing the oxygen mask for 3 min and continuously observing the oxygen saturation. If the oxygen saturation fell to less than 90%, the patient's mask was repositioned so that he received supplemental oxygen, and thus no patient was allowed to become hypoxic. Sao_2 was measured for each patient within 5 min of arrival in the PACU and again when the patient was comfortable. Minimum Sao_2 and per cent change in Sao_2 from preoperative values were recorded for each patient upon arrival in the PACU, after medication, and just prior to discharge from the PACU.

All patients' charts were later reviewed for evidence of postoperative complications. Although not part of the original study design, a record was made of all narcotics administered in the first 24 h postoperatively. Five patients (two from the bupivacaine group and three from the saline group) received patient controlled analgesia (PCA), and were excluded from the analysis because totals were not available.

Data were analyzed by non-parametric Mann Whitney U-test with $P < 0.05$ considered significant.

RESULTS

Study and control groups were not different in patient age, operative procedure, or length of surgery (Table 2). The time from discontinuation of anesthesia until the patient was able to respond to verbal commands and the time from awakening until the first spontaneous complaint of pain were also not significantly different between groups (Table 3). Upon arrival in the PACU, patients in the two groups were equally alert (Table 3); however, patients receiving bupivacaine had significantly lower analog pain scores ($P =$

Table 2
Characteristics of patient groups.

Characteristic	Saline	Bupivacaine	Significance
N	10	10	ns
Age	54.6 ± 4.0 yr*	55.4 ± 4.5 yr	ns
Procedures (n)	cholecystectomy (5) ventral hernia repair (3) pelvic node dissection (1) staging laparotomy (1)	cholecystectomy (5) ventral hernia repair (2) nephrectomy (1) staging laparotomy (2)	
Length of surgery	204 ± 24 min	232 ± 27 min	ns

* mean ± standard error.

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0.02. Table 3). Their initial respiratory rate was significantly less (15.6 ± 1.48 for the bupivacaine group vs 19.1 ± 1.64 for the saline group, $P = 0.02$).

Total intraoperative narcotics were not different between groups. Patients receiving incisional bupivacaine required significantly less narcotic in the PACU, however (4.4 ± 1.26 mg MS vs 11.4 ± 1.7, $P = 0.003$), and were discharged from the PACU *almost an hour* sooner than patients receiving saline ($P < 0.02$, Table 3). In addition, retrospective analysis of narcotics used in the first 24 h postoperatively showed that patients who were randomized to bupivacaine infiltration received an average of approximately 30% less narcotic than those in the saline group (255.1 ± 61 mg meperidine compared to 406.9 ± 50, $P = 0.006$). Narcotic orders for these patients were for 75 mg meperidine up to every 4 h, as required for pain, so patients had to request pain medication.

With respect to arterial oxygen saturation, two effects were seen. First, there was a negative correlation between age and preoperative Sao_2 ($r = -0.51$, $P < 0.05$, Fig. 1a). This correlation was no longer seen postoperatively (Fig. 1b). Second, although preoperative values were not different between the two study groups, patients receiving bupivacaine had significantly higher minimum Sao_2 values in the PACU than those receiving saline (Fig. 2, $P < 0.05$, Table 3). A similar result was seen when the change in Sao_2 from preoperative values was calculated. The difference was striking, even though supplemental oxygen was provided for any patient whose Sao_2 fell to 90% while the patient was breathing room air. This occurred in four patients in the saline group and two patients in the bupivacaine group. At the time of discharge from the PACU, oxygen saturation was no longer significantly different ($P = 0.16$, Table 3). Two patients in the saline group and no patients in the bupivacaine group were discharged from the PACU with supplemental oxygen.

In this study, postoperative morphine requirements were unrelated to patient age (Fig. 3a). Total morphine dose administered in the PACU, however, showed a significant correlation with the lowest Sao_2 values recorded ($r = -0.52$, $P < 0.05$, Fig. 3b).

Patients were medicated until comfortable in the PACU. Discharge pain scores and respiratory rates were not significantly different between bupivacaine and saline groups. Mild nausea was observed in one patient in the bupivacaine group and in two patients in the saline group. Hypertension was observed in a single patient in each group. No postoperative complications were noted in either group.

Table 3

Effects of incisional bupivacaine vs saline.

Characteristic	Saline	Bupivacaine	Significance
Recorded times (min)			
Time to awaken	12.5 ± 1.4*	7.5 ± 0.9	ns
Time to 1st complaint	21.5 ± 2.1	19.8 ± 2.6	ns
Time to PACU discharge	204.5 ± 40.8	145.3 ± 14.1	$P = 0.02$
Alertness score			
PACU arrival	2.7 ± 0.3	2.7 ± 0.2	ns
PACU discharge	4.0 ± 0.0	3.8 ± 0.1	ns
Respiratory rate (breaths/min)			
PACU arrival	19.1 ± 1.6	15.6 ± 1.5	ns
PACU discharge	16.3 ± 0.7	16.4 ± 1.1	ns
Narcotic administered			
Intra-op (μg fentanyl IV)	615.0 ± 89	775.0 ± 156	ns
PACU (mg morphine IV)	11.0 ± 1.8	4.5 ± 1.3	$P = 0.003$
Next 24 h (mg meperidine IM)	406.9 ± 50	255.5 ± 61	$P = 0.006$
Oxygen saturation (Sao_2, per cent)			
Pre-op	97.0 ± 0.7	97.3 ± 0.5	ns
Lowest intra-op	97.9 ± 0.5	97.0 ± 0.8	ns
Lowest post-op	89.9 ± 0.9	93.3 ± 0.9	$P = 0.04$
Change from pre-op	7.5 ± 0.9	4.3 ± 0.7	$P = 0.02$
PACU discharge	93.3 ± 0.8	95.2 ± 0.9	ns
Analog pain score			
PACU arrival	8.3 ± 0.6	6.0 ± 0.6	$P = 0.02$
PACU discharge	4.8 ± 0.8	4.5 ± 0.7	ns

* mean ± standard error.

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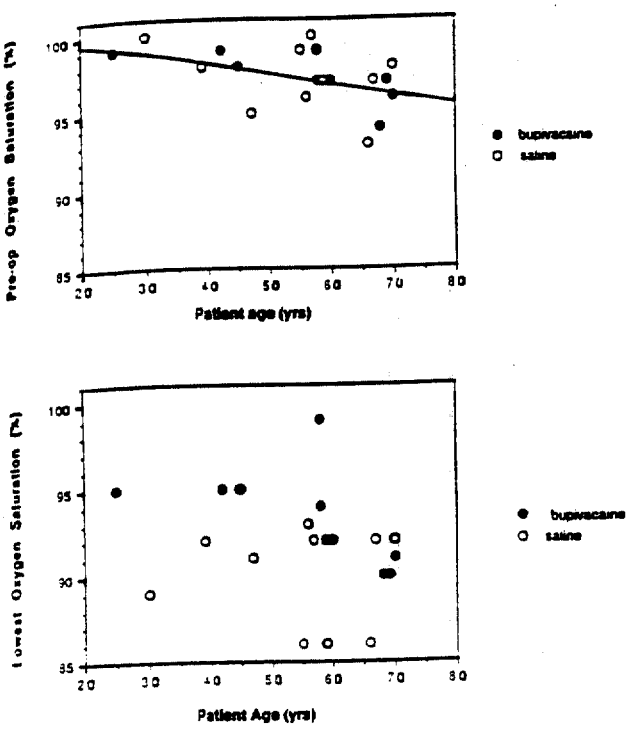


Fig. 1a. Correlation of preoperative oxygen saturation with patient age ($r = 0.52$, $P < 0.01$). Darkened circles represent patients in the bupivacaine group, open circles represent controls. b: Relationship of lowest postoperative saturation with patient age. The correlation demonstrated preoperatively is no longer seen, presumably because of the significant differences in narcotics received by different patients. Symbols as in Fig. 1a.

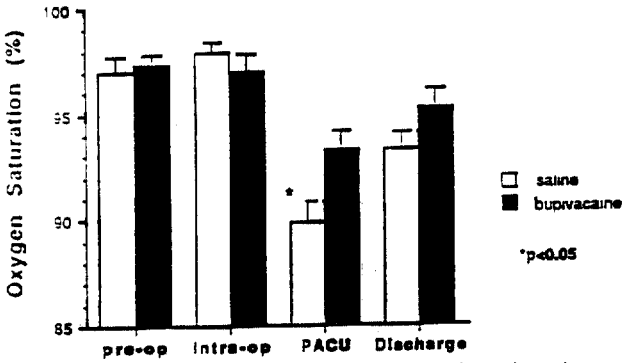
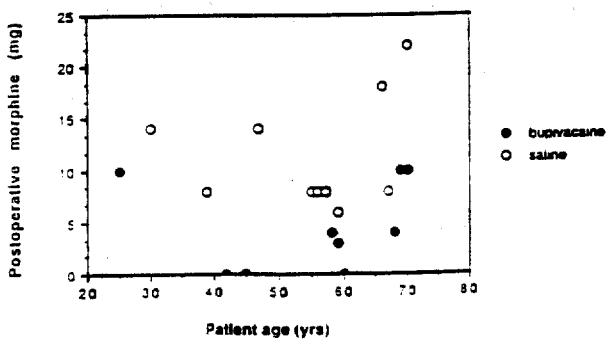


Fig. 2. Comparison of oxygen saturation measured by pulse oximeter in patients receiving bupivacaine (darkened bars) or saline (open bars). Shown are mean values ± standard error for preoperative Sao_2, lowest intraoperative measurement, lowest Sao_2 in the PACU and Sao_2 at discharge from the PACU. Significant differences between bupivacaine and saline groups are seen for postoperative Sao_2.

DISCUSSION

Postoperative pain control remains a serious problem in modern anesthesia and surgery. Intrathecal and continuous epidural narcotics provide excellent postoperative analgesia, but are costly, may require extended patient monitoring (2) and, may not be superior to PCA (5) or regularly scheduled narcotics (14, 15). As a result, they are not available in many hospitals. In the immediate postoperative period, when patients are drowsy but experiencing pain, administration of narcotics poses a potentially dangerous dilemma. On the one hand, severe pain, associated with catecholamine release and hypertension may be deleterious, but, on the other hand, administration of narcotics to a drowsy patient increases the risk of respiratory depression and loss of airway reflexes. This study demonstrates that incisional infiltration of a long-acting local anesthetic significantly lowered initial pain scores and requirement for narcotics in the PACU. The lower requirement for postoperative narcotics was accompanied by higher oxygen saturation in the PACU and shorter PACU stays.

The effects of infiltration with bupivacaine may be even greater than recorded here. In the interests of



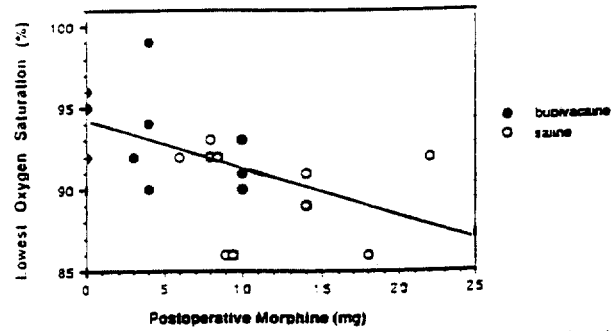


Fig. 3a. Narcotic administered in the PACU as a function of patient age. No significant correlation is seen between narcotic requirement and patient age. Patients in the bupivacaine group (darkened circles) required significantly less narcotic than those in the saline group (open circles). b: Postoperative Sao_2 as a function of narcotic administered in the PACU. A significant correlation is seen between the total morphine dose and lowest Sao_2 recorded in the PACU ($r = 0.51$, $P < 0.1$, symbols as in Fig. 3a).

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patient safety, we immediately provided supplemental oxygen to any patient whose Sao_2 fell to 90% during the 3-min tests of breathing room air. Nonetheless, Sao_2 continued to fall in some patients before it rose in response to provision of supplemental oxygen. Thus minimum Sao_2 values recorded were sometimes below 90%. It is likely that Sao_2 would have fallen even further in those patients had we not provided supplemental oxygen, accentuating the difference between control subjects and those receiving bupivacaine.

Previous studies on the effect of local anesthetic injection into the operative incision on postoperative narcotic requirements have yielded conflicting results. Some previous studies have found decreased narcotic requirements after abdominal surgical procedures, similar to those reported here (16, 17). Those studies examined the period after discharge from the PACU, however, and no measurement was made of oxygen saturation or length of PACU stay. Results from studies performed after inguinal herniorraphy have been equivocal. Hashimi & Middleton (18) found significantly decreased narcotic requirement after infiltration with bupivacaine. Another, unblinded, study, however, reported no difference between control and treated patients (19). In that study, injection of bupivacaine into a deep-lying indwelling catheter in patients following inguinal herniorraphy appeared to have no effect, and was associated with some evidence of wound infection (19). The difference between studies may lie in technique: superficial infiltration appears efficacious; deep infiltration of underlying muscle does not.

Moss et al. (17) compared a group of 43 patients who received 40–50 ml 0.5% bupivacaine infiltration into the incision at the time of cholecystectomy with a historical control group of previously operated patients and found greatly reduced narcotic requirements. No description is given of intraoperative anesthetic technique or narcotic administration, however, and significant differences in patient instruction, surgical technique and postoperative care make it difficult to determine what role the bupivacaine played. In a double-blind study of bupivacaine vs saline in cholecystectomy patients, Patel et al. (16) reported a 36% decrease in narcotic requirements over the first 3 postoperative days, a value in complete agreement with that observed here. Patel et al. did not report on anesthetic technique or examine narcotic requirements in the PACU. They did examine pulmonary function and demonstrated a smaller decrement in forced vital capacity and forced expiratory volume on the first postoperative day. No significant differences were seen, however, in arterial blood gases drawn on the second postoperative day.

One recent study advocated intraperitoneal (IP) administration of bupivacaine to control pain and to reduce postoperative ileus after abdominal operations (20). Scott et al. (21) investigated the effect of continuous IP infusion of bupivacaine in patients receiving both upper and lower abdominal procedures and found no effect on the stress response (as measured by serum levels of cortisol and glucose) or on pulmonary function. Interestingly, they also noted very poor pain control in their patients, suggesting that a major part of postoperative pain was incisional and not visceral in nature.

It was not the aim of this study to examine outcome variables of morbidity and mortality, since to do so would have required a much larger sample size. Nonetheless, it seems reasonable to assume that the higher postoperative Sao_2 seen in the bupivacaine group should result in reduced morbidity from respiratory complications. Splinting from incisional pain after upper abdominal operations is associated with a higher incidence of postoperative pulmonary complications (3, 4). Control of pain with narcotics may cause drowsiness and interfere with cooperation in deep breathing (11). This notion is supported by evidence of a reduced incidence of postoperative atelectasis in patients receiving incisional bupivacaine (16). The optimal dose of incisional bupivacaine remains to be determined. Studies employing 0.5% bupivacaine have claimed reduced narcotic requirements lasting several days (16, 17).

Thus the benefits of incisional bupivacaine compared to placebo include lower analog pain scores upon awakening from anesthesia, lower narcotic requirements in the PACU and lasting up to 24 h and improved pulmonary function. Patients in the bupivacaine group experienced less pain in the PACU and required a shorter PACU stay which should reduce hospital costs.

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Intraarticular Morphine, Bupivacaine, and Morphine/Bupivacaine for Pain Control after Knee Videoarthroscopy

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Evidence has accumulated that opioids can produce potent antinociceptive effects by interacting with opioid receptors in peripheral tissues. This study sought to compare the effects of morphine with those of bupivacaine administered intraarticularly upon pain following arthroscopic knee surgery. In a double-blind, randomized manner, 33 patients received either morphine (1 mg in 20 ml NaCl; n = 11), bupivacaine (20 ml, 0.25%; n = 11), or a combination of the two (n = 11) intraarticularly at the completion of surgery. After 1, 2, 3, and 4 h and at the end of the 1st and 2nd postoperative days, pain was assessed by a visual analogue scale, and supplemental analgesic requirements were recorded. Pain scores were significantly greater in the morphine group than in the other two groups at 1 h. There were no significant differences at 2 and 3 h. From 4 h until the end of the study period, pain scores were significantly greater in the bupivacaine group than in the other two groups. Analgesic requirements were significantly greater in the morphine group than in the other groups at 1 h but were significantly greater in the bupivacaine group than in the other groups throughout the remainder of the study period. We conclude that intraarticular morphine produces an analgesic effect of delayed onset but of remarkably long duration. The combination of these two drugs results in satisfactory analgesia throughout the entire observation period. (Key words: Analgesics, opioid: morphine. Anesthetics, local: bupivacaine. Anesthetic techniques: intraarticular. Pain: postoperative.)

OPIOID ANALGESIA has been associated with activation of opioid receptors within the central nervous system. Evidence has also accumulated that exogenous[1–3] as well as endogenous[4,5] opioids can produce pronounced antinociceptive effects by interacting with opioid receptors in peripheral tissues. We have been able to differentiate the types of opioid receptors involved[6] and to demonstrate such receptors on peripheral terminals of primary afferent neurons functionally[7] and *in situ*.[8] Furthermore, we have shown that peripherally administered opioids can elicit significant analgesic effects in humans.[8,9] Thus, low doses of intraarticular morphine, injected at the completion of arthroscopic knee surgery, can produce relatively long-lasting postoperative analgesia apparently *via* activation of local opioid receptors in the knee joint.[9]

Postoperative analgesia after arthroscopy has also been examined after the intraarticular administration of conventional local anesthetics.[10,11] So far, however, the results are equivocal. Thus, in patients receiving intraarticular bupivacaine, Henderson *et al.*[10] found no effect, whereas Chirwa *et al.*[11] found significantly reduced pain reports and supplemental analgesic use compared to controls.

The present study was designed 1) to examine the analgesic effect of intraarticular administration of a small dose of morphine upon postoperative pain in patients who had undergone arthroscopic knee surgery; 2) to compare the effect to that produced by a conventional local anesthetic, bupivacaine; and 3) to examine the effect of a combination of morphine and bupivacaine.

Materials and Methods

Patients

The project was institutionally approved, and informed consent was obtained from each patient before surgery. Thirty-three outpatients undergoing arthroscopic knee surgery were studied. Surgical procedures included diagnostic tissue excisions, partial or total meniscectomies, and lateral release, with approximately equal representation among the groups. The criteria for exclusion from the study were ASA physical status rating of 3 and greater[12] and the requirement for postoperative intraarticular drainage. All patients received meperidine (1 mg/kg intramuscularly) and midazolam (0.03 mg/kg intramuscularly) 1 h before surgery. Anesthesia was induced with thiopental (4 mg/kg). Succinylcholine (1 mg/kg) was administered to facilitate tracheal intubation, after which anesthesia was maintained with O_2/N_2O and isoflurane (0.8–2.0%).

Experimental Design

At the conclusion of surgery but before the arthroscope was removed, patients received one of the following so-

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lutions intraarticularly in a double-blind, randomized manner: 1 mg morphine-sulfate in 20 ml NaCl (n = 11), 20 ml 0.25% bupivacaine (n = 11), or 1 mg morphine sulfate in 20 ml 0.25% bupivacaine (n = 11). These doses were chosen based on previous animal and human studies.[6,8,9,11] Thereafter, general anesthesia was terminated. Since previous studies had shown that both intraarticular morphine and bupivacaine were more effective than saline,[3,9,11,13] we did not use such a control group, for ethical considerations.

Pain Assessment

Postoperative pain was assessed using a 10-cm visual analogue scale (VAS)[14] ranging from "no pain" to "unbearable pain." Scores were taken at 1, 2, 3, and 4 h after drug injection and at the end of the 1st and 2nd postoperative days, respectively. Supplemental analgesic medication was available upon request and was recorded at the above intervals. In the recovery room, fentanyl was given in increments of 0.05 mg and titrated to the patient's subjective level of comfort. Upon discharge from the hospital, the patients were instructed to use 1 or 2 codeine tablets every 3 h when needed, and were given a sheet of paper that had two VAS and a space for analgesics. They were asked to rate their pain intensity over the preceding 24 h and at the end of each postoperative day on the VAS and to record their analgesic usage at the same time. These sheets were then mailed back to the hospital by about 70% of the patients in each group.

Data Analysis

Demographic data were analyzed by analysis of variance (ANOVA).[15] To score the VAS, the distance (in millimeters) from the "no pain" end to the mark provided by the patient was measured. To determine supplemental analgesic requirements, meperidine doses were converted into codeine equivalents based on an equianalgesic ratio of 1:1.6.[16] Each patient's total consumption during their stay in the recovery room (1st h), in the outpatient department (2nd–4th h), and at home (1st and 2nd postoperative days) was calculated. Comparisons of p[illegible] between groups were made using the Kruskal-Wallis te and Dunn's procedure for *post hoc* evaluation. Compa sons of analgesic consumption between groups were ma using an ANOVA and Fisher's least significant differen (LSD) procedure for *post hoc* testing.[15] A P value $\leq 0.$ was considered significant.

