CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-175

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Review and Evaluation of Clinical Data

NDA (Serial Number)	**21-175(BL)**
Sponsor:	**United States Army**
Drug:	**ATNAA (Atropine & Pralidoxine)**
Proposed Indication:	**Nerve Agent Antidote**
Material Submitted:	**Correspondance-Minor Amendement**
Correspondence Date:	**11/21/01**
Date Received / Agency:	**11/26/01**
Date Review Completed	**12/19/01**
Reviewer:	**Kevin Prohaska, D.O.**

1. Introduction

This submission contains the sponsor's response to our facsimile dated October 23, 2001 and teleconference of November 2, 2001.

The following is the four issues contained in the facsimile and the Sponsor's response:

1. An assurance that the Army accepts the changes contained in the FDA facsimile of October 23, 2001.
   Response: The Army agrees with the changes and modified the Package Insert and Patient Instruction Card accordingly.
2. An assurance that the Patient Instruction Card will be a component of the Package Insert.
   Response: The Army agrees to the request and has incorporated the patient Instruction Card as part of the Package Insert.
3. An assurance that the pictograms will match across the Package Insert, Patient Instruction Card, and the ATNAA label.
   Response: The Army states the manufacturer claims the five pictograms will not fit on the ATNAA label. The Army states that all five pictograms will be included in the Package Insert and Patient Information Card however the Army proposes to place only the first three pictograms with "no text" on the ATNAA label. The Army states any text inside the pictogram would be too small to be legible. The sponsor requests our concurrence.
   Comment: The sponsor does not include a marked up ATNAA container label with the three pictograms for my review so I am unable to review this modification or provide concurrence. In a previous submission (serial N-AZ, dated 8/15/01) prior to the modification of the pictograms the sponsor also limited the container label with the first three pictograms however the phrase "10 sec" was included in the third pictogram depicting thigh injection. This bit of information is intended to relay to the user the duration of time the injection must remain in contact with the thigh and is essential for the proper use of ATNAA. This approach seems adequate however it needs to be clarified whether the Army intends to keep the "10 sec" in the recently modified third pictogram. Clarification of this issue has been requested from the sponsor. (Addendum: In a fax received 18 December 2001 the sponsor provided us with a copy of the container label for our review. The "10 sec" will be retained in the third pictogram. The modification to the container label is acceptable.)

4. A sample of the revised Package Insert and Patient Instruction Card.
Comment: The submitted items are photocopies of the originals. The Package Insert contains the five pictograms at the end without comment from the sponsor. As presently arranged the print is legible albeit small however no smaller than the references at the end of the label. The pictograms contain the modifications requested by the Agency in previous discussions with the sponsor.

2. Recommendations

I recommend the approval of the ATNAA product.

Kevin Prohaska, D.O.
Medical Reviewer

J. Feeney, M.D. _____

cc:
HFD-120

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kevin Prohaska
12/20/01 08:44:20 AM
MEDICAL OFFICER

John Feeney
12/31/01 12:37:31 PM
MEDICAL OFFICER

Nerve Agent Antidote Delivery System (atropine/2-PAM)

Department of the Army, Office of the Surgeon General

NDA 21-175

Submission Date: December 7, 1999

Received by the OCPB: December 15, 1999

Reviewer : Iftekhar Mahmood, Ph.D.

Introduction

The US Army is currently in the process of developing a Nerve Agent Antidote Delivery System (NAADS). The NAADS will deliver atropine (2.1 mg in 0.7 mL) and pralidoxime chloride (600 mg in 2 mL) from one autoinjector, through a single needle for self-aid and/or buddy-aid of military personnel. Currently these two antidotes are available in separate autoinjectors (Mark-I, Nerve Agent Antidote Kit (MK-I NAAK). MK-I NAAK consists of 1.67 mg atropine and 600 mg pralidoxime chloride. The existing kit requires the service member to take two separate injections in a specific order. The goal of the army is to reduce the number of injections required and to reduce the bulk carried by the service member. The US Army has attempted to develop several single lumen multichambered Auto-injectors (MA). Comparative bioavailability studies have been performed with a number of different MA designs and the Mark-I auto-injector. The final MA-design (IDMA-III), which is the subject of this application has the same characteristics as the injectors found in the Mark-I NAAK, with the exception of needle size and atropine concentration. The needle gauge for the IDMA-III is 23 gauge vs 20-22 gauge for the MK-I injectors. In addition, the IDMA-III contains 2.09 mg atropine which is 25% higher than that contained in the Mark-I NAAK (1.67 mg).

The Sponsor has conducted two comparative bioavailability studies to demonstrate that IDMA-II and IDMA-III are comparable to Mark-I NAAK.

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APPEARS THIS WAY
ON ORIGINAL

Study #1

Title: A comparative bioavailability study of atropine and pralidoxime chloride administered by two different auto-injector delivery systems in healthy volunteers.

Products

Test: Atropine alkaloid 1.67 mg (equivalent to 2 mg atropine sulfate) and pralidoxime chloride (2-PAM), 600 mg, multichambered auto-injector delivery system **(MA).**

Manufacturer: [redacted]

Reference: Atropine alkaloid 1.67 mg (equivalent to 2 mg atropine sulfate) and pralidoxime chloride (2-PAM), 600 mg, Mark-I auto-injector delivery system **(MK-I).**

Manufacturer: [redacted]

Objective

To determine the absorption characteristics and comparative bioavailability of atropine and pralidoxime chloride (2-PAM) delivered from the multichambered (MA) auto-injector delivery system (IDMA II) versus the Mark-I (MK-I) auto-injector delivery system.

Study Design

Twenty-four healthy male (n = 17) and female (n = 7) subjects were enrolled in this two-treatment crossover study. They received a single intramuscular injection of 2 mg atropine sulfate and 600 mg pralidoxime chloride on two occasions, separated by at least 48 hours. Subjects fasted for ten hours before and six hours after each dose. Twelve mL venous blood samples were obtained at 20 time points from predose (0 hour) until 12 hours postdose. The blood samples were separated into serum samples to be assayed for atropine and plasma samples to be assayed for pralidoxime. Pharmacokinetic parameters such as Areas under the concentration-time curve from time zero to infinity $AUC_{(0\text{-Infinity})}$, the maximum drug concentration (C_{max}), the time to maximum drug concentration (T_{max}), and

half-life ($T_{1/2}$) were estimated. The effect of gender on the pharmacokinetics of atropine and pralidoxime was also evaluated.

Results

Twenty-two subjects (17 males and 5 females) completed the study. All of the subjects experienced adverse events during the study.

Atropine:

The C_{max} for the test was about 18% lower than the reference (MK-1) product (Table 1). The AUC(0-Infinity) and the half-life between the test and the reference products were comparable. The T_{max} of the test product was about 10 minutes longer than the reference product (Table 1) (Figures 1-3).

Pralidoxime:

The C_{max} of pralidoxime for the test product was about 15% lower than the reference (MK-1) product (Table 1). The AUC(0-Infinity), the half-life and the T_{max} between the test and the refernce products were comparable (Table 1) (Figures 4-6).

Table 1

Pharmacokinetic parameters of atropine and pralidoxime following the administration of two different auto-injector delivery systems in healthy volunteers

Parameters	Test: multichambered	Reference: MK-1
Atropine:		
C_{max} (ng/mL)	10.76 ± 2.90	13.19 ± 3.91
T_{max} (mins)	36.4 ± 30.7	26.2 ± 18.3
$T_{1/2}$ (mins)	160.4 ± 22.4	147.2 ± 22.20
AUC(0-inf) (ng*hr/mL)	2956 ± 628	2990 ± 514
Pralidoxime:		
C_{max} (µg/mL)	6.34 ± 1.88	7.45 ± 2.76
T_{max} (mins)	24.1 ± 11.8	25.05 ± 15.9
$T_{1/2}$ (mins)	312.3 ± 171.2	300.0 ± 93.92
AUC(0-inf) (µg*hr/mL)	1378 ± 496	1461 ± 351

The 90% confidence interval for log transformed data indicated that the $AUC_{(0\text{-inf})}$ for both atropine and pralidoxime was within the limits of bioequivalence criteria, but the C_{max} for both these compounds failed to meet this criteria (Table 2).

TABLE 2

The confidence intervals for atropine and pralidoxime following the administration of two different auto-injector delivery systems in healthy volunteers

Analyte	C_{max} (90% CI)	AUC (90% CI)
Atropine	0.75 - 0.90	0.95 - 1.02
Pralidoxime	0.79 - 0.96	0.85 - 1.09

Gender effect:

For atropine, the $AUC_{(0\text{-inf})}$ and C_{max} were 20% and 46% higher in females than males. The half-life of atropine was comparable between the two genders. For pralidoxime, the $AUC_{(0\text{-inf})}$ and C_{max} were 14% and 21% higher in females than males. The half-life of pralidoxime was approximately one hour longer in females than males. Due to small sample size (17 males and 5 females) it is difficult to draw any conclusion about the effect of gender on the pharmacokinetics of atropine or pralidoxime.

Conclusion

The multichambered device (MA) and the MK-I device are equivalent in terms of AUC but the C_{max} of MA device is slightly lower than the MK-I device for both atropine and pralidoxime. There may be gender difference in the pharmacokinetics of atropine but a definite conclusion can not be drawn due to the presence of few females in the study.

Pharmacodynamics of Atropine

Title: The comparison of the elevation in heart rate of healthy volunteers after a single dose of atropine sulfate and pralidoxime chloride from two different auto-injector delivery systems.

Objective

Heart rate was measured throughout the study to provide data for the description of the pharmacological effect of atropine and for exploration of the relationship between effect and the drug concentration of atropine.

Study Design

Subjects fasted for ten hours before and six hours after each dose. The heart rate was measured three times before dosing and 19 times after each dose at 1, 3, 6, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, 360, 540 and 720 minutes. The subjects remained supine for six hours after drug administration. The pharmacological effect of atropine was characterized by calculating the maximum change in heart rate (E_{max}), the time of maximum effect (T_{Emax}), the effect corresponding to the time of the maximum atropine concentration (E_{Cmax}), and the area(s) under the effect curve (AUEC).

Results

Twenty-two subjects completed the study. Based on the arithmetic means, heart rate was significantly increased from 10 to 720 minutes for the test product and from 3 to 720 minutes for the reference product. The mean maximum change in heart rate was 40 beats/minute at 74 minutes for the MA product and 42 beats/minute at 66 minutes for the MK-I product. There was no significant difference in the maximum increase in heart rate after administration of the two products. The AUEC was comparable between the two delivery systems (Table 3) (Figures 7 & 7a).

Table 3

Pharmacodynamic parameters of atropine following the administration of two different auto-injector delivery systems in healthy volunteers

Parameters	Test: multichambered	Reference: MK-1
$AUEC_{(0\text{-}720\ min)}$	10760 ± 8880	10228 ± 7114
E_{max} (beats/min)	39.6 ± 16.7	42.2 ± 13.5
TE_{max} (min)	74.4 ± 112.6	66.0 ± 150.2
EC_{max} (beats/min)	22.5 ± 18.8	29.8 ± 17.2

The unit of AUEC is in beats

E_{max} = maximum change in heart rate or maximum effect

T_{Emax} = time of maximum effect

E_{Cmax} = effect at C_{max} concentration.