Table 1. Demographic Data

	Age (yr)	Weight (kg)	Duration of Surgery (min)
Morphine (n = 11)	44.0 ± 9.5	[illegible]	67 ± 12
Bupivacaine (n = 11)	45.2 ± 5.[illegible]	[illegible]	59 ± [illegible]
Morphine + bupivacaine (n = 11)	44.9 ± 6.5	73.1 ± 2.2	61 ± [illegible]

Means ± SEM are given.

Results

There were no significant differences (ANOVA) in tient demographics (table 1) and preoperative pain sco (average 12.4 ± 4 mm).

VAS scores were not different between groups up 3 h postoperatively ($P > 0.05$, Dunn's test) except for 1st h, when the morphine group displayed significa greater values than the other two groups ($P < 0.0$ Dunn's test). From the 4th postoperative hour until end of the study period (2nd postoperative day), scores were significantly greater in the bupivacaine gr than in the other two groups ($P < 0.05$, Dunn's (table 2).

Supplemental analgesic consumption was significa greater in the bupivacaine group than in the other groups throughout the study period ($P < 0.05$, LSD except for the 1st h, during which time th group required significantly more than the other groups ($P < 0.001$, LSD test) (table 3).

Discussion

In patients who have undergone arthroscopic surgery, intraarticular morphine produces more nounced analgesia than intraarticular bupivacain tween the 4th h and the end of the 2nd postoper day, whereas bupivacaine is a superior analgesic d the 1st h postinjection. The combination of both stances produces satisfactory analgesia throughou entire study period.

The analgesic efficacy of these treatments is mented by a direct subjective measure of pain inte the VAS,[14,17] and an indirect indicator, supplement algesic requirements. Both measures appear well, in that during the 1st h both VAS scores and gesic requirements were significantly greater in the receiving morphine alone than in the other two g and between the 4th h and the end of the study p both measures were greater in the group pivacaine alone than in the other two group larger amounts of requested additional an spective differences in reported VAS scor distinct. These differences might have be in the absence of additional medication, wh was impossible to withhold for obvious ethical rea

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TABLE 2. Visual Analogue Scores

Time	1 h	2 h	3 h	4 h	1 day	2 days
Morphine (G1)	56.0 ± 10 24.15	28.3 ± 11 17.33	22.8 ± 7 12.33	13.9 ± 7 14.66	18.6 ± 6 12.72	13.9 ± 5 13.67
Bupivacaine (G2)	22.3 ± 9 12.18	26.5 ± 11 15.30	22.5 ± 6 16.95	32.8 ± 9 20.40	36.8 ± 7 21.23	28.6 ± 6 21.55
Morphine + bupivacaine	20.0 ± 4 13.86	14.3 ± 6 14.18	20.6 ± 5 16.77	8.6 ± 4 11.72	20.2 ± 3 13.46	13.0 ± 4 12.56
F value	10.07	0.74	1.74	5.71	5.76	6.67
P value	0.006	NS	NS	0.05	0.05	0.04
Post hoc Comparison	G1 > G2 G1 > G3			G2 > G1 G2 > G3	G2 > G1 G2 > G3	G2 > G1 G2 > G3

Means ± SEM (millimeters) and mean ranks are given. Data were analyzed by Kruskal-Wallis' and Dunn's procedures. NS = difference not significant.

The present data suggest that intraarticular bupivacaine produces an immediate analgesic effect of relatively short duration, while morphine produces a much longer-lasting effect but with a delayed onset. These characteristics agree with previous reports examining the intraarticular administration of bupivacaine,[10,11,18] or morphine.[8,9,18]

To discuss these time courses of action, one has to consider several aspects. First, the question arises as to the site of action of these drugs. It is generally accepted that local anesthetics exert their effects through an action upon peripheral nerves, and the duration of action of bupivacaine observed here is entirely consistent with previous studies.[11,15,19] In the case of opioids, however, such effects have been demonstrated only recently. Thus, low doses of peripherally administered opioids can produce potent antinociceptive effects mediated by peripheral opioid receptors in inflamed tissue of the rat.[3,6,20] Moreover, in humans, low doses of intraarticular morphine can significantly inhibit postoperative pain by an activation of peripheral opioid receptors within the joint.[9] Similar to the spinal application of opioids, the duration of analgesia after intraarticular morphine appears to be considerably longer than after systemic administration.[21] The remote possibility of a central action of this small dose of morphine, although not examined here, has been excluded in a previous study.[9] Other possible explanations are morphine's low lipid solubility[21] and its slow rate of absorption into the circulation resulting therefrom, or a relatively low blood flow to the articular area. In contrast, the relatively high lipophilicity of bupivacaine[19] could account for its faster uptake into the circulation and consequent removal from the joint. On the other hand, if one assumes sensory nerves to be the common site of action of these drugs (see below), these physicochemical characteristics could explain morphine's delayed and bupivacaine's immediate onset of action.

Second, the mechanisms of action of these drugs have to be taken into account. Local anesthetics are thought to produce their effects through inhibition of the generation and/or propagation of action potentials at the neuronal membrane and a resulting blockade of afferent nociceptive barrage.[19] In the case of opioids, two different peripheral mechanisms may result in a decreased nociception. On the one hand, morphine may diminish local posttraumatic inflammation through actions on leuko-

TABLE 3. Postoperative Analgesic Consumption

Time	Fentanyl (μg)	Codeine (mg)		
	1 h	2–4 h	Day 1	Day 2
Morphine (G1)	130.0 ± 16.7	45.0 ± 14.3	50.0 ± 21.0 (95.0 ± 14.5)	33.3 ± 21.6 (128.3 ± 13.9)
Bupivacaine (G2)	21.4 ± 6.4	105.0 ± 22.2	120.0 ± 26.6 (225.0 ± 23.9)	84.5 ± 23.2 (309.5 ± 21.2)
Morphine + bupivacaine (G3)	31.8 ± 10.1	36.0 ± 5.7	66.0 ± 11.8 (72.0 ± 5.6)	33.0 ± 6.6 (105.0 ± 5.8)
Value	24.54	5.73	2.92	6.51
Value	<0.001	0.008	0.049	0.005
Post hoc Comparison	G1 > G2 G1 > G3	G2 > G1 G2 > G3	G2 > G1 G2 > G3	G2 > G1 G2 > G3

The patients' total consumption during their stay in the recovery room (1 h), in the outpatient department (2–4 h), and at home (postoperative days 1 and 2) is given in means ± SEM. Data were analyzed by analysis of variance and Fisher's least significant difference procedure. Cumulative amounts of codeine are given in brackets.

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cytes,[22,23] inhibition of bradykinin formation,[22] or inhibition of plasma extravasation.[24] On the other hand, opioid binding sites have been shown on primary afferent neurons.[25–27] We have demonstrated such receptors functionally[7] and immunohistochemically.[5] Conceivably, activation of these neuronal receptors can cause attenuation of the excitability or nociceptive input terminals[28–30] and/or inhibition of release of excitatory transmitters[31,32] and ultimately result in antinociception.

In summary, we have shown that in patients having undergone arthroscopic surgery, intraarticular bupivacaine yields postoperative analgesia of immediate onset but only of short duration (2–3 h), whereas intraarticular morphine produces an analgesic effect of delayed onset (about 2 h postinjection), but of remarkably long duration (as long as 2 days postoperatively). The combination of these two drugs results in satisfactory analgesia throughout the entire observation period.

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Comparison of Postoperative Analgesic Effects of Intraarticular Bupivacaine and Morphine Following Arthroscopic Knee Surgery

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Recent studies have shown that, in the presence of inflammation, the local administration of opioids results in analgesia. The analgesic efficacy of local anesthetics and morphine administered intraarticularly was compared in patients undergoing arthroscopic knee surgery under epidural anesthesia. We compared postoperative pain scores (VAS) and opioid requirements among 47 patients receiving, in a randomized, double-blinded fashion, one of three intraarticular medications (20 ml): normal saline with 100 μg epinephrine (group 1, n = 16); 0.25% bupivacaine with 100 μg epinephrine (group 2, n = 15); and 3 mg morphine sulfate and 100 μg epinephrine in normal saline (group 3, n = 16). VAS scores were similar in the groups preoperatively and on arrival in the recovery room. At the end of the first postoperative hour, the residual sensory blockade was minimal in all three groups (mean = 3.8–4.1 segments) and almost total recovery occurred in all three groups before the second postoperative hour. The VAS in group 3 was not significantly different than group 1 at any time interval. Intraarticular bupivacaine (group 2) provided significantly better analgesia than did saline or morphine (group 1 vs 3) in the first 2 postoperative hours (ANOVA, $P < .05$). Subsequent VAS scores were not significantly different in the three groups. While one patient in group 2 requested analgesics during the first postoperative hour, nine patients in group 3 required systemic analgesics ($P < .01$). We conclude that no evidence for a peripheral opiate-receptor mediated analgesia could be demonstrated in patients undergoing arthroscopic knee surgery under epidural anesthesia. (Key words: Analgesics, opioid: morphine. Anesthetics, local: bupivacaine. Pain: postoperative. Receptors: opioid. Surgery: arthroscopy.)

THE RECENT GROWTH in outpatient surgery has presented new challenges in the field of postoperative pain management. Difficulties in adapting common methods of acute postoperative pain management in hospitalized patients to outpatients has resulted in inadequate treatment of pain following outpatient surgery.[1,2] Thus, the search continues for an ideal analgesic technique that is site specific, long-lasting, easily administered and has a high therapeutic safety index.

Arthroscopic surgery of the knee is a common outpatient procedure. Although intraarticular injection of bupivacaine following arthroscopy has been demonstrated to be safe[3–5] and effective[6,7] in providing postoperative analgesia, the mean duration of analgesia is only 2 h.[7] In a recent report, intraarticular morphine resulted in prolonged analgesia following arthroscopic knee surgery.[8] Intraarticular injection of opioids theoretically has the potential to fulfill several of the above-listed criteria of an ideal analgesic following arthroscopy.

Contemporary research has focussed on "peripheral sites" in the region of tissue injury as potential targets of analgesic drugs. For example, the traditional view that opioids produce analgesia solely by action on opiate receptors in the central nervous system has been challenged by evidence for peripheral opiate receptor-mediated analgesia.[9–12] Russell and coworkers[13] demonstrated in an electrophysiologic study in cats that close arterial injection of opioids inhibited the spontaneous discharges of a majority of the small diameter afferents from inflamed knee joints in a dose-dependent manner. This effect was naloxone reversible, suggesting an opiate receptor-mediated mechanism.

The present study was designed to determine whether intraarticular administration of opiates results in postoperative analgesia following arthroscopic surgery. In addition, the analgesic effect of an intraarticular opioid was compared to that of local anesthetics.

Material and Methods

Patients (ASA physical status 1–3) scheduled for elective outpatient arthroscopic surgery of the knee performed by a single surgeon (C. A. J.) were enrolled in the study. The study protocol was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions. Informed consent was obtained from all patients. Patients younger than 18 yr or with cruciate ligament tears were not included in the study. Exclusion criteria were acute traumatic injury to the knee, the use of oral narcotics preoperatively, history of allergy to any study medication, and the refusal of epidural anesthesia. Surgical procedures were similar in the three groups and included debridement of fat pad and adhesions, synovectomies, and partial or total meniscectomies.

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TABLE 1. Patient Profiles

	Group 1	Group 2	Group 3	P Value
N	16	15	16	
Age (yr)	46 ± 4	44 ± 3	35 ± 3	.08
Recovery room time (h)	2.8 ± 0.3	2.7 ± 0.2	2.4 ± 0.1	.4
Volume of epidural lidocaine (ml)	15.6 ± 0.5 (13–20)	16.5 ± 0.4 (15–20)	17.1 ± 0.6 (13–20)	.14
No. of dermatomes anesthetized (intraoperatively)	12.3 ± 0.4	11.0 ± 0.8	10.3 ± 1.0	.23
No. of anesthetized dermatomes (1 h postoperation)	3.8 ± 1.1	4.1 ± 1.0	3.9 ± 1.3	.97
Surgical time (h)	1.5 ± 0.1	1.5 ± 0.1	1.6 ± 0.1	.76

Values are mean ± SEM with ranges in parentheses.

Patients did not receive any medication prior to coming to the operating room.

Patients were randomized prospectively to one of three groups. Patients were asked to mark the intensity of their ongoing knee pain on a 10-cm visual analog pain scale (VAS) prior to the start of the anesthetic. The VAS was anchored at 0 (no pain) and 10 (most intense pain). The VAS has been validated for both clinical and experimental pain by previous studies.§[14] The anesthetic regimen consisted of lumbar epidural anesthesia using 2% lidocaine hydrochloride with 1:200,000 epinephrine (range 13–20 ml). The mean dermatomal level of analgesia to pinprick was T_{10} (range T_8–T_{12}). Midazolam for sedation was titrated in increments of 1 mg (median dose 4 mg). Epidural and parenteral opioids were avoided pre- and intraoperatively. All patients underwent arthroscopic surgery after inflation of a thigh tourniquet to 300–350 mmHg.

At the conclusion of the procedure, the appropriate study drug was administered in a double-blinded, randomized manner from a coded syringe into the joint space via an 18-G needle. Patients in group 1 received 20 ml of normal saline and 100 μg epinephrine. Patients in group 2 received 20 ml 0.25% bupivacaine and 100 μg epinephrine, and patients in group 3 received 3 mg of preservative-free morphine and 100 μg epinephrine in a total volume of 20 ml of normal saline.

The tourniquet was deflated and the patient was taken to the postanesthesia recovery unit and subsequently to the Same Day Care Center prior to discharge. An observer blinded to the patients' group assignment obtained hemodynamic data, VAS scores, and noted the level of residual epidural block upon arrival in the recovery unit and each hour until discharge (3–6 h). The observer also recorded the time at which the patient first requested pain medication. Analgesic therapy in the immediate postoperative period was managed by a physician not directly involved in the study. The usual analgesic regimen was oral Tylox® (5 mg oxycodone hydrochloride and 500 mg acetaminophen, McNeil Pharmaceuticals, Fort Washington, PA). If pain was uncontrolled with oral opioids, iv fentanyl was administered with an initial bolus dose of 50 μg and additional doses titrated as needed.

All patients were discharged home with 20 capsules of Tylox® and a supply of VAS sheets. Patients were advised to take their analgesic medication on a 4-h as-needed basis and rate their pain intensity on the VAS scale at 6-h intervals. Patients were seen at follow-up by the surgeon at 48 or 72 h, at which time a final VAS was completed, the number of unused Tylox® capsules counted, the average 24-h use of opioid calculated, and the presence of any complications ascertained.

STATISTICS

A one-way analysis of variance was used to compare pain scores in the three groups, and the least significant difference method used for pairwise comparisons of means at each time point (Statistix v3.1, Analytical Software, St. Paul, MN). The time to first analgesic dose and the 24-hr analgesic requirement were analyzed using a one-way analysis of variance. A chi-square analysis of contingency table was used for comparison of categorized data such as ASA physical status and gender. Results are shown as mean ± SEM. A P value of $< .05$ was considered to be statistically significant.

Results

Forty-nine patients were enrolled in the study; one patient was lost to follow-up, and one patient was too sedated in the recovery unit to obtain measurements of postoperative pain. Data from these two patients were excluded from further analysis. There were no significant differences among the groups in ASA physical status, gender, height, or weight. The male/female ratios were similar in the three groups (M:F = 11:5, 12:3, 12:4 in groups 1, 2, and 3, respectively). Additional patient demographics, anesthetic doses, surgical time, and times for recovery from the epidural anesthetic for the 47 patients included in the study are given in table 1. No significant differences

§ Price DD, Harkins SW. Combined use of experimental pain and visual analogue scales in providing standardized measurement of clinical pain. Clinical Journal of Pain 3:1–8, 1987.

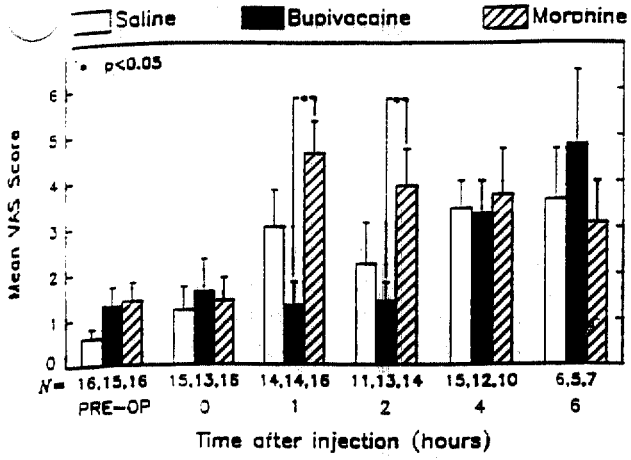

FIG. 1. Mean postoperative pain scores after arthroscopic knee surgery. Visual analog scores (VAS) of pain were obtained before and after the surgery. At the end of the surgery, patients were injected with 20 ml of one of the following three solutions intrarticularly: 100 μg epinephrine in 0.9% normal saline (saline); 0.25% bupivacaine and 100 μg epinephrine (bupivacaine); or 3 mg morphine sulfate and 100 μg epinephrine (morphine). The only significant differences were between the bupivacaine and morphine groups at the 1- and 2-h periods after the injection.

between the groups in any of the above-mentioned parameters (ANOVA, $P > .05$) were observed.

The preoperative and postoperative VAS scores during the first 6 h after surgery for the three groups are shown in figure 1. The difference in group scores are significant at the first and second postoperative hours. There are no other significant differences throughout the postoperative period. The lower number of patients during the sixth postoperative hour reflects that most patients were discharged prior to that time. The 24- and 48-hr VAS scores were 2.2 ± 0.6 and 1.9 ± 0.6 in group 1, 1.9 ± 0.6 and 1.5 ± 0.3 in group 2, and 2.2 ± 0.5 and 1.9 ± 0.6 in group 3 ($P > .8$).

Patients in group 3 (morphine) requested pain medication earlier than those in group 2 (bupivacaine; $P < .01$; table 2). Nine of 16 patients in the morphine group (group 3) and 2 of 16 patients in the control group (group 1) required supplemental analgesics during the first postoperative hour ($P < .05$). In contrast, none of the patients in the bupivacaine group required analgesics during the same hour ($P < .01$ compared to group 3). Despite the additional analgesic use in the morphine group, the VAS scores during the first 2 postoperative hours were higher in this group of patients compared to patients in the bupivacaine group ($P < .05$; fig. 1). Patients took pain medication *ad lib* over the first 2–3 postoperative days until follow-up. The Tylox® consumption per day did not differ by group (table 2).

Complications included two hemarthroses in each of the bupivacaine and morphine groups that resolved with either aspiration or conservative therapy and resulted in no long term sequelae.

Discussion

Our results indicate that, in patients undergoing arthroscopic knee surgery under regional anesthesia, intraarticular bupivacaine results in analgesia in the immediate postoperative period. In contrast, intraarticular morphine failed to provide significant analgesia during the same period. Our results are in agreement with those of earlier studies on the effects of intraarticular local anesthetics on postoperative analgesia in patients undergoing arthroscopy under general anesthesia.[7,15–17] Our observations of a lack of analgesic effect of morphine during the first 2 postoperative hours are also similar to the observations of Stein *et al.*[8] However, unlike in the reports of Stein *et al.*[8] and Khoury *et al.*,[17] we failed to observe a prolonged or perhaps delayed and prolonged analgesic effect with morphine. Our results are in agreement with those of Heard *et al.*,[18] who failed to demonstrate significant postoperative analgesia following intraarticular morphine in patients undergoing arthroscopic surgery either under general or regional anesthesia. The reasons for the discrepancy between the studies are not clear at present, but possible explanations are discussed.

Opiate receptors and endogenous opiates have been demonstrated not only in brain and spinal cord but in peripheral nerves and the dorsal root ganglia.[19,20] Neurophysiologic studies in uninjured skin have, however, failed to demonstrate an effect of opiates on response of cutaneous nociceptive afferent fibers innervating normal

TABLE 2. Postoperative Opioid Requirements

	Group 1 (Saline)		Group 2 (Bupivacaine)		Group 3 (Morphine)		
	n	Mean ± SEM		Mean ± SEM	n	Mean ± SEM	P
Time to first opioid dose (h)	13	2.9 ± 0.7	13	5.7 ± 1.6*	12	1.6 ± [illegible]	.01
# of opioid tablets per day	15	3.0 ± 0.6	13	2.3 ± 0.6	15	2.7 ± [illegible]	.5

*Group 2 significantly greater than groups 1 and 3 ($P < .01$); group 3 not different from group 1 ($P > .05$).

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skin in cat and monkey.[21,22] Several behavioral studies have demonstrated a site-specific analgesia by peripherally administered opiates in models of peripheral inflammation in rats.[10,12,23,24] It is possible that the activation of the peripheral opiate receptors depends on the presence of chemical mediators of inflammation. Behavioral and pharmacologic studies suggest a peripheral site of action of opiates in inflamed tissue. Joris *et al.* demonstrated that ethylketocyclazocine, a kappa opiate receptor agonist, and fentanyl, a mu receptor agonist, when injected subcutaneously blocked the thermal hyperalgesia induced by local inflammation of carrageenan in the rat paw. The same doses of opiate had no effect when given systemically. Opiates also inhibit cutaneous vasodilatation and extravasation induced by antidromic nerve stimulation[25,26] by inhibiting neuropeptide release from the sensory terminals. In addition, the peripheral release of substance P following C-fiber-strength stimulation of the peripheral nerve can be blocked by opioids.[27,28] The presence of periarticular opiate receptors also has been demonstrated in neurophysiologic studies in the cat following a chemically induced inflammation.[13]

Two possible explanations could account for the discrepancy between the results of this study and the recent reports of Stein *et al.*,[8] who observed a delayed, but prolonged, analgesic effect with intraarticular morphine. All patients in this study, including the control group, had intraarticular injection of epinephrine. If the local presence of epinephrine altered the inflammatory process, and thereby interfered with the activation of the opiate receptors, a peripheral opiate-receptor mediated analgesia may have been masked in our study. A second, more intriguing possibility pertains to the different anesthetic regimens in the two studies. Patients in this study underwent arthroscopy with epidural anesthesia, in contrast to the study by Stein *et al.*,[3] in which patients had general anesthesia. If the activation of the peripheral opiate receptors depends on neuroendocrine responses secondary to the afferent barrage of impulses along nociceptive pathways,[29–31] epidural anesthesia may prevent this activation. Recent reports indicate that protecting the nervous system from the noxious insults of surgery, using regional analgesic techniques, results in blunting of the neuroendocrine response[30,31] and confers long-term reduction in pain.[32,33] Thus, if the activation of peripheral opiate receptors is critically dependent on input to the central nervous system along nociceptive afferents, our anesthetic regimen would have precluded a peripheral opiate-receptor mediated analgesia. The observations by Heard *et al.*[18] that the patients who had regional anesthesia had lower VAS scores, irrespective of intraarticular drug treatment, compared to patients undergoing similar arthroscopic procedures under general anesthesia adds credence to this hypothesis.

The mechanism by which intraarticular morphine is associated with higher pain scores in the immediate postoperative period is obscure. Local histamine release or differences in pH may be contributory, though these factors were not analyzed in this study. However, increase in pain during the first 2 h following arthroscopy was also observed by Khoury *et al.*[17]

In conclusion, intraarticular bupivacaine provides better analgesia than does saline in the immediate postoperative period in this randomized prospective double-blind study. Our study fails to demonstrate functional opiate receptors in the knee joint in a clinical model of acute injury.

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INTRAOPERATIVE IRRIGATION WITH BUPIVACAINE FOR ANALGESIA AFTER ORCHIOPEXY AND HERNIORRHAPHY IN CHILDREN

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ABSTRACT

Effective postoperative analgesia is important, especially in pediatric surgery. The efficacy of intraoperative surgical wound irrigation with bupivacaine for postoperative analgesia was investigated in 90 children undergoing elective inguinoscrotal surgery. We found that this method effectively reduced postoperative pain and narcotic drug requirement. Bupivacaine irrigation was simple and complication-free. We believe that the irrigation of surgical wounds with bupivacaine should be a routine procedure in elective inguinoscrotal surgery in children.

KEY WORDS: bupivacaine, postoperative care, analgesia, hernia, inguinal, cryptorchism

Pain after surgery is a common complaint that may restrict early mobilization and hospital discharge of surgical patients. The use of local anesthetic agents as adjuvants to general anesthesia is gaining popularity in general and pediatric surgery.[1] We investigated the use of intraoperative irrigation of surgical wounds with bupivacaine to improve postoperative pain control.

MATERIALS AND METHODS

A total of 90 patients 5 months to 11 years old was enrolled in the study. Patient characteristics are summarized in table 1. All patients were hospitalized for elective inguinoscrotal surgery for undescended testis or inguinal hernia. Children with a history of allergy to local anesthetic agents or of previous surgery in the ipsilateral inguinal region were excluded. Informed parental consent was obtained in every case. Patients were premedicated with 70 mg./kg. chloral hydrate and anesthetized with mixed oxygen, 70% nitrous oxide and halothane with a face mask. No additional intraoperative sedatives or narcotics were administered.

Patients were randomly assigned to 2 groups of 45 by alternately allocating children to 1 group or the other as they entered the study. Group 1 was treated with irrigation of the surgical wound with 0.25 cc/kg. 0.25% bupivacaine solution before closure of the inguinal canal and before suturing the subcuticular layer. The bupivacaine solution was left in place for 30 seconds for each irrigation and the excess was then removed by suction. Group 2 (control) was treated with normal saline instead of bupivacaine.

Postoperatively 1 mg./kg. meperidine was administered intramuscularly as required for postoperative analgesia. No other analgesic drugs were used. The decision as to when to administer meperidine was made by the regular nursing staff of the pediatric surgery ward based on verbal complaint of pain, crying that was not responsive to parental attention, flexion of the hip, holding the operated groin region or elevated blood pressure. The severity of the pain was not considered in the decision to administer meperidine, which is our usual practice for postoperative pain control. The nursing staff was not aware of patient group allocation.

The total number of doses of meperidine administered during the first 12 hours postoperatively, and the interval between the end of anesthesia and the initially required dose of meperidine were recorded and used to assess the efficacy of intraoperative wound irrigation with bupivacaine for postoperative analgesia. In addition the parents or the child (if old enough to understand and answer relevant questions) were asked 12 hours after surgery to report on how painful the postoperative period was in its entirety. To measure the responses we used a fixed interval 4-point pain scale (fig. 1). The standard pain scale was modified to facilitate comprehension by younger children. We preferred a fixed interval pain scale to a visual analogue scale because it is simpler to use with children.[2]

Demographic data were compared between the groups using the Student t test for interval data (age and weight) and the z statistic for nominal data (sex and type of operation). Differences between the groups in the number of required doses of meperidine, interval to initial required dose and the subjective pain scale were analyzed using the Mann-Whitney rank sum test, and $p < 0.05$ was considered statistically significant.

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TABLE 1. *Demographic data on the 2 experimental groups*

	Bupivacaine Group	Control Group
Total No. pts.	45	45
Procedure:		
Herniorrhaphy	27	26
Orchiopexy	18	19
Sex:		
Male	37	34
Female	8	11
Mean pt. age (yrs.):	4.6	4.3
Younger than 1	5	7
1 to 5	24	23
Older than 5	16	15

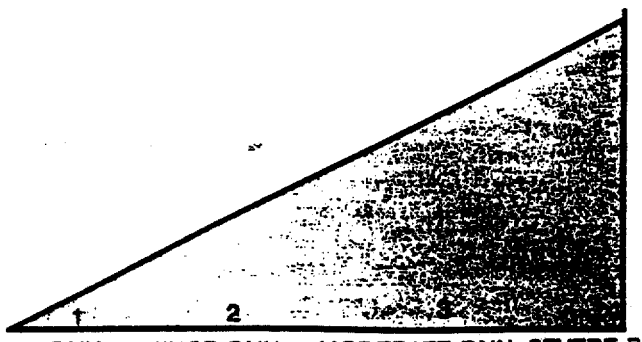

FIG. 1. Modified fixed interval 4-point pain scale used to question children and parents about postoperative pain.

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RESULTS

There were no significant differences in demographic data between the 2 groups. The children in the bupivacaine group required significantly less postoperative medication for analgesia than those in the control group (fig. 2). The average number of doses of meperidine required per child in the bupivacaine group was 0.066 ± 0.043 (mean plus or minus standard error of mean) compared to 0.844 ± 0.16 doses per child in the control group, which was statistically significant ($p = 0.001$). Average interval between the end of anesthesia and the initial required dose of meperidine was also longer in the bupivacaine group (252 ± 62.7 minutes) than in the control group (100 ± 21.42 minutes), which was statistically significant ($p = 0.02$). On the subjective pain scale the bupivacaine group reported less pain than the control group (score 1.5 ± 0.11 versus 2.6 ± 0.18, respectively, $p = 0.001$). While 13 children in the control group experienced postoperative nausea or vomiting only 3 in the bupivacaine group had these complaints. The statistical significance of these differences remained when the groups were analyzed by type of operation. No wound infection or delayed wound healing occurred in any of the patients.

DISCUSSION

The control of postoperative pain is of interest to surgeons and anesthesiologists alike. In children it is particularly important to achieve effective postoperative pain control to minimize the psychological trauma associated with surgery. The methods used to control postoperative pain are diverse and narcotic drugs, such as meperidine, are the mainstay of treatment. Although quite effective, these drugs cause somnolence and emesis,[3] which can delay early patient ambulation and hospital discharge of those who undergo outpatient surgery.[4–6]

Caudal epidural block is effective for postoperative analgesia[7] and in children it can be administered preoperatively or at the end of the surgical procedure before the termination of anesthesia. Caudal block provides excellent postoperative pain control, diminishes the level of general anesthesia and shortens the period needed to awaken from general anesthesia. The disadvantages of caudal block are that it is time-consuming and requires 2 anesthesiologists to perform it safely on an anesthetized patient. Another disadvantage is the relatively large volume of anesthetic agents injected into the epidural space, which may result in high plasma levels of these drugs.[8] Some children with paresthesia in the lower extremities dislike the altered sensation associated with caudal block. In addition the caudal block technique is not free of the risk of complications, such as inadvertent intravascular injection of the anesthetic agent.

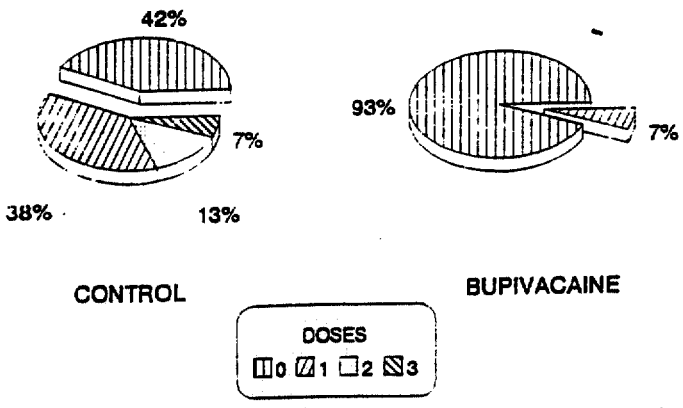

FIG. 2. Number of doses of meperidine received by patients in treatment and control groups.

The use of local anesthetic agents for postoperative analgesia was first reported in 1935 by Capelle[9] and it has become the object of renewed interest since long acting local anesthetic agents, such as bupivacaine, have become available. Bupivacaine was administered for postoperative analgesia via a catheter implanted in subcostal incisions in lecystectomy patients.[10] This method reduced the requirement of narcotics needed to control postoperative pain and improved postoperative pulmonary function, which was assessed by measuring forced vital capacity. Although no cases of wound infections or delayed wound healing were reported, it is obvious that most surgeons would be reluctant to place an indwelling catheter in the surgical wounds of clean operations, such as orchiopexy or herniorrhaphy.

The use of local anesthetic agents in local block techniques, such as ilioinguinal iliohypogastric blocks for inguinoscrotal surgery, has also been effective in the control of postoperative pain in children.[11] These methods are relatively simple to use and are as effective as the caudal epidural block without the dangers associated with a large volume of anesthetic.[12–15] However, with ilioinguinal iliohypogastric blocks there is the risk of inadvertent intravascular or intraperitoneal injection, and poor placement of the anesthetic injection may cause insufficient analgesia. Furthermore, cases of transient quadriceps muscle paresis have been reported after these nerve blocks.[16] These facts have led to the use of local anesthetic agents infiltrated directly into the region of the surgical wound.[17, 18] This method has been effective for postoperative pain control with relatively few complications but there remains the possibility of intravascular injection, hematoma formation and an increased risk of wound infections.

Topical application of local anesthetic agents has been tried for the relief of post-circumcision pain[19] and post-herniorrhaphy pain in adults.[20] Additional studies showed that surgical wound irrigation with bupivacaine was as effective as a local nerve block for the control of pain in child undergoing herniorrhaphy.[21] Our study demonstrated the irrigation of surgical wounds with bupivacaine reduced postoperative pain effectively in children and significantly reduced the requirement of narcotic drugs. In addition the pain-free postoperative period was lengthened in children who underwent herniorrhaphy or orchiopexy (table 2).

Because perception of pain is subjective and difficult to quantify, we used postoperative consumption of meperidine for analgesia as a method to compare postoperative pain between the treatment and control groups. Meperidine was administered to the patients according to the normal criteria used by the nursing staff at our postoperative ward, thus ensuring the validity of the comparison. In addition we used the subjective pain scale to measure whether children and parents considered the entire postoperative period to be painful.

Since it is our normal practice to irrigate surgical wounds with saline toward the end of the operation, irrigation with bupivacaine does not entail any complication of the surgical procedure. It seems to us that irrigation of surgical wounds with bupivacaine is not only effective for postoperative analgesia but also the simplest and least invasive technique applicable and, therefore, it has the least risk of complications and side effects.

TABLE 2. *Distribution of doses of meperidine administered*

No. Doses Meperidine	No. Control Group (%)		No. Bupivacaine Group (%)	
	Orchiopexy	Herniorraphy	Orchiopexy	Herniorraphy
0	8 (45)	10 (40)	17 (94)	25 (92)
1	4 (20)	14 (52)	1 (6)	2 (8)
2	6 (30)	0	0	0
3	1 (5)	2 (8)	0	0
Totals	19 (100)	26 (100)	18 (100)	27 (100)

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Postoperative Pain After Inguinal Herniorrhaphy with Different Types of Anesthesia

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TVERSKOY M, COZACOV C, AYACHE M, BRADLEY EL, Jr, KISSIN I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg 1990;70:29–35.

In a randomized, double-blind study, postoperative pain was assessed in 36 patients undergoing inguinal herniorrhaphy with three types of anesthesia: general (thiopental-nitrous oxide-halothane); general with the addition of local (infiltration of the abdominal wall with 0.25% bupivacaine along the line of the proposed incision); and spinal (0.5% bupivacaine). The severity of constant incisional pain, movement-associated incisional pain, and pain upon pressure applied to the surgical wound using an algometer was assessed with a visual analogue self-rating method at 24 h, 48 h, and 10 days after surgery. The addition of local anesthesia significantly decreased the intensity of all types of postoperative pain. This effect was especially evident with constant incisional pain that disappeared almost completely 24 h after surgery. With pain caused by pressure on the site of the surgical incision, the pain score difference between general and general plus local anesthesia was obvious even 10 days after the surgery (with 0.4-kg/cm^2 pressure, the pain scores were 16 ± 3 vs 2 ± 1, $P < 0.01$). The difference in postoperative pain scores between spinal and general anesthesia groups indicated that spinal anesthesia also decreases the pain intensity. However, this decrease is less pronounced than that seen with the addition of local anesthesia: movement-associated pain scores 24 h after surgery were 72 ± 5 in the general anesthesia group, 40 ± 6 in the spinal anesthesia group, and 16 ± 3 in the general plus local anesthesia group (with $P < 0.002$ between the groups).

Our results indicate that postoperative pain after inguinal herniorrhaphy can be significantly decreased if the surgery is performed with the use of local or spinal anesthesia. We hypothesize that neural blockade, by preventing nociceptive impulses from entering the central nervous system during and immediately after surgery, suppresses the formation of the sustained hyperexcitable state in the central nervous system that is responsible for the maintenance of postoperative pain.

Key Words: PAIN, POSTOPERATIVE.

There is a renewed interest in the use of local anesthesia for reduction of postoperative pain (1–3). It was reported that infiltration of the abdominal wall along the line of the proposed incision for inguinal herniorrhaphy with 0.25% bupivacaine results in a postoperative pain-free period of approximately 10 h (4). Administration of a local anesthetic in the wound before its closure (bupivacaine instillation or application of lidocaine aerosol) has been found to decrease opioid requirements and accumulated pain score during the first 24 h postoperatively (2,3). In the initial studies, to obtain long-lasting postoperative analgesia, the investigators implanted catheters in the surgical wound and injected local anesthetics at regular intervals after surgery (5–7).

The aims of the present study were to determine (a) whether local anesthesia used during surgery decreases the severity of pain beyond the immediate postoperative period, when the pain relief cannot be explained by prolonged presence of the local anesthetics in the body; and (b) whether spinal anesthesia (which does not provide the significant direct effect of a local anesthetic on tissues in the area of surgery) relieves postoperative pain similar to local anesthesia.

Methods

With approval from the Institutional Human Investigation Committee and informed consent, 36 male patients, 35–75 yr of age, scheduled for elective

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inguinal hernia repair at the Safed Hospital, were investigated in a double-blind, randomized study. Patients with severe hepatic, renal, or cardiovascular disease were excluded. Hernia repair was carried out by the same surgeon using the Bassini technique. The patients were divided randomly (systematic random sample technique) into three groups: general anesthesia (G), general plus local anesthesia (G + L), and spinal anesthesia (S), with 12 patients in each group. In the G group, patients received preanesthetic medication consisting of atropine (0.5 mg SC) and promethazine (25 mg IM). Anesthesia was induced with thiopental (4 mg/kg), and after the administration of 1 mg of pancuronium to prevent fasciculations, tracheal intubation was performed with the aid of succinylcholine (1 mg/kg). After intubation, 5 mg of pancuronium was given, with additional doses (1 mg) as indicated during surgery. Anesthesia was maintained with nitrous oxide in oxygen (N_2O/O_2; 2:1) and 0.5% halothane. At the conclusion of the surgery, 1 mg of atropine followed by 2.5 mg of neostigmine was administered. No narcotic was used for premedication or during surgery. In the G + L group, in addition to the general anesthesia performed as described above, subcutaneous and intramuscular infiltration of the abdominal wall with 0.25% bupivacaine (40 mL) along the line of the proposed incision was made 5 min before the surgery. About 2 mL of the bupivacaine solution was injected around the neck of the sac at the appropriate stage of the surgery. In the S group, under conscious sedation with midazolam (0.07 mg/kg IV), the spinal anesthesia was achieved using 0.5% solution of bupivacaine (12.5 mg). The subarachnoid puncture was performed at the L3-4 interspace with a 25-gauge needle.

Postoperatively, patients from all three groups were treated for pain in exactly the same way. When a patient complained of pain, meperidine (50 mg IM), was given, and the time from the end of the surgery to the first request for analgesic was recorded (time to first analgesic). After the first injection each patient received 25 mg of meperidine every 4 h on the first day and every 6 h on the second day after surgery. Starting with the third day the patients were given 500 mg of acetaminophen every 4 h orally.

The intensity of postoperative pain was assessed by the patients blinded to the possible association between the type of anesthesia and postoperative pain. The investigator participating in the pain assessment was blinded to the patient group. The assessment was made three times in each patient: at 24 h, 48 h, and 10 days after the surgery (at follow-up visit). The assessment of pain was performed with a visual analogue self-rating method (8). The visual analogue scale consisted of a 100-mm horizontal line without gradation connecting points marked as "no pain at all" and "as severe as it could be." All assessments of pain intensity were made 3–4 h after meperidine administration. The patients were told to indicate how they felt at the moment by placing a mark perpendicular to the line. The scales were scored by measuring the distance (in millimeters) of the perpendicular mark from the left side of the line.

Three types of pain were assessed: constant incisional pain, movement-associated incisional pain, and pain upon pressure on the surgical wound. The movement-associated incisional pain was assessed,

Table 1. Characteristics of Patients

Variable	Types of anesthesia		
	General	General plus local	Spinal
n (all males)	12	12	12
Age (yr)	59 ± 9	53 ± 7	54 ± 13
Weight (kg)	69 ± 9	73 ± 10	71 ± 14
Duration of surgery (min)	32 ± 6	31 ± 5	30 ± 6

Values are mean ± SD.

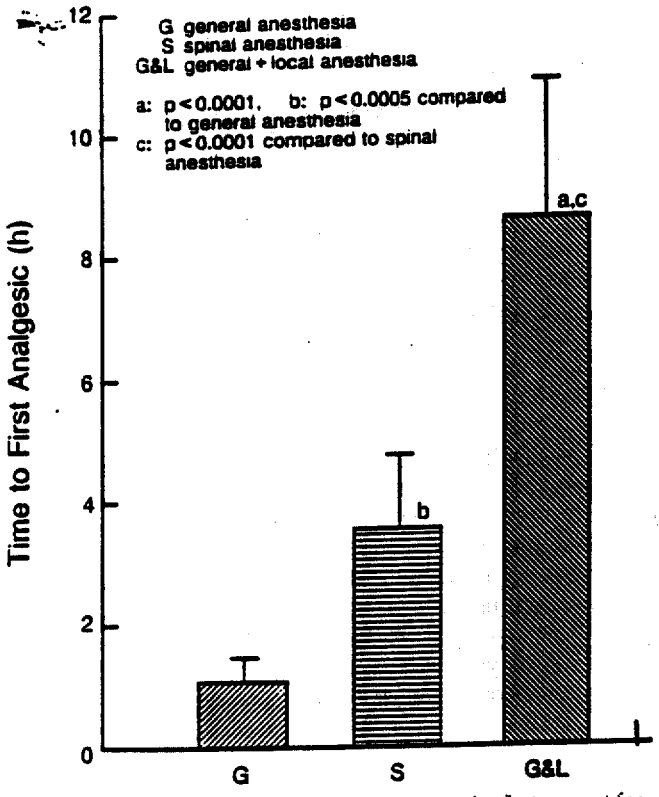

Figure 1. Times from the end of the surgery to the first request for analgesic after three different types of anesthesia (mean ± SEM).