For males, the mean heart rate was significantly increased from 10 to 720 minutes for the test product and from 3 to 720 minutes for the reference product. The mean maximum change in heart rate was 39 beats/minute at 86 minutes for the MA product in males and 42 beats/minute at 35 minutes for the MA product in females. The mean maximum change in heart rate was 43 beats/minute at 80 minutes for the MK-1 product in males and 40 beats/minute at 17 minutes for the MK-1 product in females. The AUEC in males and females for MA product was 11504 ± 7348 min and 8231 ± 13700 min, respectively. The AUEC in males and females for MK-I product was 11331 ± 4841 min and 6478 ± 12215 min, respectively. It should be noted that there are only 5 females in the study, therefore, it is difficult to draw any conclusion regarding gender effect from this study.

Concentration-Effect Relationship:

The plot of mean change in heart rate vs mean atropine concentration at each time point revealed counter-clockwise hysteresis after both the test and reference doses (Figure 8). From the mean plots there appears to be a steep increase in heart rate of 4 beats per

minute to 30 beats per minute over atropine concentration from 7 ng/ml to 9 ng/ml (Figure 8) for the multichamber device and from 9 ng/mL to 11 ng/mL for the Mark-I device. As the atropine concentration drops, heart rate does not return to predose rates as quickly. In the presence of hysteresis, however, no attempt was taken by the Sponsor to collapse the hysteresis by the use of effect compartment. The plot of change in heart rate vs atropine concentration at each time point for individual subjects also revealed counter-clockwise hysteresis.

The hysteresis may be an indication of a delayed effect but looking at the individual data (time of C_{max} and the maximum effect or maximum change in heart rate), the following observations were noted:

Ten subjects in whom the maximum effect occurred after C_{max}

Seven subjects in whom the maximum effect occurred before C_{max}

Two subjects in whom the maximum effect occurred around C_{max}

In three subjects the heart rate was lower than the baseline heart rate after C_{max}.

Therefore, it is difficult to conclude whether the effect produced by atropine is delayed or immediate. Overall, administration of atropine has resulted in increase in heart rate which may not be of any clinical significance.

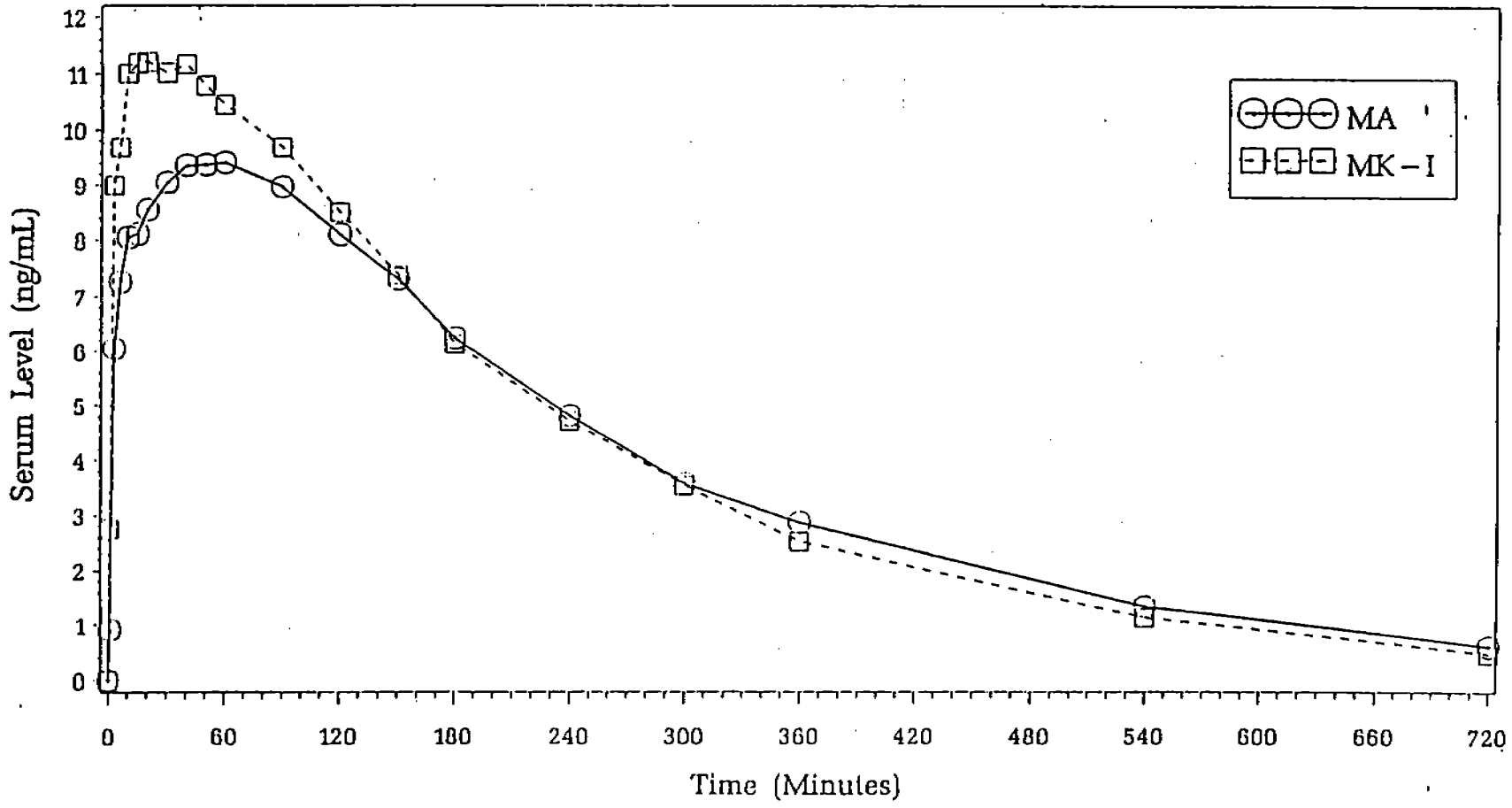
Conclusion

The atropine/pralidoxime injections resulted in increased heart rates when administered by either device. Small sample size does not permit the appropriate evaluation of gender effect on the pharmacodynamics of atropine.