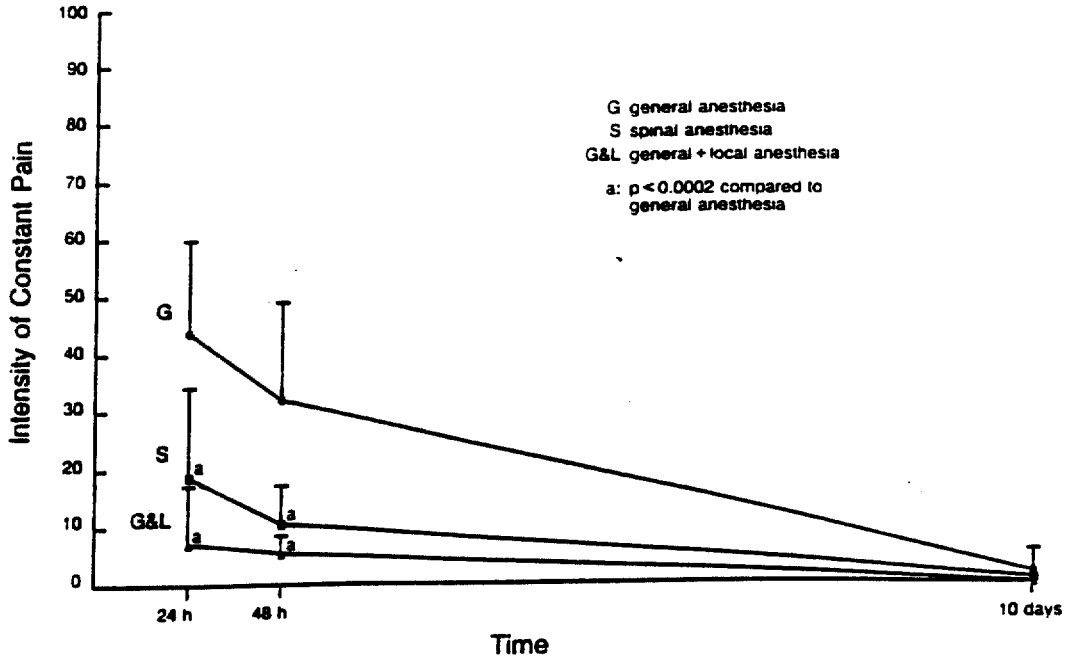

Figure 2. Intensity of constant postoperative incisional pain after three different types of anesthesia. The pain score is presented in millimeters on a 100-mm visual analogue scale (mean ± SEM).

on request of an investigator, after the patient got out of the bed. An algometer (PDT Co., Great Neck, N.Y.) with a pressure surface of 4 cm^2 was used for the determination of the pain on pressure. The pressure was applied on the wound for 10 s through the dressing. At 24 h and 48 h 0.2-kg/cm^2 and 0.3-kg/cm^2 pressures were used, and on day 10, 0.4 kg/cm^2 and 0.6 kg/cm^2. Severity of the pain resulting from pressure on the wound was also assessed with the visual analogue self-rating method. In addition, the threshold for wound pain elicited by pressure was measured. With the use of the algometer, pressure on the wound was increased at a constant speed of 0.02 $kg \cdot cm^{-2} \cdot s$ until the patient indicated the pressure was painful. The pain threshold was measured 24 h, 48 h, and 10 days after surgery.

The data were summarized as mean ± SEM for each group. A one-way analysis of the variance was used to assess the differences in mean pain scores and in mean times to first administration of meperidine among the three groups utilized (9). Multiple comparisons among pairs of stage means used the Fisher's protected least significant difference test (9,10). Differences were declared statistically significant if $P < 0.05$.

Results

The study groups were comparable with respect to age, weight, and duration of surgery (Table 1). In addition, all patients were male and had the same type of surgery performed by the same surgeon. The duration of analgesia (time from the end of the surgery to the first request for analgesic) was 64 ± 8 min in group G, 212 ± 21 min in group S, and 515 ± 39 min in group G + L, with statistically significant differences between each of the groups (Figure 1). The most dramatic effect of local and spinal anesthesia was observed with regard to the constant incisional pain. In group G + L, this type of pain was essentially absent 24 h after the surgery at a time when the pain intensity score in group G was 44 ± 5 and 32 ± 5 at 24 h and 48 h respectively. In group S the constant pain score was significantly lower than in group G and not statistically different from group G + L (Figure 2). The score of the movement-associated incisional pain at 24 h was the highest in group G (72 ± 5) and the lowest in group G + L (16 ± 3), with group S occupying the intermediate position (40 ± 6). At 48 h the movement-associated pain scores were proportionally decreased in the G and S groups without any significant change in group G + L (Figure 3).

Pain intensity at pressure on the wound also was highest in group G and lowest in group G + L, with group S in the intermediate position, for both 24 h and 48 h. Ten days after surgery the difference between the G and the G + L groups still was present

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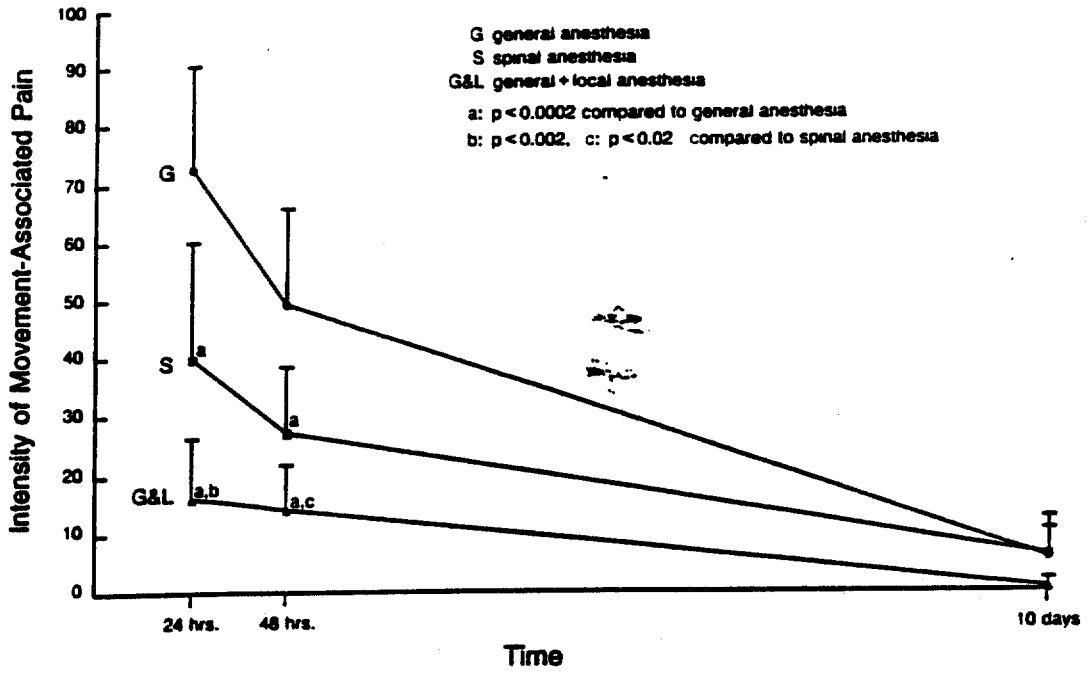

Figure 3. Intensity of movement-associated postoperative incisional pain after three different types of anesthesia. The pain caused by getting out of bed is presented in millimeters on a 100-mm visual analogue scale (mean ± SEM).

(pain score 16 ± 3 vs 2 ± 1, $P < 0.01$, with 0.4-kg/cm^2 pressure, and 35 ± 4 vs 16 ± 3, $P < 0.01$, with 0.6-kg/cm^2 pressure). At the same time, no difference was found between the G and S groups (Figure 4). The threshold to pain on pressure data basically confirmed the pain intensity to pressure results. The wound pain threshold was much lower in the G and S groups than in the G + L group. The difference between the G and S groups was statistically significant only at 48 h (Figure 5).

Discussion

The addition of local anesthesia to general anesthesia resulted in an increase in the postoperative time to the first request for analgesic from 1 h to approximately 9 h. at a time when this period with spinal anesthesia was 3.5 h. A prolonged pain-free period (10 h) after local anesthesia (0.25% bupivacaine administered before incision) for inguinal herniorrhaphy was reported by Kingsnorth et al. (4). It is well known that analgesia with bupivacaine-induced infiltration anesthesia lasts longer than with bupivacaine spinal anesthesia and that some bupivacaine-induced peripheral nerve blocks have anesthetic effect up to 12 h (11). It should be noted also that analgesia after bupivacaine infiltration persists longer than does anesthesia (12). If given this, the prolonged period from the end of surgery to the first request for analgesic in our G + L anesthesia group is no surprising.

Our results indicate that the addition of local anesthesia to general anesthesia significantly decreases the intensity of postoperative pain. This effect was especially evident with constant incisional pain, which was almost completely absent at both 24 and 48 h after surgery. With the pain caused by pressure on the site of the surgical incision, the pain score difference between general anesthesia alone and general anesthesia plus local anesthesia was obvious even 10 days after the surgery.

Two recent studies on the use of local anesthetics in the surgical wound before closure of the incision also demonstrate a significant reduction in postoperative pain at 24 h but not at 48 h after surgery (2,3). The discrepancy between these results and our present findings might be due to the fact that in our study the postoperative use of analgesics was the same in all three groups of patients. Therefore, the postoperative pain difference between the groups could find its expression only in one index—pain score (otherwise this difference might be disguised by fragmentation of the changes between two indices: consumption of analgesics and pain score). Patel et al. (13), using a single injection of bupivacaine into the wound after cholecystectomy, demonstrated a

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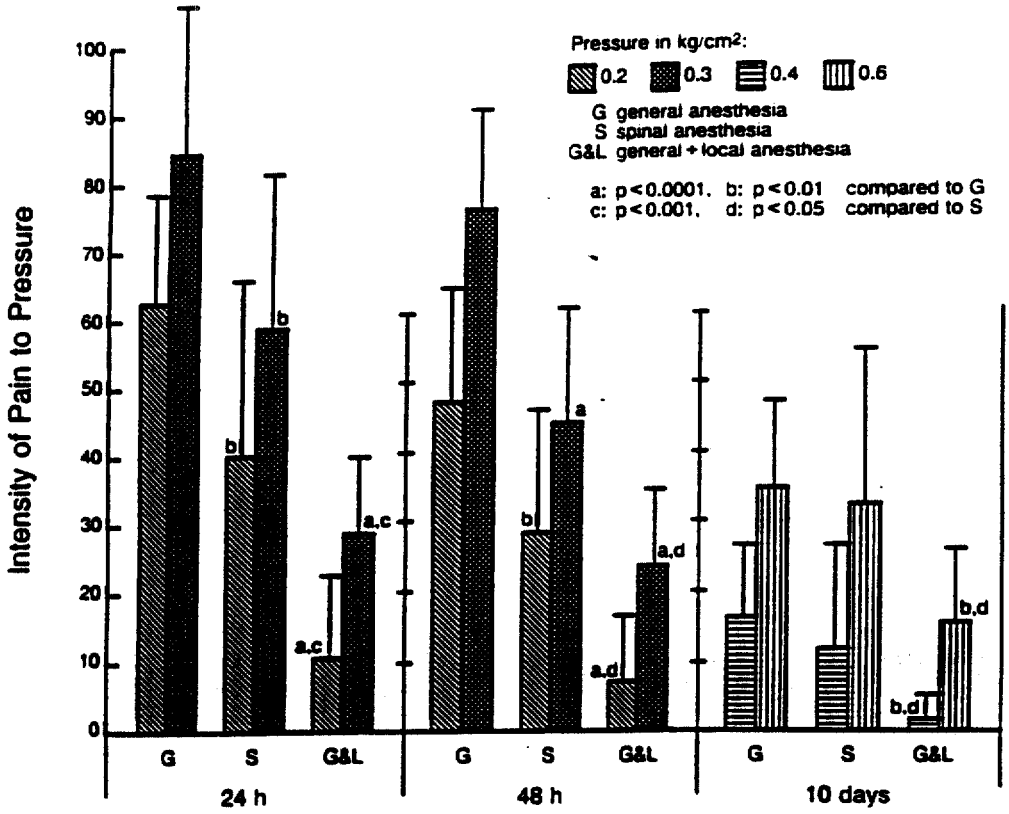

Figure 4. Intensity of pain caused by pressure on the surgical wound after three different types of anesthesia. The pain score is presented in millimeters on a 100-mm visual analogue scale (mean ± SEM).

reduction in postoperative narcotic requirement for 3 days and a decrease in deterioration of pulmonary function tests after surgery. A subsequent study with continuous infusion of bupivacaine into an upper abdominal wound after cholecystectomy did not report better postoperative pain relief than perfusion with normal saline (14).

The difference in postoperative pain intensity between the spinal anesthesia group and the group given general anesthesia alone seen in our study indicates that spinal anesthesia also decreases postoperative pain. However, this decrease was less pronounced than that with local anesthetic injected into the operative site, especially with movement-associated pain and pain caused by the pressure on the wound. Pain upon pressure on the site of the surgical wound 10 days after surgery performed under spinal anesthesia was not different from that seen in the group given general anesthesia alone. We suggest that a less profound effect of spinal anesthesia on postoperative pain was due to a shorter duration of its effect (3.5 h vs 9 h with local infiltration). Powerful nociceptive impulses are generated not only the surgical procedure itself, but also by the action of proteolytic and inflammatory agents released into the wound tissues. The effect of the latter might be very strong for several hours after surgery. Hence a 9-h effect with bupivacaine infiltration probably offered a better protection than spinal bupivacaine anesthesia, which lasted only 3.5 h.

Thus, our results indicate that infiltration at the surgical incision with a local anesthetic or spinal anesthesia can decrease postoperative pain and that this effect cannot be explained by prolonged presence of a local anesthetic in the body because pain relief was evident in 48 h and, with pressure-induced pain, even 10 days after the surgery. Such long-lasting differences in pain intensity with different types of anesthesia appear to represent more a consequence of the initial anesthetic effect, not an extended pharmacologic action. Recent experimental data indicate that nociceptive impulses may set off a prolonged and widespread increase in spinal cord excitability (15–17). It also has been shown that maximal injury discharge transmitted along C-fiber afferents may even cause transneuronal morphologic changes in the spinal cord (18). Spinal cord hyperexcitability produced by massive nociceptive impulses may be sustained and thus constitute a pathophysiologic mechanism underlying postoperative pain (19). Gen-

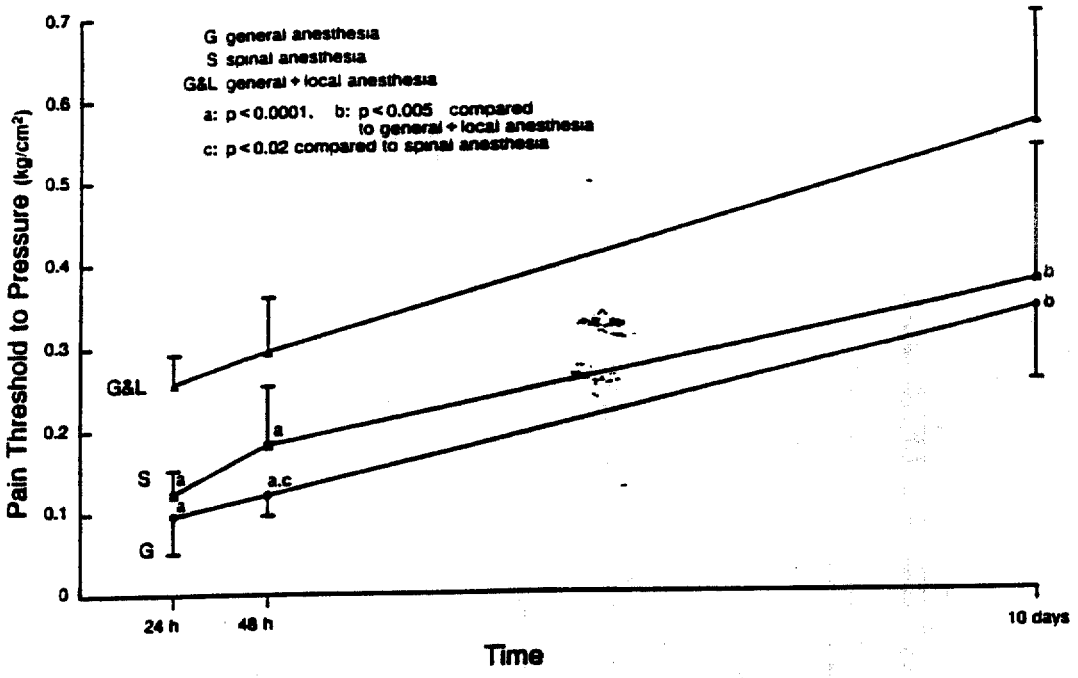

Figure 5. Postoperative pain thresholds to pressure on the surgical wound after three different types of anesthesia (mean ± SEM).

eral anesthesia, in contrast to local infiltration and spinal anesthesia, cannot prevent the transmission of nociceptive impulses from the operative site to the spinal cord. A relatively light level of general anesthesia, which is now a common practice, probably cannot prevent the creation of sustained hyperexcitability in the central nervous system, which most likely is involved in determining the intensity and duration of postoperative pain.

At the beginning of this century, Crile (20) wrote that patients given inhalational anesthesia still need to be protected from stressful surgical stimuli by regional anesthesia; otherwise they might suffer persistent central nervous system changes. Hannington-Kiff (21) has suggested that some patients with persistent pain in the region of previous surgery (despite the absence of any obvious clinical signs) "might have had a scar imprinted on the central nervous system at the time of operation under light general anesthesia" (21). Our data can provide support for this point of view.

In conclusion, postoperative pain after inguinal herniorrhaphy can be significantly decreased if the surgery is performed with local infiltration anesthesia or spinal anesthesia instead of general anesthesia, perhaps because neural blockade prevents nociceptive impulses from entering the central nervous system during and immediately after surgery and thus suppresses formation of the sustained hyperexcitable state in the central nervous system that is responsible for the maintenance of postoperative pain.

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Randomized placebo-controlled trial of local anaesthetic infusion in day-case inguinal hernia repair

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Background This study investigated the efficacy of local anaesthetic wound perfusion following day-case inguinal hernia repair.

Methods Seventy-two patients entered a randomized controlled trial with three patient groups: group 1, pump containing bupivacaine; group 2, pump containing normal saline; and group 3, control group without a pump. All patients had a Lichtenstein hernia repair together with ilioinguinal and iliohypogastric nerve blocks and were prescribed oral analgesia. Postoperative pain was assessed over 5 days using a visual analogue scale.

Results Patients who had a local anaesthetic infusion had significantly less pain than either the placebo or control groups. This was greatest during the first 48 h (day 1, $P = 0{\cdot}028$ and $0{\cdot}011$ respectively; day 2, $P = 0{\cdot}012$ and $0{\cdot}037$ respectively).

Conclusion A portable infusion pump for the delivery of local anaesthetic reduced pain after day-case inguinal hernia repair.

Day surgery is increasing in the UK; it is predicted that it will account for up to 50 per cent of all surgical procedures performed in the next decade[1,2]. Postoperative pain is a major factor which reduces its acceptability to patients[3]. After day-case inguinal hernia repair 10 per cent of patients have severe postoperative pain requiring the services of a general practitioner (GP) to administer intramuscular opiates[4]. This can be reduced by the use of oral opiates, and pre-emptive and postoperative blockade with locoregional anaesthesia[5–8]. Oral opiates may cause nausea unacceptable to some patients[9]. Locoregional anaesthesia is effective[5,7,8] but is limited in duration of action, even when using long-acting agents such as bupivacaine[7]. Continuous infusion of local anaesthetic into a surgical wound can reduce postoperative opiate requirements[10–12]. Until recently there was not a delivery system suitable for use in day-case surgery.

The authors investigated the use of an infusion pump for the delivery of local anaesthetic for day-case hernia repair.

Patients and methods

Seventy-two consecutive patients undergoing standard unilateral inguinal hernia repair as a day case were included in the trial. Informed consent, as approved by the local ethics committee, was obtained in each case. Each patient was randomized to one of three groups: group 1, pump containing bupivacaine; group 2, pump containing normal saline; and group 3, control group without a pump. Group 3 was included to demonstrate the size of the placebo effect and to exclude the possibility of a negative effect of the placebo.

A Lichtenstein hernia repair[13] was used in every case. Standard sutures were 2/0 polypropylene to sew in the polypropylene mesh, 1/0 polyglactin to close the external oblique aponeurosis and 3/0 subcuticular polydioxanone for skin. Surgery was carried out under general anaesthesia with additional ilioinguinal and iliohypogastric nerve blocks performed before the skin incision using 0·5 per cent bupivacaine 10 ml in every patient. The wound catheter (16-G epidural catheter) was inserted under direct vision under the external oblique aponeurosis before closure and brought out through a separate stab wound laterally. At the end of the procedure the wound was dressed and the pump connected to the wound catheter.