Figure 1

Figure 1–A: Mean Atropine Serum Levels

n = 22

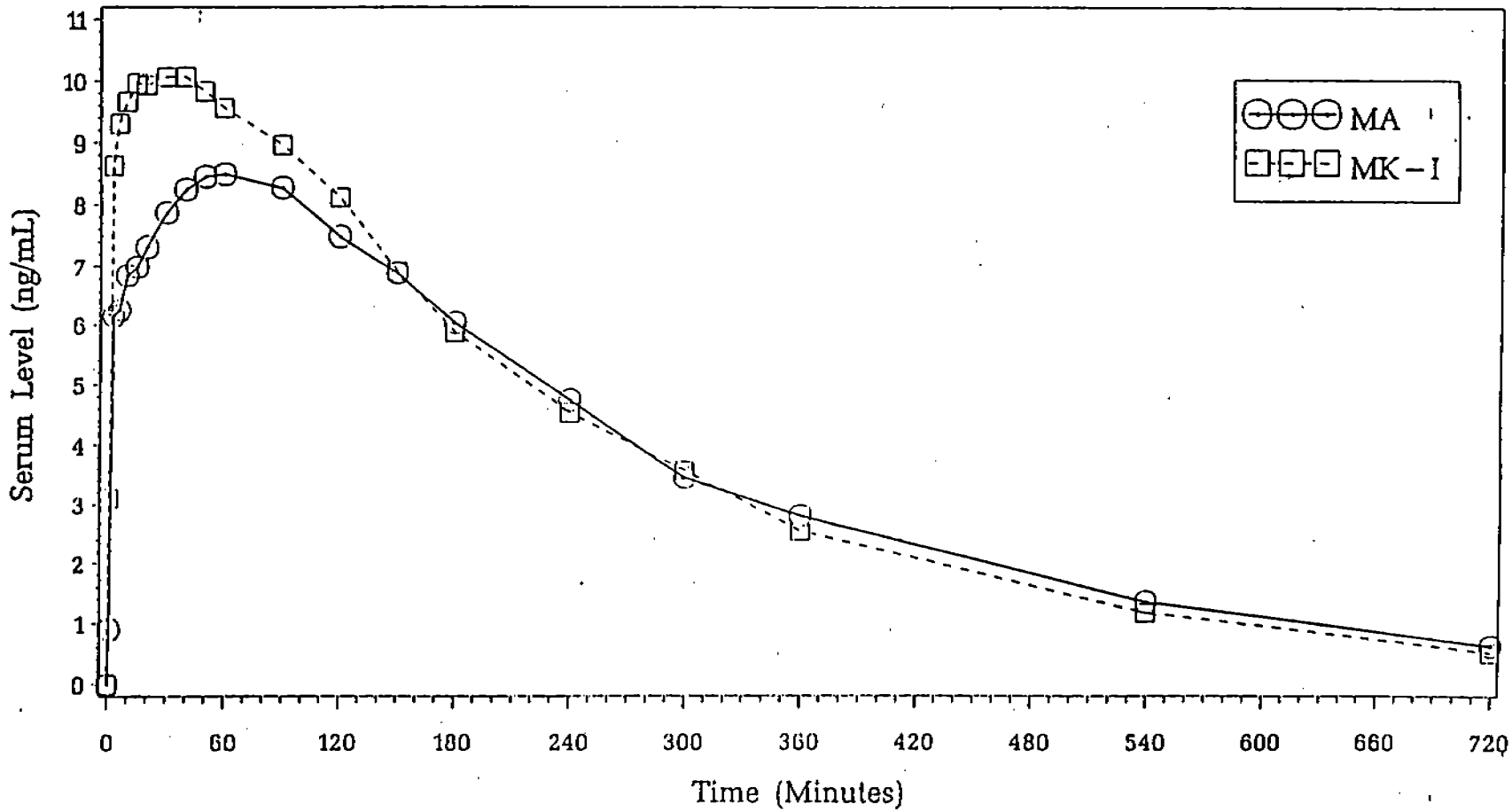


Note: MA = Multichambered Delivery System MK–I = MARK I Delivery System

Figure 2

Figure 2 – A: Mean Atropine Serum Levels for Males

n = 17



Note: MA = Multichambered Delivery System MK – I = MARK I Delivery System

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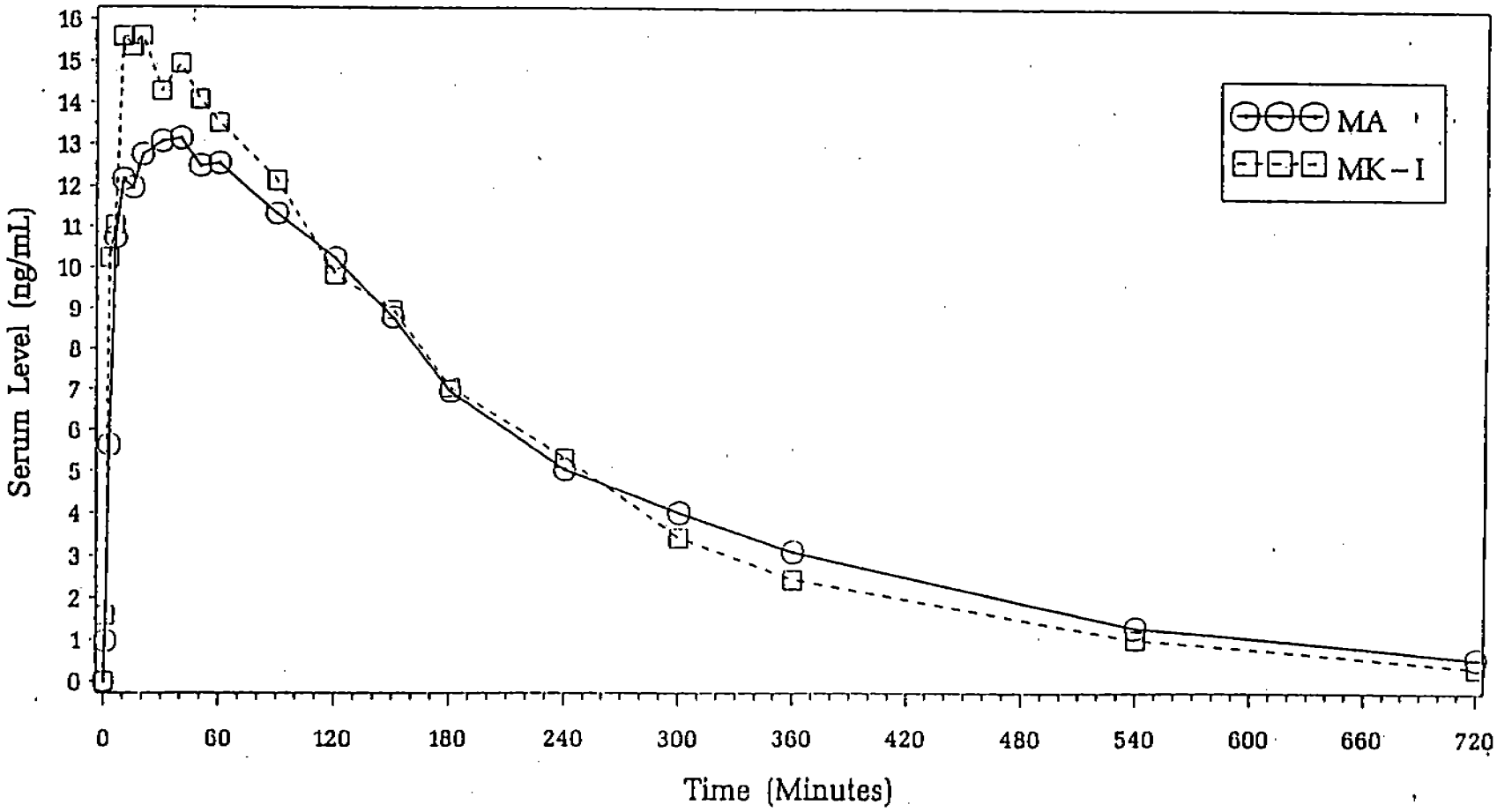
Figure 3 – A: Mean Atropine Serum Levels for Females