The pump, a Baxter Daymate Elastomeric infusion device (Baxter Healthcare, Thetford, UK) (*Fig. 1*), delivered 2 ml/h and was filled with 100 ml of either normal saline or 0·5 per cent bupivacaine in accordance with a randomization envelope, hence providing an infusion for 50 h. The surgeons, patient and liaison nurse visiting the patient at home remained blinded to the randomization until the end of the trial.

All patients were prescribed oral analgesia with Aspav (Hoechst Marion Roussel, Uxbridge, UK) which they were instructed to take every 4–6 h, to a maximum of eight tablets every 24 h. If necessary, opiates were given in the recovery area or by the GP and their use was recorded.

A liaison nurse visited the patient at home, approximately 48 h after the operation (routine practice) and, as well as her usual checks, removed the pump and wound catheter.

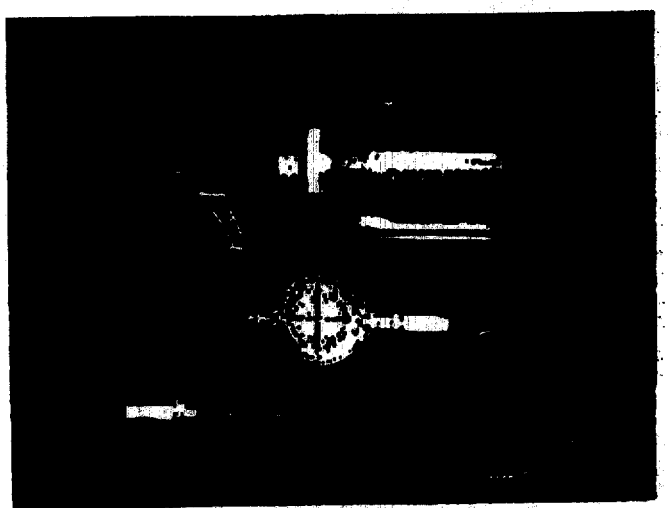

Fig. 1 Baxter device primed with local anaesthetic and attached to the wound catheter. Also shows the trocar used to bring the catheter out through the skin and the bacterial filter

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Patients were asked to complete a questionnaire recording the pain they had felt over the previous 24 h for each of the 5 days following operation. This was recorded on a visual analogue scale (VAS). Patients were also asked to record additional analgesics used including any injections given by an emergency doctor.

All patients were reviewed in the outpatient department 4 weeks after surgery and the wounds inspected.

Analysis of the results was made with the Mann–Whitney *U* test using Minitab for Windows (Microsoft) version 10.2. $P < 0{\cdot}05$ was considered significant.

Results

The patient groups were comparable in age and sex (*Table 1*).

Infusion of bupivacaine for 50 h after operation significantly reduced the VAS score recorded by patients when compared with placebo and control groups (day 1, $P = 0{\cdot}028$ and 0·011 respectively; day 2, $P = 0{\cdot}012$ and 0·037 respectively) (*Fig. 2*). Over the remaining 3 days recorded pain differences between the groups slowly equilibrated. There was no rebound increase in pain at the end of the bupivacaine infusion.

There was no significant difference in the analgesic requirement between the groups (*Table 2*). Four patients developed a wound infection (one in group 1, one in group 2 and two in group 3). No patient developed nerve entrapment or significant hypoaesthesia and all wounds were well healed at the 4-week review.

Table 1 Age and sex distribution

Group	No. of patients	Mean (range) (years)	Sex ratio (M:F)
1	25	53 (17–83)	23:2
2	24	58 (21–78)	22:2
3	23	56 (23–81)	23:0

Table 2 Analgesic use

Group	Median no. of Aspav tablets per day	No. of patients requiring intramuscular analgesia
1	3·0	1
2	3·5	2
3	4·0	3

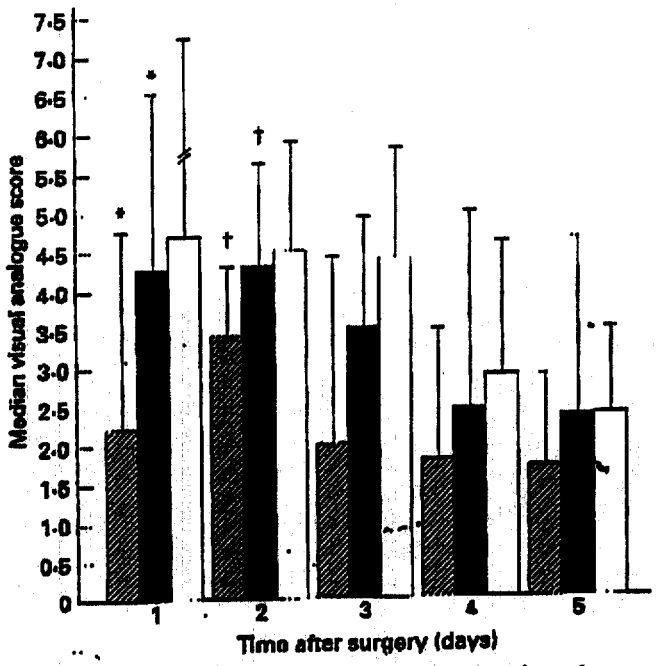

Fig. 2 Daily median pain scores reported by patients in each study group as measured with the visual analogue scale. ▨, Pump containing bupivacaine; ▩, pump containing normal saline; □, no pump. Scores are presented as median with 75th percentile (bars). *$P = 0{\cdot}028$; †$P = 0{\cdot}012$ (Mann–Whitney *U* test)

Discussion

The Baxter Daymate Elastomeric Infusion Device is a portable, disposable, low-cost perfusion pump that delivers fluid reliably at a fixed rate. The pump provides postoperative analgesia safely and at a level equivalent to that of oral opiates without the associated nausea[9]. In the present study the infusion of bupivacaine for 50 h after operation resulted in significantly less pain than in either the placebo or the control group as measured with a standardized 10-cm VAS. This effect seemed to be prolonged after the end of the infusion possibly because of prevention of sensitization of the central nervous system. This effect may be potentiated by an increase in the duration of the neuronal blockade[14,15]. These results were obtained in patients having the hernia repair believed to produce the least postoperative pain[13] together with ilioinguinal and iliohypogastric nerve blocks[4,7]. The clinical advantage of this method for day-case surgery is the ability to provide adequate analgesia safely with regard to the peak plasma levels of bupivacaine[8,16]. There was no increase in the incidence of wound infection and no patient in the study had a deep wound infection.

The position of the catheter under the aponeurosis is a more effective site than subcutaneously[17]. No patient suffered an iatrogenic femoral nerve block. There was no significant difference in the additional analgesic use between the groups. Of the 72 patients in the study, six required additional parenteral analgesia, but only one after bupivacaine infusion.

The use of a pump for local anaesthetic wound perfusion after inguinal hernia repair is an effective method of reducing postoperative pain and is suitable for day surgery.

Acknowledgements

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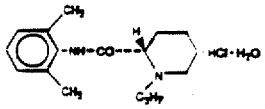
Naropin™
(ropivacaine HCl Injection)

DESCRIPTION

Naropin™ (ropivacaine HCl Injection) is a member of the amino amide class of local anesthetics. Naropin injections are sterile, isotonic solutions that contain the enantiomerically pure drug substance, sodium chloride for isotonicity and Water for Injection. Sodium hydroxide and/or hydrochloric acid may be used for pH adjustment. These solutions are administered parenterally.

Naropin contains ropivacaine HCl which is chemically described as S-(-)-1-propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate. The drug substance is a white crystalline powder, with a chemical formula of $C_{17}H_{26}N_2O{\cdot}HCl{\cdot}H_2O$, molecular weight of 328.89 and the following structural formula:



At 25°C ropivacaine HCl has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 141 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1) and is similar to that of mepivacaine (7.7). However, ropivacaine has an intermediate degree of lipid solubility compared to bupivacaine and mepivacaine.

Naropin is preservative free and is available in single dose containers in 2.0, 5.0, 7.5 and 10.0 mg/mL concentrations. The specific gravity of Naropin solutions range from 1.002 to 1.005 at 25°C.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ropivacaine is a member of the amino amide class of local anesthetics and is supplied as the pure S-(-)-enantiomer. Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

PHARMACOKINETICS

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug administered, the route of administration, the patient's hemodynamic/circulatory condition and the vascularity of the administration site.

From the epidural space, ropivacaine shows complete and biphasic absorption. The half-lives of the two phases, (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively. The slow absorption is the rate limiting factor in the elimination of ropivacaine which explains why the terminal half-life is longer after epidural than after intravenous administration. Ropivacaine shows dose-proportionality up to the highest intravenous dose studied, 80 mg, corresponding to a mean ± SD peak plasma concentration of 1.9 ± 0.3 µg/mL.

Distribution

After intravascular infusion, ropivacaine has a steady state volume of distribution of 41 ± 7 liters. Ropivacaine is 94% protein bound, mainly to α_1-acid glycoprotein. An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a postoperative increase of α_1-acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentrations have been less than in total plasma concentration. Ropivacaine readily crosses the placenta and equilibrium in regard to unbound concentration will be rapidly reached (see PRECAUTIONS, Labor and Delivery).

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P4501A to 3-hydroxy ropivacaine. Approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentrations of 4-hydroxy ropivacaine have been found in the plasma. Urinary excretion of the 4-hydroxy and both the 3-hydroxy and 4-hydroxy N-dealkylated metabolites accounts for less than 3% of dose. An additional metabolite, 2-hydroxy-methyl-ropivacaine, has been identified but not quantified in the urine. Both 3-hydroxy and 4-hydroxy ropivacaine have a local anesthetic activity in animal models less than that of ropivacaine. There is no evidence of *in vivo* racemization in urine of S-(-)-ropivacaine to R-(+)-ropivacaine.

Elimination

The kidney is the main excretory organ for most local anesthetic metabolites. In total, 86% of the ropivacaine dose is excreted in the urine after intravenous administration of which only 1% relates to unchanged drug. Ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min, and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h after intravascular administration and 4.2 ± 1.0 h after epidural administration (see Absorption).

Pharmacodynamics

Studies in humans have demonstrated that, unlike most other local anesthetics, the presence of epinephrine has no major effect on either the time of onset or the duration of action of ropivacaine. Likewise, addition of epinephrine to ropivacaine has no effect on limiting systemic absorption of ropivacaine.

Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems. At blood concentrations achieved with therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias and to cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression or both. Apparent central stimulation is usually manifested as restlessness, tremors and shivering, progressing to convulsions, followed by depression and coma, progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited stage.

In two clinical pharmacology studies (total n=24) ropivacaine and bupivacaine were infused at 10 mg/min in human volunteers until the appearance of CNS symptoms, e.g., visual or hearing disturbances, perioral numbness, tingling and others. Similar symptoms were seen with both drugs. In one study, the mean ± SD maximum tolerated intravenous dose of ropivacaine infused (124 ± 38 mg) was significantly higher than that of bupivacaine (99 ± 30 mg) while in the other study the doses were not different (115 ± 29 mg of ropivacaine and 103 ± 30 mg of bupivacaine). In the latter study, the number of subjects reporting each symptom was similar for both drugs with the exception of muscle twitching which was reported by more subjects with bupivacaine than ropivacaine at comparable intravenous doses. At the end of the infusion, ropivacaine in both studies caused significantly less depression of cardiac conductivity (less QRS widening) than bupivacaine. Ropivacaine and bupivacaine caused evidence of depression of cardiac contractility, but there were no changes in cardiac output.

In nonclinical pharmacology studies comparing ropivacaine and bupivacaine in several animal species, the cardiac toxicity of ropivacaine was less than that of bupivacaine, although both were considerably more toxic than lidocaine. Arrhythmogenic and cardiodepressant effects were seen in animals at significantly higher doses of ropivacaine than bupivacaine. The incidence of successful resuscitation was not significantly different between the ropivacaine and bupivacaine groups.

Clinical Trials

Ropivacaine was studied as a local anesthetic both for surgical anesthesia and for acute pain management. (SEE DOSAGE AND ADMINISTRATION.)

The onset, depth and duration of sensory block are, in general, similar to bupivacaine. However, the depth and duration of motor block, in general, are less than that with bupivacaine.

Epidural Administration in Surgery

There were 25 clinical studies performed in 900 patients to evaluate Naropin epidural injection for general surgery. Naropin was used in doses ranging from 75 to 250 mg. In doses of 100-200 mg, the median (1st-3rd quartile) onset time to achieve a T10 sensory block was 10 (5-13) minutes and the median (1st-3rd quartile) duration at the T10 level was 4 (3-5) hours. (SEE DOSAGE AND ADMINISTRATION.)

Higher doses produced a more profound block with a greater duration of effect.

Epidural Administration in Cesarean Section

There were 8 studies performed in 218 patients to evaluate Naropin for cesarean section. 5 mg/mL (0.5%) Naropin was used in doses up to 150 mg. Median onset measured at T6 ranged from 11 to 26 minutes. Median duration of sensory block at T6 ranged from 1.7 to 3.2 h, and duration of motor block ranged from 1.4 to 2.9 h. Naropin provided adequate muscle relaxation for surgery in all cases.

Epidural Administration in Labor And Delivery

There were 10 double-blind clinical studies performed to evaluate Naropin versus bupivacaine for epidural block for management of labor pain (Naropin, n=258; bupivacaine, n=231). When administered in doses up to 278 mg as intermittent injections or as a continuous infusion, Naropin produced adequate pain relief.

A prospective meta-analysis on 6 of these studies provided detailed evaluation of the delivered newborns and showed no difference in clinical outcomes compared to bupivacaine. There were significantly fewer instrumental deliveries in mothers receiving ropivacaine as compared to bupivacaine.

LABOR AND DELIVERY META-ANALYSIS: MODE OF DELIVERY

Delivery Mode	Naropin n=199		Bupivacaine n=188	
	n	%	n	%
Spontaneous Vertex	116	58	92	49
Vacuum Extractor	26	13*	33	18*
Forceps	28	14	42	22
Cesarean Section	29	15	21	11

*p=0.004 versus bupivacaine

Epidural Administration in Postoperative Pain Management

There were 8 clinical studies performed in 382 patients to evaluate Naropin for postoperative pain management after upper and lower abdominal surgery and after orthopedic surgery. The studies utilized intravascular morphine via PCA as a rescue medication and as an efficacy variable. Epidural anesthesia with Naropin was used intraoperatively for each of these procedures prior to initiation of postoperative Naropin. The incidence and intensity of the motor block were dependent on the dose rate of Naropin and the site of injection. Cumulative doses of up to 770 mg of ropivacaine were administered over 24 hours (intraoperative block plus postoperative continuous infusion). The overall quality of pain relief, as judged by the patients, in the ropivacaine groups was rated as good or excellent (73% to 100%). The frequency of motor block was greatest at 4 hours and decreased during the infusion period in all groups. At least 80% of patients in the upper and lower abdominal studies and 42% in the orthopedic studies had no motor block at the end of the 21-hour infusion period. Sensory block was also dose rate-dependent and a decrease in spread was observed during the infusion period. Clinical studies with 2 mg/mL (0.2%) Naropin have demonstrated that infusion rates of 6-10 mL (12-20 mg) per hour provide adequate analgesia with only slight and non-progressive motor block in cases of moderate to severe postoperative pain. In these studies, this technique resulted in a significant reduction in patients' morphine rescue dose-requirement. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

Epidural infusion of Naropin has, in some cases, been associated with transient increases in temperature to > 38.5°C. This occurred more frequently at doses >16 mg/h.

Peripheral Nerve Block

Naropin, 5 mg/mL, (0.5%), was evaluated for its ability to provide anesthesia for surgery using the techniques of Peripheral Nerve Block. There were 13 studies performed including a series of 4 pharmacodynamic and pharmacokinetic studies performed on minor nerve blocks. From these, 235 Naropin treated patients were evaluable for efficacy. Naropin was used in doses up to 275 mg. When used for brachial plexus block, onset depended on technique used. Supraclavicular blocks were consistently more successful than axillary blocks. The median onset of sensory block (anesthesia) produced by ropivacaine 0.5% via axillary block ranged from 30 minutes (medial brachial cutaneous nerve) to 45 minutes (musculocutaneous nerve). Median duration ranged from 3.7 hours (medial brachial cutaneous nerve) to 8.7 hours (ulnar nerve). The 5 mg/mL (0.5%) Naropin solution gave success rates from 56% to 86% for axillary blocks, compared with 92% for supraclavicular blocks.

Local Infiltration

There were 7 clinical studies performed to evaluate the local infiltration of Naropin to produce anesthesia for surgery and analgesia in postoperative pain management. In these studies, 297 patients who received Naropin in doses up to 200 mg were evaluable for efficacy. With infiltration of 100-200 mg Naropin, the time to first request for analgesic was 2-6 hours. When compared to placebo, Naropin produced lower pain scores and a reduction of analgesic consumption.

INDICATIONS AND USAGE

Naropin is indicated for the production of local or regional anesthesia for surgery, for postoperative pain management and for obstetrical procedures.

Surgical Anesthesia:	epidural block for surgery including cesarean section: major nerve block: local infiltration
Acute Pain Management:	epidural continuous infusion or intermittent bolus e.g., postoperative or labor: local infiltration

Standard current textbooks should be consulted to determine the accepted procedures and techniques for the administration of local anesthetic agents.

CONTRAINDICATIONS

Naropin is contraindicated in patients with a known hypersensitivity to Naropin or to any local anesthetic agent of the amide type.

WARNINGS

FOR CESAREAN SECTION, THE 5 MG/ML (0.5%) NAROPIN SOLUTION IN DOSES UP TO 150 MG IS RECOMMENDED. AS WITH ALL LOCAL ANESTHETICS, NAROPIN SHOULD BE ADMINISTERED IN INCREMENTAL DOSES. SINCE NAROPIN SHOULD NOT BE INJECTED RAPIDLY IN LARGE DOSES, IT IS NOT RECOMMENDED FOR EMERGENCY SITUATIONS. WHERE A FAST ONSET OF SURGICAL ANESTHESIA IS NECESSARY. HISTORICALLY, PREGNANT PATIENTS WERE REPORTED TO HAVE A HIGH RISK FOR CARDIAC ARRHYTHMIAS, CARDIAC/CIRCULATORY ARREST AND DEATH WHEN BUPIVACAINE WAS INADVERTENTLY RAPIDLY INJECTED INTRAVENOUSLY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN THE DIAGNOSIS AND MANAGEMENT OF DOSE RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE IMMEDIATE (WITHOUT DELAY) AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

SOLUTIONS OF NAROPIN SHOULD NOT BE USED FOR THE PRODUCTION OF OBSTETRICAL PARACERVICAL BLOCK ANESTHESIA, RETROBULBAR BLOCK OR SPINAL ANESTHESIA (SUBARACHNOID BLOCK) DUE TO INSUFFICIENT DATA TO SUPPORT SUCH USE. INTRAVENOUS REGIONAL ANESTHESIA (BIER BLOCK) SHOULD NOT BE PERFORMED DUE TO A LACK OF CLINICAL EXPERIENCE AND THE RISK OF ATTAINING TOXIC BLOOD LEVELS OF NAROPIN.

It is essential that aspiration for blood, or cerebrospinal fluid (where applicable), be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does *not* ensure against an intravascular or subarachnoid injection.

A well-known risk of epidural anesthesia may be an unintentional subarachnoid injection of local anesthetic. Two clinical studies have been performed to verify the safety of Naropin at a volume of 3 mL injected into the subarachnoid space since this dose represents an incremental epidural volume that could be unintentionally injected. The 15 and 22.5 mg doses injected resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes, extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. The results of these two clinical studies showed that a 3 mL dose did not produce any serious adverse events when spinal anesthesia blockade was achieved.

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

PRECAUTIONS

General

The safe and effective use of local anesthetics depends on proper dosage, correct technique, adequate precautions and readiness for emergencies.

Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use (see WARNINGS and ADVERSE REACTIONS). The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Injections should be made slowly and incrementally, with frequent aspirations before and during the injection to avoid intravascular injection. When a continuous catheter technique is used, syringe aspirations should also be performed before and during each supplemental injection. During the administration of epidural anesthesia, it is recommended that a test dose of a local anesthetic with a fast onset be administered initially and that the patient be monitored for central nervous system and cardiovascular toxicity, as well as for signs of unintended intrathecal administration before proceeding. When clinical conditions permit, consideration should be given to employing local anesthetic solutions which contain epinephrine for the test dose because circulatory changes compatible with epinephrine may also serve as a warning sign of unintended intravascular injection. An intravascular injection is still possible even if aspirations for blood are negative. Administration of higher than recommended doses of Naropin to achieve greater motor blockade or increased duration of sensory blockade may negate the advantages of Naropin's favorable cardiovascular depression profile in the event that an inadvertent intravascular injection occurs.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients, and acutely ill patients and children should be given reduced doses commensurate with their age and physical condition. Local anesthetics should also be used with caution in patients with hypotension, hypovolemia or heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, light-headedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Because amide-type local anesthetics such as Naropin are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for malignant hyperthermia. Amide-type local anesthetics are not known to trigger this reaction. However, since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available.