n = 5

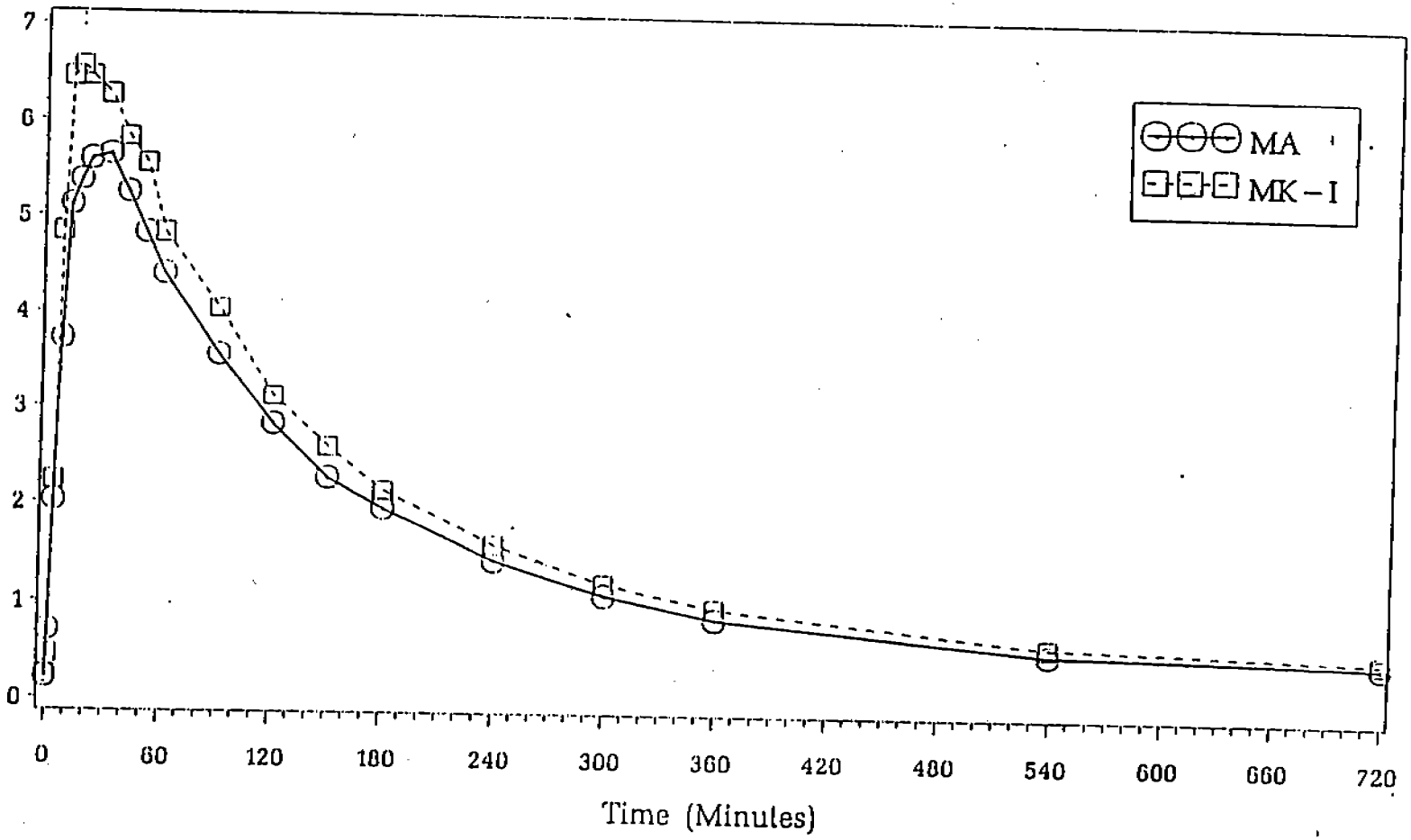


Note: MA = Multichambered Delivery System MK – I = MARK I Delivery System

Figure 4

Figure 4 – A: Mean Pralidoxime Plasma Levels

n = 22

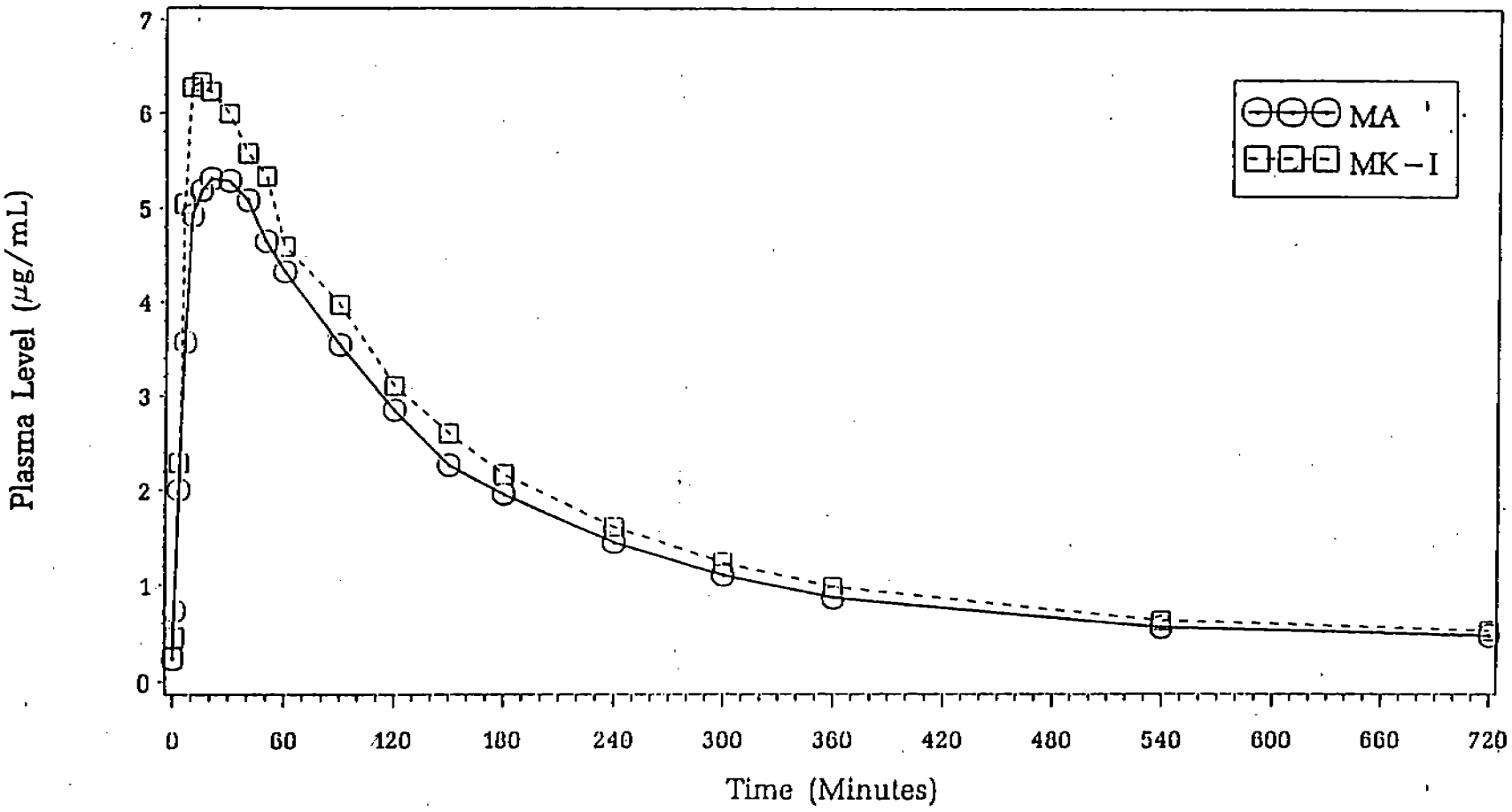


Note: MA = Multichambered Delivery System MK – I = MARK I Delivery System

Figure 5

Figure 5 – A: Mean Pralidoxime Plasma Levels for Males

n = 17

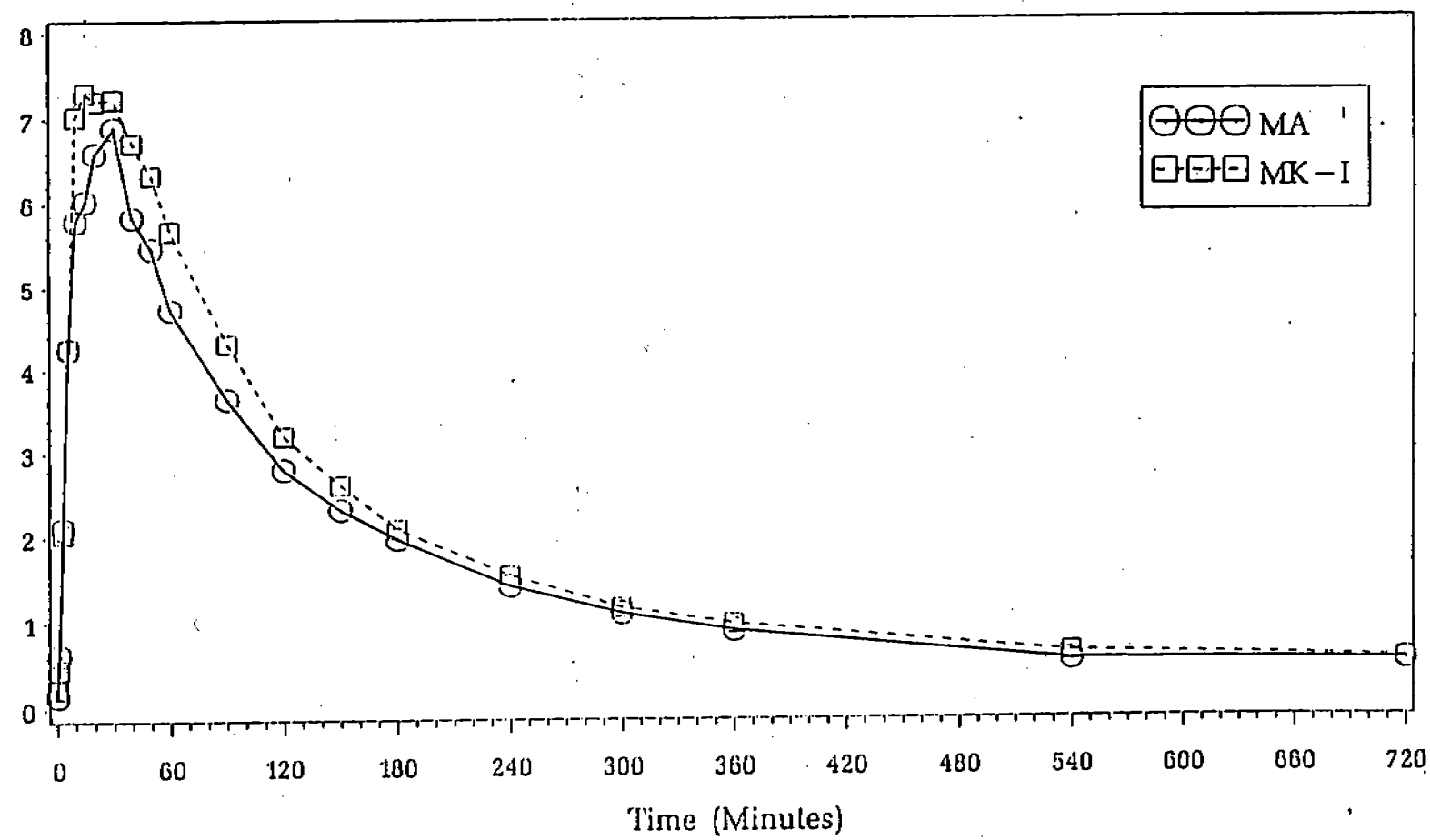


Note: MA = Multichambered Delivery System MK – I = MARK I Delivery System

Figure 6

Figure 6 – A: Mean Pralidoxime Plasma Levels for Females

n = 5



Note: MA = Multichambered Delivery System MK – I = MARK I Delivery System

Figure 7

Figure 7 – A: Mean Heart Rate (beats/min)