Epidural Anesthesia

During epidural administration, Naropin should be administered in incremental doses of 3 to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When clinical conditions permit, the test dose should contain epinephrine (10 to 15 µg have been suggested) to serve as a warning of unintentional intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and systolic blood pressure, circumoral pallor, palpitations and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart should be continuously monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a rise in systolic blood pressure. A test dose of a short-acting amide anesthetic such as 30 to 40 mg of lidocaine is recommended to detect an unintentional intrathecal administration. This will be manifested within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Use in Head and Neck Area

Small doses of local anesthetics injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see DOSAGE AND ADMINISTRATION).

Use in Ophthalmic Surgery

The use of Naropin in retrobulbar blocks for ophthalmic surgery has not been studied. Until appropriate experience is gained, the use of Naropin for such surgery is not recommended.

Information for Patients

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity in the anesthetized part of the body following proper administration of lumbar epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the Naropin package insert.

Clinically Significant Drug-Drug Interactions

Naropin should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics, since the toxic effects of these drugs are additive.

In vitro studies indicate that cytochrome P4501A is involved in the formation of 3-hydroxy ropivacaine, the major metabolite. Thus agents likely to be administered concomitantly with Naropin, which are metabolized by this isozyme family may potentially interact with Naropin. Such interaction might be a possibility with drugs known to be metabolized by P4501A2 via competitive inhibition such as theophylline, imipramine and with potent inhibitors such as fluvoxamine and verapamil.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals of most local anesthetics, including Naropin, to evaluate the carcinogenic potential have not been conducted.

Weak mutagenic activity was seen in the mouse lymphoma test. Mutagenicity was not noted in the other assays, demonstrating that the weak signs of *in vitro* activity in the mouse lymphoma test were not manifest under diverse *in vivo* conditions.

Studies performed with ropivacaine in rats did not demonstrate an effect on fertility or general reproductive performance over two generations.

Pregnancy Category B

Teratogenicity studies in rats and rabbits did not show evidence of any adverse effects on organogenesis or early fetal development in rats or rabbits. The doses used were approximately equal to 5 and 2.5 times, respectively, the maximum recommended human dose (250 mg) based on body weight. There were no treatment related effects on late fetal development, parturition, lactation, neonatal viability or growth of the offspring in 2 perinatal and postnatal studies in rats, at dose levels up to approximately 5 times the maximum recommended human dose based on body weight. In another study with a higher dose, 23 mg/kg, an increased pup loss was seen during the first 3 days postpartum, which was considered secondary to impaired maternal care due to maternal toxicity.

There are no adequate and well-controlled studies in pregnant women of the effects of Naropin on the developing fetus. Naropin should be used during pregnancy only if clearly needed. This does not preclude the use of Naropin after fetal organogenesis is completed or for obstetrical anesthesia or analgesia. (See Labor and Delivery).

Labor and Delivery

Local anesthetics, including Naropin, rapidly cross the placenta, and when used for epidural block can cause varying degrees of maternal, fetal and neonatal toxicity (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus and neonate involve alterations of the central nervous system, peripheral vascular tone and cardiac function.

Maternal hypotension has resulted from regional anesthesia with Naropin for obstetrical pain relief. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.

Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Spontaneous vertex delivery occurred more frequently in patients receiving Naropin than in those receiving bupivacaine.

Nursing Mothers

Some local anesthetic drugs are excreted in human milk and caution should be exercised when they are administered to a nursing woman. The excretion of ropivacaine or its metabolites in human milk has not been studied. Based on the milk/plasma concentration ratio in rats, the estimated daily dose to a pup will be about 4% of the dose given to the mother. Assuming that the milk/plasma concentration in humans is of the same order, the total Naropin dose to which the

baby is exposed by breast feeding is far lower than by exposure in utero in pregnant women at term (see PRECAUTIONS).

Pediatric Use

No special studies were conducted in pediatrics. Until further experience is gained in children younger than 12 years, administration of Naropin in this age group is not recommended.

ADVERSE REACTIONS

Reactions to Naropin are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs may be associated with excessive plasma levels, which may be due to overdosage, unintentional intravascular injection or slow metabolic degradation.

The reported adverse events are derived from controlled clinical trials in the U.S. and other countries. The reference drug was usually bupivacaine. The studies were conducted using a variety of premedications, sedatives, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Of the 3558 patients enrolled in the clinical trials, 2404 were exposed to Naropin. Each patient was counted once for each type of adverse event.

Incidence >5%

hypotension, fetal bradycardia, nausea, bradycardia, vomiting, paresthesia, back pain

Incidence 1-5%

fever, headache, pain, postoperative complications, urinary retention, dizziness, pruritus, rigors, anemia, hypertension, tachycardia, anxiety, oliguria, hypoesthesia, chest pain, fetal disorders including tachycardia and fetal distress, and neonatal disorders including jaundice, tachypnea, fever, respiratory disorder and vomiting

A comparison has been made between Naropin and bupivacaine for events with a frequency of 1% or greater. Tables 1a and 1b show adverse events (number and percentage) in patients exposed to *similar doses* in double-blind controlled clinical trials. In the trials, Naropin was administered as an epidural anesthetic/analgesic for surgery, labor, or cesarean section. In addition, patients that received Naropin for peripheral nerve block or local infiltration are included.

Table 1a.
Adverse Events Reported in ≥1% of Adult Patients Receiving Regional Or Local Anesthesia (Surgery, Labor, Cesarean Section, Peripheral Nerve Block and Local Infiltration)

Adverse Reaction	Naropin total N = 742		Bupivacaine total N = 737	
	N	(%)	N	(%)
hypotension	237	(31.9)	225	(30.5)
nausea	92	(12.4)	96	(13.0)
paresthesia	51	(6.9)	44	(6.0)
vomiting	48	(6.5)	38	(5.2)
back pain	36	(4.9)	47	(6.4)
pain	39	(5.3)	40	(5.4)
bradycardia	32	(4.3)	38	(5.2)
headache	23	(3.1)	26	(3.5)
fever	25	(3.4)	20	(2.7)
chills	16	(2.2)	14	(1.9)
dizziness	18	(2.4)	10	(1.4)
pruritus	16	(2.2)	11	(1.5)
urinary retention	10	(1.3)	12	(1.6)
hypoesthesia	8	(1.1)	10	(1.4)

Table 1b.
Adverse Events Reported in ≥1% of Fetuses or Neonates of Mothers Who Received Regional Anesthesia (Cesarean Section and Labor Studies)

Adverse Reaction	Naropin total N = 337		Bupivacaine total N = 317	
	N	(%)	N	(%)
fetal bradycardia	58	(17.2)	53	(16.7)
neonatal jaundice	12	(3.6)	12	(3.8)
neonatal tachypnea	8	(2.4)	11	(3.5)
fetal tachycardia	7	(2.1)	8	(2.5)
neonatal fever	6	(1.8)	8	(2.5)
fetal distress	4	(1.2)	8	(2.5)
neonatal respiratory distress	5	(1.5)	4	(1.3)
neonatal vomiting	5	(1.5)	1	(0.3)

Incidence <1%

The following list includes all adverse and intercurrent events which were recorded in more than one patient, but occurred at an overall rate of less than one percent, and were considered clinically relevant.

Application Site Reactions - injection site pain

Cardiovascular System - vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities

Female Reproductive - poor progression of labor, uterine atony

Gastrointestinal System - fecal incontinence, tenesmus

General and Other Disorders - hyperthermia, malaise, asthenia, accident and/or injury

Hearing and Vestibular - tinnitus, hearing abnormalities

Heart Rate and Rhythm - extrasystoles, non-specific arrhythmias, atrial fibrillation

Liver and Biliary System - jaundice

Metabolic Disorders - hypokalemia, hypomagnesemia

Musculoskeletal System - myalgia, cramps

Myo/Endo/Pericardium - ST segment changes, myocardial infarction

Nervous System - tremor, Horner's syndrome, paresis, dyskinesia, neuropathy, vertigo, coma, convulsion, hypokinesia, hypotonia, ptosis, stupor

Psychiatric Disorders - agitation, confusion, somnolence, nervousness, amnesia, hallucination, emotional lability, insomnia, nightmares

Respiratory System - dyspnea, bronchospasm, coughing

Skin Disorders - rash, urticaria

Urinary System Disorders - urinary incontinence, urinary tract infection, micturition disorder

Vascular - deep vein thrombosis, phlebitis, pulmonary embolism

Vision - vision abnormalities

For the indication epidural anesthesia for surgery, the 15 most common adverse events were compared between different concentrations of Naropin and bupivacaine. Table 2 is based on data from trials in the U.S. and other countries where Naropin was administered as an epidural anesthetic for surgery.

Table 2. Common Events (Epidural Administration)

Adverse Reaction	Naropin						Bupivacaine			
	5 mg/mL total N=256		7.5 mg/mL total N=287		10 mg/mL total N=287		5 mg/mL total N=236		7.5 mg/mL total N=174	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
hypotension	99	(38.7)	146	(49.2)	113	(54.6)	91	(38.6)	89	(51.1)
nausea	34	(13.3)	68	(22.9)			41	(17.4)	36	(20.7)
bradycardia	29	(11.3)	58	(19.5)	40	(19.3)	32	(13.6)	25	(14.4)
back pain	18	(7.0)	23	(7.7)	34	(16.4)	21	(8.9)	23	(13.2)
vomiting	18	(7.0)	33	(11.1)	23	(11.1)	19	(8.1)	14	(8.0)
headache	12	(4.7)	20	(6.7)	16	(7.7)	13	(5.5)	9	(5.2)
fever	8	(3.1)	5	(1.7)	18	(8.7)	11	(4.7)		
chills	6	(2.3)	7	(2.4)	6	(2.9)	4	(1.7)	3	(1.7)
urinary retention	5	(2.0)	8	(2.7)	10	(4.8)	10	(4.2)		
paresthesia	5	(2.0)	10	(3.4)	5	(2.4)	7	(3.0)		
pruritus			14	(4.7)	3	(1.4)			7	(4.0)

Using data from the same studies, the number (%) of patients experiencing hypotension is displayed by patient age, drug and concentration in Table 4. In Table 3, the adverse events for Naropin are broken down by gender.

Table 3.
Most Common Adverse Events by Gender (Epidural Administration)
Total N: Females = 405, Males = 355

Adverse Reaction	Female		Male	
	N	(%)	N	(%)
hypotension	220	(54.3)	138	(38.9)
nausea	119	(29.4)	23	(6.5)
bradycardia	65	(16.0)	56	(15.8)
vomiting	59	(14.6)	8	(2.3)
back pain	41	(10.1)	23	(6.5)
headache	33	(8.1)	17	(4.8)
chills	18	(4.4)	5	(1.4)
fever	16	(4.0)	3	(0.8)
pruritus	16	(4.0)	1	(0.3)
pain	12	(3.0)	4	(1.1)
urinary retention	11	(2.7)	7	(2.0)
dizziness	9	(2.2)	4	(1.1)
hypoesthesia	8	(2.0)	2	(0.6)
paresthesia	8	(2.0)	10	(2.8)

Table 4.
Effects of Age on Hypotension (Epidural Administration)
Total N: Naropin = 760, bupivacaine = 410

AGE	Naropin						Bupivacaine			
	5 mg/mL		7.5 mg/mL		10 mg/mL		5 mg/mL		7.5 mg/mL	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
<65	68	(32.2)	99	(43.2)	87	(51.5)	64	(33.5)	73	(48.3)
≥65	31	(68.9)	47	(69.1)	26	(68.4)	27	(60.0)	16	(69.6)

Systemic Reactions

The most commonly encountered acute adverse experiences that demand immediate countermeasures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production or competition with other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System Reactions

These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the route of administration and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1 percent of local anesthetic administrations.

Cardiovascular System Reactions

High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Allergic Reactions

Allergic type reactions are rare and may occur as a result of sensitivity to the local anesthetic (see WARNINGS). These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitively established.

Neurologic Reactions

The incidence of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose and concentration of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the drug.

During lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and the physiological and physical effects of a dural puncture. These observations may include spinal block of varying magnitude (including high or total spinal block), hypotension secondary to spinal block, urinary retention, loss of bladder and bowel control (fecal and urinary incontinence), and loss of perineal sensation and sexual function. Signs and symptoms of subarachnoid block typically start within 2-3 minutes of injection. Doses of 15 and 22.5 mg of Naropin resulted in sensory levels as high as T5 and T4, respectively. Sensory analgesia started in the sacral dermatomes in 2-3 minutes and extended to the T10 level in 10-13 minutes and lasted for approximately 2 hours. Other neurological effects following unintentional subarachnoid administration during epidural anesthesia may include persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control, all of which may have slow, incomplete or no recovery. Headache, septic meningitis, meningismus, slowing of labor, increased incidence of forceps delivery, or cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid have been reported (see DOSAGE AND ADMINISTRATION discussion of Lumbar Epidural Block). A high spinal is characterized by paralysis of the arms, loss of consciousness, respiratory paralysis and bradycardia.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid or intravascular injection of local anesthetic solution. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies

The practitioner should be familiar with standard contemporary textbooks that address the management of local anesthetic emergencies. No specific information is available on the treatment of overdosage with Naropin; treatment should be symptomatic and supportive. Therapy with Naropin should be discontinued.

The first consideration is prevention, best accomplished by incremental injection of Naropin, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection and during continuous infusion. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and, when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or epinephrine to enhance myocardial contractile force).

The mean dosages of ropivacaine producing seizures, after intravenous infusion in dogs, nonpregnant and pregnant sheep were 4.9, 6.1 and 5.9 mg/kg, respectively. These doses were associated with peak arterial total plasma concentrations of 11.4, 4.3 and 5.0 µg/mL, respectively. In rats, the LD_{50} is 9.9 and 12 mg/kg by the intravenous route for males and females respectively.

In human volunteers given intravenous Naropin, the mean maximum tolerated total and free arterial plasma concentrations were 4.3 and 0.6 µg/mL respectively, at which time moderate CNS symptoms (muscle twitching) were noted.

Clinical data from patients experiencing local anesthetic induced convulsions demonstrated rapid development of hypoxia, hypercarbia and acidosis within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated, endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask.

The supine position is dangerous in pregnant women at term because of aorta-caval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels should be accomplished. Resuscitation of obstetrical patients may take longer than resuscitation of non-pregnant patients and closed-chest cardiac compression may be ineffective. Rapid delivery of the fetus may improve the response to resuscitative efforts.

DOSAGE AND ADMINISTRATION

The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered.

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention although regional anesthesia is frequently indicated in these patients. To reduce the risk of potentially serious adverse reactions, attempts should be made to optimize the patient's condition before major blocks are performed, and the dosage should be adjusted accordingly.

Use an adequate test dose (3-5 mL of a short acting local anesthetic solution containing epinephrine) prior to induction of complete block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. Allow adequate time for onset of anesthesia following administration of each test dose.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered. For specific techniques and procedures, refer to standard contemporary textbooks.

Dosage Recommendations

	Conc mg/mL(%)	Volume mL	Dose mg	Onset min	Duration hours
SURGICAL ANESTHESIA					
Lumbar Epidural Administration	5.0 (0.5%)	15-30	75-150	15-30	2-4
Surgery	7.5 (0.75%)	15-25	113-188	10-20	3-5
	10.0 (1.0%)	15-20	150-200	10-20	4-6
Lumbar Epidural Administration Cesarean Section	5.0 (0.5%)	20-30	100-150	15-25	2-4
Thoracic Epidural Administration To establish block for postoperative pain relief	5.0 (0.5%)	5-15	25-75	10-20	n/a
Major Nerve Block (e.g. brachial plexus block)	5.0 (0.5%)	35-50	175-250	15-30	5-8
Field Block (e.g. minor nerve blocks and infiltration)	5.0 (0.5%)	1-40	5-200	1-15	2-6
LABOR PAIN MANAGEMENT					
Lumbar Epidural Administration Initial Dose	2.0 (0.2%)	10-20	20-40	10-15	0.5-1.5
Continuous infusion[2]	2.0 (0.2%)	6-14 mL/h	12-28 mg/h	n/a[1]	n/a
Incremental injections (top-ups)[2]	2.0 (0.2%)	10-15 mL/h	20-30 mg/h	n/a[1]	n/a
POSTOPERATIVE PAIN MANAGEMENT					
Lumbar Epidural Administration Continuous infusion[3]	2.0 (0.2%)	6-10 mL/h	12-20 mg/h	n/a[1]	n/a[1]
Thoracic Epidural Administration Continuous infusion[3]	2.0 (0.2%)	4-8 mL/h	8-16 mg/h	n/a[1]	n/a[1]
Infiltration (e.g. minor nerve block)	2.0 (0.2%)	1-100	2-200	1-5	2-6
	5.0 (0.5%)	1-40	5-200	1-5	2-6

1 = Not Applicable

2 = Median dose of 21 mg per hour was administered by continuous infusion or by incremental injections (top-ups) over a median delivery time of 5.5 hours.

3 = Cumulative doses up to 770 mg of Naropin over 24 hours for postoperative pain management have been well tolerated in adults.

The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use in adults. Individual variations in onset and duration occur. The figures reflect the expected average dose range needed. For other local anesthetic techniques standard current textbooks should be consulted.

When prolonged blocks are used, either through continuous infusion or through repeated bolus administration, the risks of reaching a toxic plasma concentration or inducing local neural injury must be considered. Experience to date indicates that a cumulative dose of up to 770 mg Naropin administered over 24 hours is well tolerated in adults when used for postoperative pain management.

For treatment of postoperative pain, the following technique can be recommended: If regional anesthesia was not used intraoperatively, then an epidural block with Naropin is induced via an epidural catheter. Analgesia is maintained with an infusion of Naropin, 2 mg/mL (0.2%). Clinical studies have demonstrated that infusion rates of 6-10 mL (12-20 mg), per hour provide adequate analgesia with only slight and nonprogressive motor block in cases of moderate to severe postoperative pain. If patients require additional pain relief, higher infusion rates of up to 14 mL (28 mg) per hour may be used. With this technique a significant reduction in the need for opioids was demonstrated. Clinical experience supports the use of Naropin epidural infusions for up to 24 hours.

HOW SUPPLIED

Naropin® Astra E-Z Off® Single Dose Vials:		
7.5 mg/mL	10 mL	NDC 0186-0867-41
10.0 mg/mL	10 mL	NDC 0186-0868-41
Naropin® Single Dose Vials:		
2.0 mg/mL	20 mL	NDC 0186-0859-51
5.0 mg/mL	30 mL	NDC 0186-0863-61
7.5 mg/mL	20 mL	NDC 0186-0867-51
10.0 mg/mL	20 mL	NDC 0186-0868-51
Naropin® Single Dose Ampules:		
2.0 mg/mL	20 mL	NDC 0186-0859-52
5.0 mg/mL	30 mL	NDC 0186-0863-62
7.5 mg/mL	20 mL	NDC 0186-0867-52
10.0 mg/mL	20 mL	NDC 0186-0868-52
Naropin® Single Dose Infusion Bottles:		
2.0 mg/mL	100 mL	NDC 0186-0859-81
2.0 mg/mL	200 mL	NDC 0186-0859-91
Naropin® Sterile-Pak® Single Dose Vials:		
2.0 mg/mL	20 mL	Product Code 0859-59
5.0 mg/mL	30 mL	Product Code 0863-69
7.5 mg/mL	20 mL	Product Code 0867-59
10.0 mg/mL	20 mL	Product Code 0868-59

The solubility of ropivacaine is limited at pH above 6. Thus care must be taken as precipitation may occur if Naropin is mixed with alkaline solutions.

Disinfecting agents containing heavy metals, which cause release of respective ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and edema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91%) or ethyl alcohol (70%) is recommended. It is recommended that chemical disinfection be accomplished by wiping the ampoule or vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol just prior to use. When a container is required to have a sterile outside, a Sterile-Pak should be chosen. Glass containers may, as an alternative, be autoclaved once. Stability has been demonstrated using a targeted F_0 of 7 minutes at 121°C.

Solutions should be stored at controlled room temperature 20° – 25°C (68° – 77°F) [see USP].

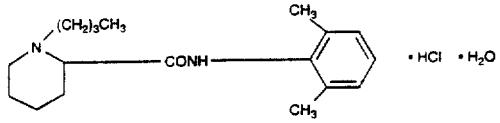
These products are intended for single use and are free from preservatives. Any solution remaining from an opened container should be discarded promptly. In addition, continuous infusion bottles should not be left in place for more than 24 hours.

Caution: Federal law prohibits dispensing without prescription.

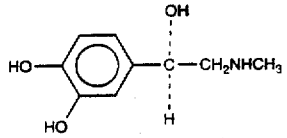
MARCAINE®
Bupivacaine Hydrochloride Injection, USP

MARCAINE®
With Epinephrine 1:200,000 (as bitartrate)
Bupivacaine Hydrochloride and Epinephrine Injection, USP

DESCRIPTION
Bupivacaine hydrochloride is 2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate, a white crystalline powder that is freely soluble in 95 percent ethanol, soluble in water, and slightly soluble in chloroform or acetone. It has the following structural formula:



Epinephrine is (-)-3,4-Dihydroxy-α-[(methylamino)methyl] benzyl alcohol. It has the following structural formula:



MARCAINE is available in sterile isotonic solutions with and without epinephrine (as bitartrate) 1:200,000 for injection via local infiltration, peripheral nerve block, and caudal and lumbar epidural blocks. Solutions of MARCAINE may be autoclaved if they do not contain epinephrine. Solutions are clear and colorless.

Bupivacaine is related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. All three of these anesthetics contain an amide linkage between the aromatic nucleus and the amino, or piperidine group. They differ in this respect from the procaine-type local anesthetics, which have an ester linkage.

MARCAINE—Sterile isotonic solutions containing sodium chloride. In multiple-dose vials, each mL also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to between 4 and 6.5 with sodium hydroxide or hydrochloric acid.

MARCAINE with epinephrine 1:200,000 (as bitartrate)—Sterile isotonic solutions containing sodium chloride. Each mL contains bupivacaine hydrochloride and 0.0091 mg epinephrine bitartrate, with 0.5 mg sodium metabisulfite, 0.001 mL monothioglycerol, and 2 mg ascorbic acid as antioxidants, 0.0017 mL 60% sodium lactate buffer, and 0.1 mg edetate calcium disodium as stabilizer. In multiple-dose vials, each mL also contains 1 mg methylparaben as antiseptic preservative. The pH of these solutions is adjusted to between 3.4 and 4.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE 0.5% with epinephrine 1:200,000 (as bitartrate) at 25° C is 1.008 and at 37° C is 1.008.

CLINICAL PHARMACOLOGY
Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

Systemic absorption of local anesthetics produces effects on the cardiovascular and central nervous systems (CNS). At blood concentrations achieved with normal therapeutic doses, changes in cardiac conduction, excitability, refractoriness, contractility, and peripheral vascular resistance are minimal. However, toxic blood concentrations depress cardiac conduction and excitability, which may lead to atrioventricular block, ventricular arrhythmias, and cardiac arrest, sometimes resulting in fatalities. In addition, myocardial contractility is depressed and peripheral vasodilation occurs, leading to decreased cardiac output and arterial blood pressure. Recent clinical reports and animal research suggest that these cardiovascular changes are more likely to occur after unintended intravascular injection of bupivacaine. Therefore, incremental dosing is necessary.

Following systemic absorption, local anesthetics can produce central nervous system stimulation, depression, or both. Apparent central stimulation is manifested as restlessness, tremors and shivering progressing to convulsions, followed by depression and coma progressing ultimately to respiratory arrest. However, the local anesthetics have a primary depressant effect on the medulla and on higher centers. The depressed stage may occur without a prior excited state.

Pharmacokinetics: The rate of systemic absorption of local anesthetics is dependent upon the total dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the anesthetic solution. A dilute concentration of epinephrine (1:200,000 or 5 mcg/mL) usually reduces the rate of absorption and peak plasma concentration of MARCAINE, permitting the use of moderately larger total doses and sometimes prolonging the duration of action.

The onset of action with MARCAINE is rapid and anesthesia is long lasting. The duration of anesthesia is significantly longer with MARCAINE than with any other commonly used local anesthetic. It has also been noted that there is a period of analgesia that persists after the return of sensation, during which time the need for strong analgesics is reduced.

The onset of action following dental injections is usually 2 to 10 minutes and anesthesia may last two or three times longer than lidocaine and mepivacaine for dental use, in many patients up to 7 hours. The duration of anesthetic effect is prolonged by the addition of epinephrine 1:200,000.

Local anesthetics are bound to plasma proteins in varying degrees. Generally, the lower the plasma concentration of drug the higher the percentage of drug bound to plasma proteins.

Local anesthetics appear to cross the placenta by passive diffusion. The rate and degree of diffusion is governed by (1) the degree of plasma protein binding, (2) the degree of ionization, and (3) the degree of lipid solubility. Fetal/ maternal ratios of local anesthetics appear to be inversely related to the degree of plasma protein binding, because only the free, unbound drug is available for placental transfer. MARCAINE with a high protein binding capacity (95%) has a low fetal/maternal ratio (0.2 to 0.4). The extent of placental transfer is also determined by the degree of ionization and lipid solubility of the drug. Lipid soluble, nonionized drugs readily enter the fetal blood from the maternal circulation.

Depending upon the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart, and brain.

Pharmacokinetic studies on the plasma profile of MARCAINE after direct intravenous injection suggest a three-compartment open model. The first compartment is represented by the rapid intravascular distribution of the drug. The second compartment represents the equilibration of the drug throughout the highly perfused organs such as the brain, myocardium, lungs, kidneys, and liver. The third compartment represents an equilibration of the drug with poorly perfused tissues, such as muscle and fat. The elimination of drug from tissue distribution depends largely upon the ability of binding sites in the circulation to carry it to the liver where it is metabolized.

After injection of MARCAINE for caudal, epidural, or peripheral nerve block in man, peak levels of bupivacaine in the blood are reached in 30 to 45 minutes, followed by a decline to insignificant levels during the next three to six hours.

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Various pharmacokinetic parameters of the local anesthetics can be significantly altered by the presence of hepatic or renal disease, addition of epinephrine, factors affecting urinary pH, renal blood flow, the route of drug administration, and the age of the patient. The half-life of MARCAINE in adults is 2.7 hours and in neonates 8.1 hours.

Amide-type local anesthetics such as MARCAINE are metabolized primarily in the liver via conjugation with glucuronic acid. Patients with hepatic disease, especially those with severe hepatic disease, may be more susceptible to the potential toxicities of the amide-type local anesthetics. Pipecoloxylidine is the major metabolite of MARCAINE.

The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH. Only 6% of bupivacaine is excreted unchanged in the urine.

When administered in recommended doses and concentrations, MARCAINE does not ordinarily produce irritation or tissue damage and does not cause methemoglobinemia.

INDICATIONS AND USAGE

MARCAINE is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures. Only the 0.25% and 0.5% concentrations are indicated for obstetrical anesthesia. (See WARNINGS.)

Experience with nonobstetrical surgical procedures in pregnant patients is not sufficient to recommend use of 0.75% concentration of MARCAINE in these patients.

MARCAINE is not recommended for intravenous regional anesthesia (Bier Block). See WARNINGS.

The routes of administration and indicated MARCAINE concentrations are:

• local infiltration	0.25%
• peripheral nerve block	0.25% and 0.5%
• retrobulbar block	0.75%
• sympathetic block	0.25%
• lumbar epidural	0.25%, 0.5%, and 0.75% (0.75% not for obstetrical anesthesia)
• caudal	0.25% and 0.5%
• epidural test dose	0.5% with epinephrine 1:200,000
• dental blocks	0.5% with epinephrine 1:200,000

(See DOSAGE AND ADMINISTRATION for additional information.)

Standard textbooks should be consulted to determine the accepted procedures and techniques for the administration of MARCAINE.

CONTRAINDICATIONS

MARCAINE is contraindicated in obstetrical paracervical block anesthesia. Its use in this technique has resulted in fetal bradycardia and death.

MARCAINE is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type or to other components of MARCAINE solutions.

WARNINGS

THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.

LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS, and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE, AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.

Local anesthetic solutions containing antimicrobial preservatives, i.e., those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because safety has not been established with regard to intrathecal injection, either intentionally or unintentionally, of such preservatives.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anesthetic, both the original dose and all subsequent doses, to avoid intravascular or subarachnoid injection. However, a negative aspiration does not ensure against an intravascular or subarachnoid injection.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because a severe persistent hypertension may occur. Likewise, solutions of MARCAINE containing a vasoconstrictor, such as epinephrine, should be used with extreme caution in patients receiving monoamineoxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Until further experience is gained in pediatric patients younger than 12 years, administration of MARCAINE in this age group is not recommended.

Mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE cannot be recommended because of insufficient data on the clinical use of such mixtures.

There have been reports of cardiac arrest and death during the use of MARCAINE for intravenous regional anesthesia (Bier Block). Information on safe dosages and techniques of administration of MARCAINE in this procedure is lacking. Therefore, MARCAINE is not recommended for use in this technique.

MARCAINE with epinephrine 1:200,000 contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Single-dose ampuls and single-dose vials of *MARCAINE* without epinephrine do not contain sodium metabisulfite.

PRECAUTIONS

General: The safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, and OVERDOSAGE.) During major regional nerve blocks, the patient should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

Epidural Anesthesia: During epidural administration of MARCAINE, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Injections should be made slowly, with frequent aspirations before and during the injection to avoid intravascular injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative.

During the administration of epidural anesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given. When using a "continuous" catheter technique, test doses should be given prior to both the original and all reinforcing doses, because plastic tubing in the epidural space can migrate into a blood

vessel or through the dura. When clinical conditions permit, the test dose should contain epinephrine (10 mcg to 15 mcg has been suggested) to serve as a warning of unintended intravascular injection. If injected into a blood vessel, this amount of epinephrine is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient. The sedated patient may exhibit only a pulse rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, the heart rate should be monitored for a heart rate increase. Patients on beta-blockers may not manifest changes in heart rate, but blood pressure monitoring can detect a transient rise in systolic blood pressure. The test dose should also contain 10 mg to 15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect an unintended intrathecal administration. This will be evidenced within a few minutes by signs of spinal block (e.g., decreased sensation of the buttocks, paresis of the legs, or, in the sedated patient, absent knee jerk). The Test Dose formulation of MARCAINE contains 15 mg of bupivacaine and 15 mcg of epinephrine in a volume of 3 mL. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or epinephrine-induced cardiovascular effects.

Injection of repeated doses of local anesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical status. Local anesthetics should also be used with caution in patients with hypotension or heartblock.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be performed after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early warning signs of central nervous system toxicity.

Local anesthetic solutions containing a vasoconstrictor should be used cautiously and in carefully restricted quantities in areas of the body supplied by end arteries or having otherwise compromised blood supply such as digits, nose, external ear, or penis. Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response. Ischemic injury or necrosis may result.

Because amide-local anesthetics such as MARCAINE are metabolized by the liver, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of AV conduction produced by these drugs.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of potent inhalation anesthetics. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Because it is not known whether amide-type local anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and prompt institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium intravenous package insert before using.)

Use in Head and Neck Area: Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded. (See DOSAGE AND ADMINISTRATION.)

Use in Ophthalmic Surgery: Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anesthetic injection. Prior to retrobulbar block, as with all other regional procedures, the immediate availability of equipment, drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be assured (see also WARNINGS and Use In Head and Neck Area, above). As with other anesthetic procedures, patients should be constantly monitored following ophthalmic blocks for signs of these adverse reactions, which may occur following relatively low total doses.

A concentration of 0.75% bupivacaine is indicated for retrobulbar block; however, this concentration is not indicated for any other peripheral nerve block, including the facial nerve, and not indicated for local infiltration, including the conjunctiva (see INDICATIONS and PRECAUTIONS, General). Mixing MARCAINE with other local anesthetics is not recommended because of insufficient data on the clinical use of such mixtures.

When MARCAINE 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Use in Dentistry: Because of the long duration of anesthesia, when MARCAINE 0.5% with epinephrine is used for dental injections, patients should be cautioned about the possibility of inadvertent trauma to tongue, lips, and buccal mucosa and advised not to chew solid foods or test the anesthetized area by biting or probing.

Information for Patients: When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of caudal or epidural anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the package insert of MARCAINE.

Patients receiving dental injections of MARCAINE should be cautioned not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

Clinically Significant Drug Interactions: The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals of most local anesthetics including bupivacaine to evaluate the carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility has not been determined. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

Pregnancy Category C: Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered to these species in doses comparable to nine and five times respectively the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the effect of bupivacaine on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE at term for obstetrical anesthesia or analgesia. (See Labor and Delivery.)

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Labor and Delivery: SEE BOXED WARNING REGARDING OBSTETRICAL USE OF 0.75% MARCAINE.
MARCAINE is contraindicated for obstetrical paracervical block anesthesia.

Local anesthetics rapidly cross the placenta, and when used for epidural, caudal, or pudendal block anesthesia, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, the type, and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously and electronic fetal monitoring is highly advisable.

Epidural, caudal, or pudendal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may be followed by diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

It is extremely important to avoid aortocaval compression by the gravid uterus during administration of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and gravid uterus displaced to the left.

Nursing Mothers: It is not known whether local anesthetic drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when local anesthetics are administered to a nursing woman.

Pediatric Use: Until further experience is gained in pediatric patients younger than 12 years, administration of MARCAINE in this age group is not recommended. Continuous infusions of bupivacaine in pediatric patients have been reported to result in high systemic levels of bupivacaine and seizures; high plasma levels may also be associated with cardiovascular abnormalities. (see WARNINGS, PRECAUTIONS, and OVERDOSAGE.)

ADVERSE REACTIONS

Reactions to MARCAINE are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

The most commonly encountered acute adverse experiences which demand immediate counter-measures are related to the central nervous system and the cardiovascular system. These adverse experiences are generally dose related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total or High Spinal"). Also, hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia may occur. This may lead to secondary cardiac arrest if untreated. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

Central Nervous System Reactions: These are characterized by excitation and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, and constriction of the pupils.

The incidence of convulsions associated with the use of local anesthetics varies with the procedure used and the total dose administered. In a survey of studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of local anesthetic administrations.

Cardiovascular System Reactions: High doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

Allergic: Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients, such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. These reactions are characterized by signs such as urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anesthetic group has been reported. The usefulness of screening for sensitivity has not been definitely established.

Neurologic: The incidences of adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration, and the physical status of the patient. Many of these effects may be related to local anesthetic techniques, with or without a contribution from the drug.

In the practice of caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by the catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and the physiological and physical effects of a dural puncture. A high spinal is characterized by paralysis of the legs, loss of consciousness, respiratory paralysis, and bradycardia.

Neurologic effects following epidural or caudal anesthesia may include spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; and cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

Neurologic effects following other procedures or routes of administration may include persistent anesthesia, paresthesia, weakness, paralysis, all of which may have slow, incomplete, or no recovery.

OVERDOSAGE

Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution. (See ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS.)

Management of Local Anesthetic Emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of immediate attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control the convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing the central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory, and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation (such as ephedrine or

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Table 1. Recommended Concentrations and Doses of MARCAINE

Type of Block	Conc.	Each Dose (mL)	Each Dose (mg)	Motor Block [1]
Local infiltration	0.25% [4]	up to max.	up to max.	—
Epidural	0.75% [2,4]	10-20	75-150	complete
	0.5% [4]	10-20	50-100	moderate to complete
	0.25% [4]	10-20	25-50	partial to moderate
Caudal	0.5% [4]	15-30	75-150	moderate to complete
	0.25% [4]	15-30	37.5-75	moderate
Peripheral nerves	0.5% [4]	5 to max.	25 to max.	moderate to complete
	0.25% [4]	5 to max.	12.5 to max.	moderate to complete
Retrobulbar [3]	0.75% [4]	2-4	15-30	complete
Sympathetic	0.25%	20-50	50-125	—
Dental [3]	0.5% w/epi	1.8-3.6 per site	9-18 per site	—
Epidural [3] Test Dose	0.5% w/epi	2-3	10-15 (10-15 micrograms epinephrine)	—

[1]With continuous (intermittent) techniques, repeat doses increase the degree of motor block. The first repeat dose of 0.5% may produce complete motor block. Intercostal nerve block with 0.25% may also produce complete motor block for intra-abdominal surgery.
[2]For single-dose use, not for intermittent epidural technique. Not for obstetrical anesthesia.
[3]See PRECAUTIONS.
[4]Solutions with or without epinephrine.

HOW SUPPLIED

These solutions are not for spinal anesthesia.

Store at controlled room temperature, between 15° C and 30° C (59° F and 86° F).

MARCAINE —Solutions of MARCAINE that do not contain epinephrine may be autoclaved. Autoclave at 15-pound pressure, 121° C (250° F) for 15 minutes.

0.25%—Contains 2.5 mg bupivacaine hydrochloride per mL
List 1559 Single-dose ampuls of 50 mL, box of 5
List 1559 Single-dose vials of 10 mL, box of 10
List 1559 Single-dose vials of 30 mL, box of 10
List 1587 Multiple-dose vials of 50 mL, box of 1

0.5%—Contains 5 mg bupivacaine hydrochloride per mL
List 1560 Single-dose ampuls of 30 mL, box of 5
List 1560 Single-dose vials of 10 mL, box of 10
List 1560 Single-dose vials of 30 mL, box of 10
List 1610 Multiple-dose vials of 50 mL, box of 1

0.75%—Contains 7.5 mg bupivacaine hydrochloride per mL
List 1582 Single-dose ampuls of 30 mL, box of 5
List 1582 Single-dose vials of 10 mL, box of 10
List 1582 Single-dose vials of 30 mL, box of 10

MARCAINE with epinephrine 1:200,000 (as bitartrate)—Solutions of MARCAINE that contain epinephrine should not be autoclaved and should be protected from light. Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

0.25%— with epinephrine 1:200,000
Contains 2.5 mg bupivacaine hydrochloride per mL
List 1746 Single-dose ampuls of 50 mL, box of 5
List 1746 Single-dose vials of 10 mL, box of 10
List 1746 Single-dose vials of 30 mL, box of 10
List 1752 Multiple-dose vials of 50 mL, box of 1

0.5%— with epinephrine 1:200,000
Contains 5 mg bupivacaine hydrochloride per mL
List 1749 Single-dose ampuls of 3 mL, box of 10
List 1749 Single-dose ampuls of 30 mL, box of 5
List 1749 Single-dose vials of 10 mL, box of 10
List 1749 Single-dose vials of 30 mL, box of 10
List 1755 Multiple-dose vials of 50 mL, box of 1

0.75%— with epinephrine 1:200,000
Contains 7.5 mg bupivacaine hydrochloride per mL
List 1750 Single-dose ampuls of 30 mL, box of 5

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epinephrine to enhance myocardial contractile force).

Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in the maintenance of a patent airway, or if prolonged ventilatory support (assisted or controlled) is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to unintentional subarachnoid injection of local anesthetic solution may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. *If cardiac arrest should occur, successful outcome may require prolonged resuscitative efforts.*

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous LD_{50} in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

DOSAGE AND ADMINISTRATION

The dose of any local anesthetic administered varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth of anesthesia and degree of muscle relaxation required, the duration of anesthesia desired, individual tolerance, and the physical condition of the patient. The smallest dose and concentration required to produce the desired result should be administered. Dosages of MARCAINE should be reduced for elderly and debilitated patients and patients with cardiac and/or liver disease. The rapid injection of a large volume of local anesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

For specific techniques and procedures, refer to standard textbooks.

In recommended doses, MARCAINE produces complete sensory block, but the effect on motor function differs among the three concentrations.

0.25%—when used for caudal, epidural, or peripheral nerve block, produces incomplete motor block. Should be used for operations in which muscle relaxation is not important, or when another means of providing muscle relaxation is used concurrently. Onset of action may be slower than with the 0.5% or 0.75% solutions.

0.5%—provides motor blockade for caudal, epidural, or nerve block, but muscle relaxation may be inadequate for operations in which complete muscle relaxation is essential.

0.75%—produces complete motor block. Most useful for epidural block in abdominal operations requiring complete muscle relaxation, and for retrobulbar anesthesia. Not for obstetrical anesthesia.

The duration of anesthesia with MARCAINE is such that for most indications, a single dose is sufficient.

Maximum dosage limit must be individualized in each case after evaluating the size and physical status of the patient, as well as the usual rate of systemic absorption from a particular injection site. Most experience to date is with single doses of MARCAINE up to 225 mg with epinephrine 1:200,000 and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case.

These doses may be repeated up to once every three hours. In clinical studies to date, total daily doses have been up to 400 mg. Until further experience is gained, this dose should not be exceeded in 24 hours. The duration of anesthetic effect may be prolonged by the addition of epinephrine.

The dosages in Table 1 have generally proved satisfactory and are recommended as a guide for use in the average adult. These dosages should be reduced for elderly or debilitated patients. Until further experience is gained, MARCAINE is not recommended for pediatric patients younger than 12 years. MARCAINE is contraindicated for obstetrical paracervical blocks, and is not recommended for intravenous regional anesthesia (Bier Block).

Use in Epidural Anesthesia: During epidural administration of MARCAINE, 0.5% and 0.75% solutions should be administered in incremental doses of 3 mL to 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. In obstetrics, only the 0.5% and 0.25% concentrations should be used; incremental doses of 3 mL to 5 mL of the 0.5% solution not exceeding 50 mg to 100 mg at any dosing interval are recommended. Repeat doses should be preceded by a test dose containing epinephrine if not contraindicated. Use only the single-dose ampuls and single-dose vials for caudal or epidural anesthesia; the multiple-dose vials contain a preservative and therefore should not be used for these procedures.

Test Dose for Caudal and Lumbar Epidural Blocks: The Test Dose of MARCAINE (0.5% bupivacaine with 1:200,000 epinephrine in a 3 mL ampul) is recommended for use as a test dose when clinical conditions permit prior to caudal and lumbar epidural blocks. This may serve as a warning of unintended intravascular or subarachnoid injection. (See PRECAUTIONS.) The pulse rate and other signs should be monitored carefully immediately following each test dose administration to detect possible intravascular injection, and adequate time for onset of spinal block should be allotted to detect possible intrathecal injection. An intravascular or subarachnoid injection is still possible even if results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, high spinal or cardiovascular effects from the epinephrine. (See WARNINGS and OVERDOSAGE.)

Use in Dentistry: The 0.5% concentration with epinephrine is recommended for infiltration and block injection in the maxillary and mandibular area when a longer duration of local anesthetic action is desired, such as for oral surgical procedures generally associated with significant postoperative pain. The average dose of 1.8 mL (9 mg) per injection site will usually suffice; an occasional second dose of 1.8 mL (9 mg) may be used if necessary to produce adequate anesthesia after making allowance for 2 to 10 minutes onset time. (See CLINICAL PHARMACOLOGY.) The lowest effective dose should be employed and time should be allowed between injections; it is recommended that the total dose for all injection sites, spread out over a single dental sitting, should not ordinarily exceed 90 mg for a healthy adult patient (ten 1.8 mL injections of 0.5% MARCAINE with epinephrine). Injections should be made slowly and with frequent aspirations. Until further experience is gained, MARCAINE in dentistry is not recommended for pediatric patients younger than 12 years.

Unused portions of solution not containing preservatives, i.e., those supplied in single-dose ampuls and single-dose vials, should be discarded following initial use.

This product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are discolored or which contain particulate matter should not be administered.

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Appendix F

Summary of Safety and Effectiveness

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SUMMARY OF SAFETY AND EFFECTIVENESS

November 11, 1998

Trade Name: Paragon Infusion Kit

Common Name: Infusion Pump Kit

Classification Name: Pump, Infusion

All questions and/or comments concerning this document should be made to:

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1.0 GENERAL INFORMATION

1.1 Purpose of Submission

1.1.1 This submission is intended to notify the Federal Food and Drug Administration that I-Flow Corporation intends to market a new intended use for the Paragon Infusion System (K923875), originally identified as the SideKick 50 Plus and SideKick 100 Plus. The Paragon will be marketed as a kit, the Paragon Infusion Kit, including labeling changes and additional components.

1.1.2 Trade Name: Paragon Infusion Kit

1.1.3 Common Name: Infusion Pump Kit

1.1.4 Classification Name: Pump, Infusion

1.1.5 Classification Panel: General Hospital and Personal Use Device

1.2 Statement of Equivalence

1.2.1 The Paragon Infusion Kit includes components that are legally marketed (either pre-amendment devices or devices that have been granted permission to market via premarket notification regulation).

1.2.2 The Paragon pump and administration set are the same as used in K923875.

1.2.3 The Paragon Kit is substantially equivalent to the I-Flow Paragon Infusion System (K923875), the I-Flow PainBuster Infusion Kit (K980558, K982946), the Sgarlato Pain Control Infusion Pump (PCIP) (K896422) and the I-Flow Homepump C-Series (K944692).

2.0 PHYSICAL SPECIFICATIONS AND DESCRIPTIONS

2.1 Description of the Paragon Infusion Kit

2.1.1 The Paragon Infusion Kit is identical to the I-Flow PainBuster Infusion Kit with the exception of the Paragon pump and administration set replacing the PainBuster pump.

2.1.2 The kit is comprised of a Paragon pump and administration set (K923875) and various kit components such as catheter, needle, syringe, Y adapter, dressing, tape, gauze and carry case.

2.1.2.1 The PainBuster kit contains all the above components except for an elastomeric pump with integrated administration set instead of the Paragon pump and administration set.

2.1.3 The Paragon administration set is intended to attach to the kit catheter at the distal end of the set to provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

2.1.4 The Paragon administration set is a disposable device intended for single patient use. The Paragon pump is reusable.

2.1.5 The Paragon is suitable for use as an ambulatory device and is intended for use in the hospital, home environment or alternative care sites.

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2.2 Description of Paragon Pump

2.2.1 The Paragon pump consists of two cylindrical shells. The top half of the pump has internal threads which mate to the external threads of the bottom half of the pump.

2.2.2 The top incorporates a pressure plate which applies a load to the pliable drug bag. The load is applied to the drug bag by way of two opposing springs which act upon a scissors mechanism. The spring/scissors mechanism creates a near constant pressure in the drug bag.

2.2.3 The bottom half of the pump is slotted to allow for positioning of the administration set.

2.2.4 When the top and bottom halves of the pump are fully threaded together, the pressure plate contacts the drug bag and acts as the pressurizing element.

2.2.5 This premarket notification proposes no changes to the Paragon pump.

2.3 Description of Paragon Administration Set

2.3.1 The Paragon administration set consists of a PVC drug bag attached to the administration line.

2.3.2 Each administration set consists of fixed diameter flow control tubing or glass orifice.

2.3.3 The flow control tubing or glass orifice is cut to a specific length L. When the PVC drug bag is pressured by the Paragon pump, the delivery times are defined by the inside diameter of the flow control orifice.

2.3.3.1 The delivery time characteristic is derived from the flow rate of the device which is in turn approximated by Poiseulle's equation:

$$Q = \frac{\Delta \rho \pi D^4}{128 \mu L}$$

2.3.3.2 Where Q is the flow rate, ρ is the pressure drop across the orifice, D is the inside diameter of the flow controlling orifice, μ is the dynamic viscosity of the fluid and L is the length of the orifice. The equation provides an approximation of the actual delivery time.

2.4 Product Configuration

2.4.1 The Paragon pump:

2.4.1.1 PG100000P: 100 ml volume

2.4.2 The Paragon administration sets:

2.4.2.1 PG100005: 100 ml volume, 0.5 ml/hr flow rate

2.4.2.2 PG100010: 100 ml volume, 1.0 ml/hr flow rate

2.4.2.3 PG100020: 100 ml volume, 2.0 ml/hr flow rate

2.4.2.4 PG100040: 100 ml volume, 4.0 ml/hr flow rate

2.4.2.5 PG100100: 100 ml volume, 10.0 ml/hr flow rate

2.4.2.6 PG100020Y: 100 ml volume, 2.0 ml/hr flow rate, dual orifice, dual catheter with Y adapter

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2.4.2.6.1 The dual orifice set consists of a standard Paragon set with dual orifice downstream from the Y adapter. Each orifice allows 2 ml/hr flow rate.

2.4.3 Each model consists of a kit with the following components:

2.4.3.1 Paragon pump (optional).

2.4.3.1.1 The reusable Paragon pump may be packaged and sold separately from the disposable kit components.

2.4.3.2 Paragon administration set.

2.4.3.3 Catheter:

2.4.3.3.1 18 to 22 G catheter, 11 to 40 in. length, polyamide, nylon, FEP (fluorinated ethylene propylene) polymer, silicone, polyurethane or Teflon.

2.4.3.3.2 A catheter connector is included to connect the catheter to the distal luer of the administration set.

2.4.3.3.3 The B. Braun Perifix® Epidural Catheter Set is an example of the type of catheter that may be used with the Paragon Infusion Kit.

2.4.3.3.3.1 Product code: EC20-0.

2.4.3.3.3.2 510(k) number: K813186.

2.4.3.4 Needle:

2.4.3.4.1 14 to 18 G, 1 ½ to 3 ¼ in. length, stainless steel.

2.4.3.4.2 The needle may be a catheter over needle as in the Angiocath™ example below.

2.4.3.4.3 The Angiocath catheter introducer needle is an example of the type of catheter introducer needle that may be used with the Paragon Infusion Kit.

2.4.3.4.3.1 Product code: 382258.

2.4.3.5 Syringe (optional):

2.4.3.5.1 60 cc plastic, luer lock syringe.

2.4.3.5.2 The syringe is used to fill the Paragon drug bag with medication.

2.4.3.5.3 The B-D 60 cc syringe is an example of the type of syringe that may be included in the Paragon Kit.

2.4.3.5.3.1 Product Code: 309663.

2.4.3.6 Dressing (optional):

2.4.3.6.1 The dressing is used to hold the catheter and/or flow restrictor in place.

2.4.3.6.2 The OpSite™ is an example of the type of dressing that may be used in the Paragon Kit.

2.4.3.6.2.1 Product Code: 4973. 224

2.4.3.7 Carry Case (optional):

2.4.3.7.1 The carry case is used to hold the Paragon pump while delivering medication.

2.4.3.7.1.1 I-Flow part numbers 1400749, 1400752 or 1400758.

2.4.3.8 Antiseptic Skin Swabs (optional):

2.4.3.8.1 The antiseptic skin swabs are used to prep the skin area of the patient prior to inserting the catheter.

2.4.3.8.2 The Alcohol Prep Pads or Iodophor PVP Scrub Swabsticks manufactured by Clinipad Corporation are examples of the type of antiseptic skin swabs that may be used in the Paragon Kit.

2.4.3.8.2.1 Model number: CL0110.

2.4.3.8.2.2 Model number: CL1244.

2.4.3.9 Tape (optional):

2.4.3.9.1 The tape may be used to the secure catheter, flow control tubing or gauze.

2.4.3.9.2 The Transpore™ Surgical Tape manufactured by 3M is an example of the type of tape that may be used in the Paragon Kit.

2.4.3.9.2.1 Model number: 3M1527-1.

2.4.3.10 Gauze (optional):

2.4.3.10.1 The gauze may be used to secure the catheter or flow control tubing.

2.4.3.10.2 The Kling® Conforming Gauze manufactured by Johnson and Johnson is an example of the type of gauze which may be used in the Paragon Kit.

2.4.3.10.2.1 Model number: JJ6923.

2.4.3.11 Y Adapter (optional)

2.4.3.11.1 The Y adapter is used for an additional catheter for a large wound or multiple wound sites.

2.4.3.11.2 The Flexible Y Fitting by Qosina is an example of the type of Y Adapter that may be used in the Paragon Kit.

2.4.3.11.2.1 Model number: 81120.

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2.5 Components and Materials

The pump and administration sets used in the Paragon Infusion Kit are currently available models of the Paragon Infusion System (K923875). No changes will be made to the Paragon pump or administration sets.

All kit components other than the pump and administration set are identical to those used in the PainBuster infusion system submitted under K980558, K982946.

The Paragon administration set is a disposable device intended for single patient use. The Paragon pump is reusable.

2.6 Power Requirements

2.6.1 The Paragon pump is a mechanical pump that utilizes spring energy for power. No additional external power source is required.

3.0 OPERATIONAL SPECIFICATIONS AND DESCRIPTIONS

3.1 Standard Operating Conditions:

Priming/Residual Volume:	< 5 ml
Operating Temperature:	31°C skin temperature (90°F)
Test Solution:	0.9% NaCl
Operating Pressure:	6.0 psi pressure source
Head Height:	0"
Accuracy:	±10% at 95% confidence interval

3.2 **Flow Rate Performance Data**: Testing occurred at standard operating conditions. All models produced an average flow rate within the ±10% accuracy claim.

	100 ml x 0.5 ml/hr	100 ml x 1 ml/hr	100 ml x 2 ml/hr	100 ml x 4 ml/hr	100 ml x 10 ml/hr
Average Flow Rate (ml/hr)	0.53	0.99	1.99	4.14	10.30
Std. Dev.	0.01	0.03	0.07	0.10	0.38
N	5	5	5	5	10

100 ml x 0.5 ml/hr: A five (5) piece sample produced an average flow rate of 0.53 ml/hr. The resulting average is well within its ±10% accuracy claim. The fastest infusion had an average flow rate of 0.54 ml/hr and the slowest infusion had an average flow rate of 0.51 ml/hr.

100 ml x 1.0 ml/hr: A five (5) piece sample produced an average flow rate of 0.99 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 1.04 ml/hr and the slowest infusion had an average flow rate of 0.96 ml/hr.

100 ml x 2.0 ml/hr: A five (5) piece sample produced an average flow rate of 1.99 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 2.05 ml/hr and the slowest infusion had an average flow rate of 1.90 ml/hr.

100 ml x 4.0 ml/hr: A five (5) piece sample produced an average flow rate of 4.14 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 4.24 ml/hr and the slowest infusion had an average flow rate of 3.99 ml/hr.

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100 ml x 10.0 ml/hr: A ten (10) piece sample produced an average flow rate of 10.30 ml/hr. The resulting average is within its ±10% accuracy claim. The fastest infusion had an average flow rate of 10.80 ml/hr and the slowest infusion had an average flow rate of 9.65 ml/hr.

Back Pressure (Head Height) Comparison: Approximately 0.57 psi pressure difference results per 16" head height. Thus, a 10% flow rate change may occur for each 16" head height difference from nominal assuming a 6 psi pressure source.

3.3 **Drug Delivery Comparison**: Local anesthetics have densities similar to normal saline (e.g. 1.002 to 1.005 for Ropivacaine HCl vs. 1.0045 for normal saline) and should not affect flow rate. Product labeling includes a statement as to delivery times and the possible deviation from nominal due to drug viscosity.

3.4 **Safety / Alarm Functions**

3.4.1 The Paragon pump and administration set provide a continuous fixed flow and as such is not subject to fluid runaway conditions similar to that of some electronic pumps.

3.4.2 The Paragon pump will not be recommended for any application that exceeds the minimum internal pressure of the system.

3.4.3 If for any reason the patient needs to stop his or her infusions, each administration set is supplied with a pinch clamp to stop the infusion.

3.4.4 This device contains no alarms or indicators for flow other than visual.

3.4.5 This device contains no alarms or indicators to detect air in line or an occlusion; however, each set may include an integrated air-eliminating filter.

4.0 BIOLOGICAL SPECIFICATIONS

4.1 Biological testing is in conformance with ISO 10993 Part 1 for all fluid path components of the Paragon administration set.

5.0 CHEMICAL AND DRUG SPECIFICATIONS

5.1 Compatibility

5.1.1 There are no specific drugs referenced in the labeling for the Paragon Infusion Kit.

5.1.2 The Paragon Infusion Kit is intended for use with general local anesthetics and epidural medications.

5.2 Drug Stability

5.2.1 There are no drugs included in the Paragon Infusion Kit.

6.0 INTENDED USE

6.1 The Paragon Infusion Kit is intended to provide continuous infusion a local anesthetic directly into an intraoperative (soft tissue / body cavity) site for general surgery for postoperative pain management.

6.2 Additional routes of administration include percutaneous, subcutaneous, intramuscular and epidural infusion.

6.3 The Paragon pump is re-usable. The disposable Paragon administration set is single patient use only.

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6.4 No testing has been conducted to determine the efficacy of the Paragon for the delivery of blood, blood products, lipids or fat emulsions. The Paragon is not intended for the delivery of blood, blood products, lipids or fat emulsions.

6.5 The Paragon is suitable for use as an ambulatory device and is intended for use in the hospital, home environment or alternative care sites.

7.0 PACKAGING

7.1 The Paragon Kit consists of an inner pouch or tray with Tyvek lid stock surrounded by a header bag with an ETO Tyvek strip.

7.2 The Paragon administration set may be packaged in either a Tyvek pouch or Form/Fill/Seal.

7.3 The Paragon Kit components are placed in the inner tray or pouch.

7.4 Packaging is suitable for either radiation or ETO sterilization.

8.0 STERILIZATION INFORMATION

Note: The kit components of the Paragon Infusion Kit may be purchased non-sterile and packaged by I-Flow or sterile from the manufacture. The Paragon administration set and non-sterile purchased components shall be sterilized as follows:

8.1 The methods of sterilization are gamma radiation (Cobalt 60) or ETO gas.

9.0 COMPARISON TO LEGALLY MARKETED DEVICES

See Table 1 that follows this section for more specific information.

9.1 Intended Use

9.1.1 The Paragon Infusion Kit, the PainBuster Infusion Kit and the Sgarlato Pain Control Infusion Pump (PCIP) have the same intended use:

9.1.1.1 To provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.

9.1.2 The predicate Paragon Infusion System and Homepump C-Series are intended for general infusion use, including chemotherapy and pain management.

9.2 Device Descriptions

9.2.1 The Paragon Infusion Kit

9.2.1.1 The Paragon Infusion Kit is identical to the predicate PainBuster Infusion Kit with the exception of the Paragon pump and administration set replacing the PainBuster pump.

9.2.1.2 The Paragon Infusion Kit uses the same mechanical, reusable Paragon pump as the predicate Paragon Infusion System.

9.2.1.3 The Paragon Infusion Kit uses the same Paragon Administration Set as the Paragon Infusion System.

9.2.2 The Paragon Infusion System

9.2.2.1 The Paragon Infusion Kit uses the same pump and administration sets as the Paragon Infusion System (K923875).

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9.2.3 The Sgarlato Pain Control Infusion Pump (PCIP)

9.2.3.1 The Sgarlato PCIP consists of a kit very similar to the Paragon and PainBuster Infusion Kit. These kits consist of an infusion pump and administration set, catheter, needle, syringe, Y adapter, carry case, dressing, tape and gauze.

9.2.3.2 The Sgarlato kit uses a disposable, spring driven syringe pump with integrated administration set.

9.2.4 The Homepump C-Series

9.2.4.1 The Homepump C-Series consists of a disposable, elastomeric infusion pump with integrated administration set.

9.2.5 Specifications

9.2.5.1 The Paragon Infusion Kit, PainBuster Infusion Kit and Sgarlato PCIP have similar fill volumes and flow rates, see Table 1.

9.2.6 Flow Control

9.2.6.1 The Paragon Infusion Kit and all its predicate devices use either a glass orifice or PVC tubing to control the flow rate.

9.2.7 Materials

9.2.7.1 The Paragon Infusion Kit uses the same Paragon Administration Set as the Paragon Infusion System. All fluid path materials of the Paragon Administration Set are in conformance with ISO 10993 Part 1.

9.2.8 Based upon the data presented in this section 9.0 and Table 1, I-Flow Corporation has determined that the Paragon Infusion Kit is substantially equivalent to the named predicate devices.

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Table 1
Comparison to Legally Marketed Devices

Comparison Element	Paragon Infusion Kit (subject device)	SE[1] Paragon Infusion System (K923875)	SE[1] PainBuster Infusion Kit (K980558, K982946)	SE[1] Sgarlato PCIP (K896422)	SE[1] Homepump C-Series (K944692)
Intended Use	To provide continuous infusion of a local anesthetic directly into the intraoperative site for general surgery for postoperative pain management.	General infusion use, including chemotherapy and pain management.	To provide continuous infusion of a local anesthetic directly into the intraoperative site for postoperative pain management.	To provide continuous infusion of a local anesthetic directly into the surgical wound site for postoperative pain management.	General infusion use, including chemotherapy and pain management.
Routes of Administration	Percutaneous, subcutaneous, intramuscular and epidural	Intravenous	Percutaneous and subcutaneous	Percutaneous, subcutaneous and epidural	Intravenous, intra-arterial, epidural or subcutaneous
Contraindications	Not intended for intravenous or intra-arterial delivery. Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for intravenous, intra-arterial or epidural delivery. Not intended for delivery of blood, blood products, lipids or fat emulsions.	Not intended for rapid infusions. Not intended for intravenous infusion.	Not intended for delivery of blood, blood products, lipids or fat emulsions.
Reuse Capability	Re-usable pump, single patient use disposable administration set	Re-usable pump, single patient use disposable administration set	Disposable, single patient use	Disposable, single patient use	Disposable, single patient use
Description	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.	Sold empty and capable of being filled via a fill port.
Fill Volumes	100 ml	100 ml	50 to 270 ml	50 to 100 ml	50 to 500 ml
Flow Rates	0.5, 1.0, 2.0, 4.0 or 10.0 ml/hr	0.5 to 200 ml/hr	0.5, 1.0, 2.0, 5.0 or 10.0 ml/hr	0.5, 1.0 or 2.0 ml/hr	0.5 to 500 ml/hr
Pump Type	Mechanical spring	Mechanical spring	Elastomeric Pump	Spring driven syringe pump	Elastomeric Pump
Power Requirements	None	None	None	None	None
Pump Mechanism	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.	Constant pressure is applied to the fluid reservoir.
Pressure Source	Mechanical spring energy	Mechanical spring energy	Strain energy of elastomeric membranes	Mechanical spring energy	Strain energy of elastomeric membranes
Fluid Reservoir	PVC drug bag	PVC drug bag	Thermoplastic (Krayton) elastomeric membrane	Polypropylene plastic syringe	Thermoplastic (Krayton) elastomeric membrane
Administration Set					
Flow Control	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.	Consistent flow rate throughout the entire course of therapy is achieved by the combination of constant pressure and flow control tubing.
Safety / Alarm Functions	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.	Fixed flow rate tubing prevents fluid runaway conditions. Each administration set is supplied with a clamp to stop the infusion if necessary.

[1]SE = Substantially Equivalent

FDA/CDRH IMAGING SYSTEM

Page Count Discrepancy Information

Page after page 129 is misnumbered.

Verifiers Initials