n = 22

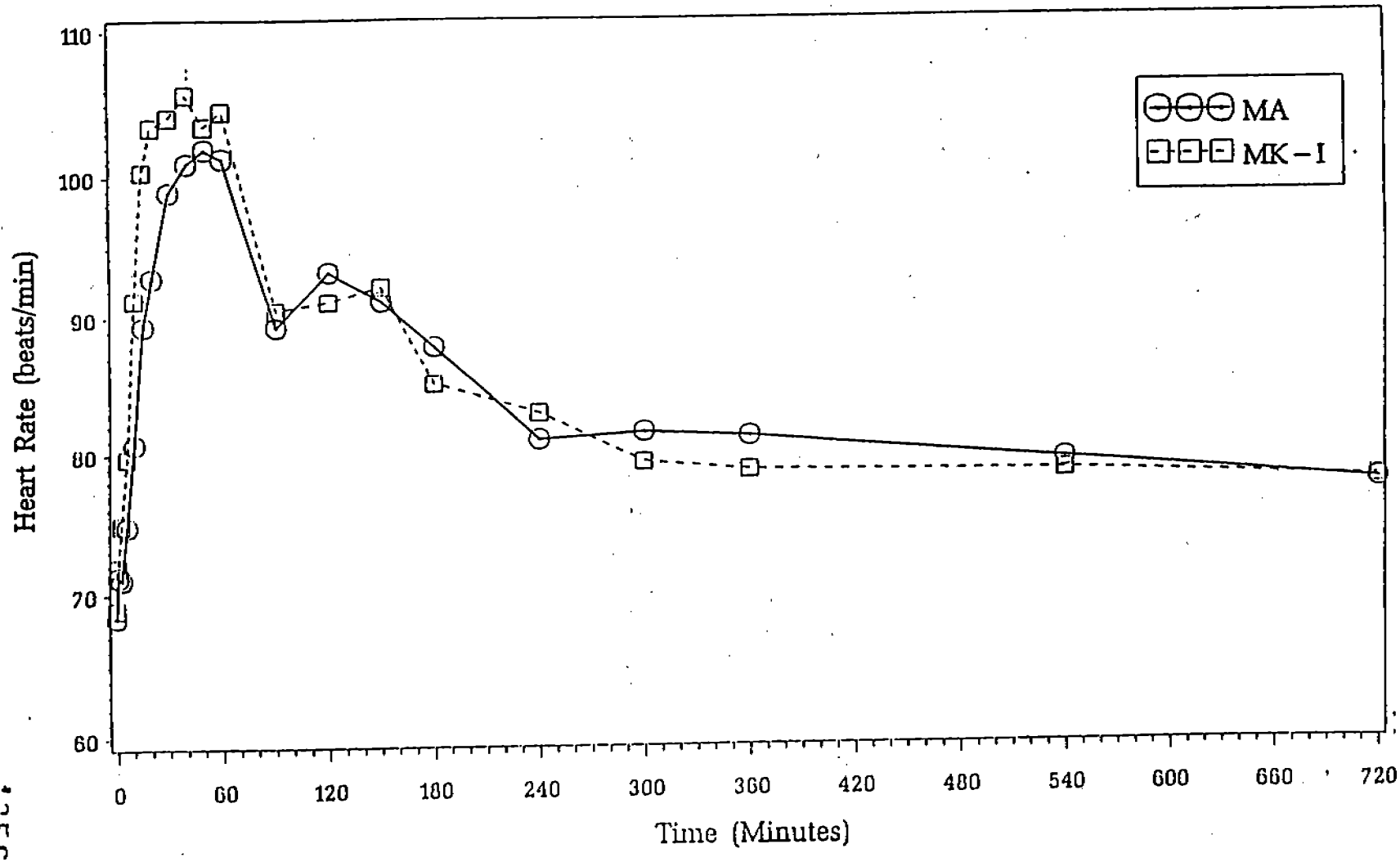


Figure 7a

Figure 7 – B: Mean Heart Rate (beats/min) Over 0 – 60 Minutes

n = 22

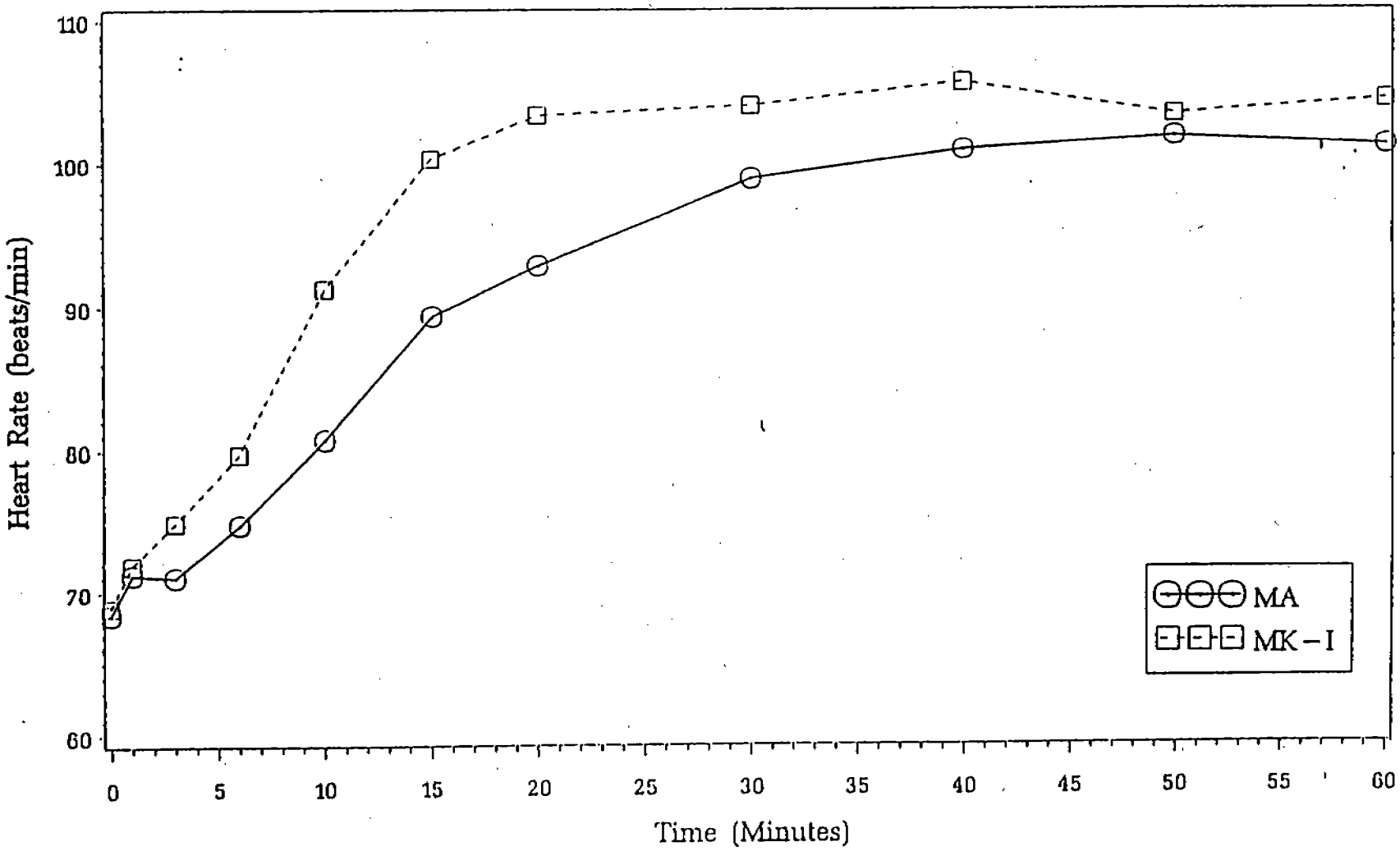


Figure 8

Comparative Bioavailability of Atropine and 2-PAM Auto-injector Systems

Figure 8-A: Mean Change in Heart Rate (beats/min) vs. Mean Serum Atropine (ng/mL)

n = 22

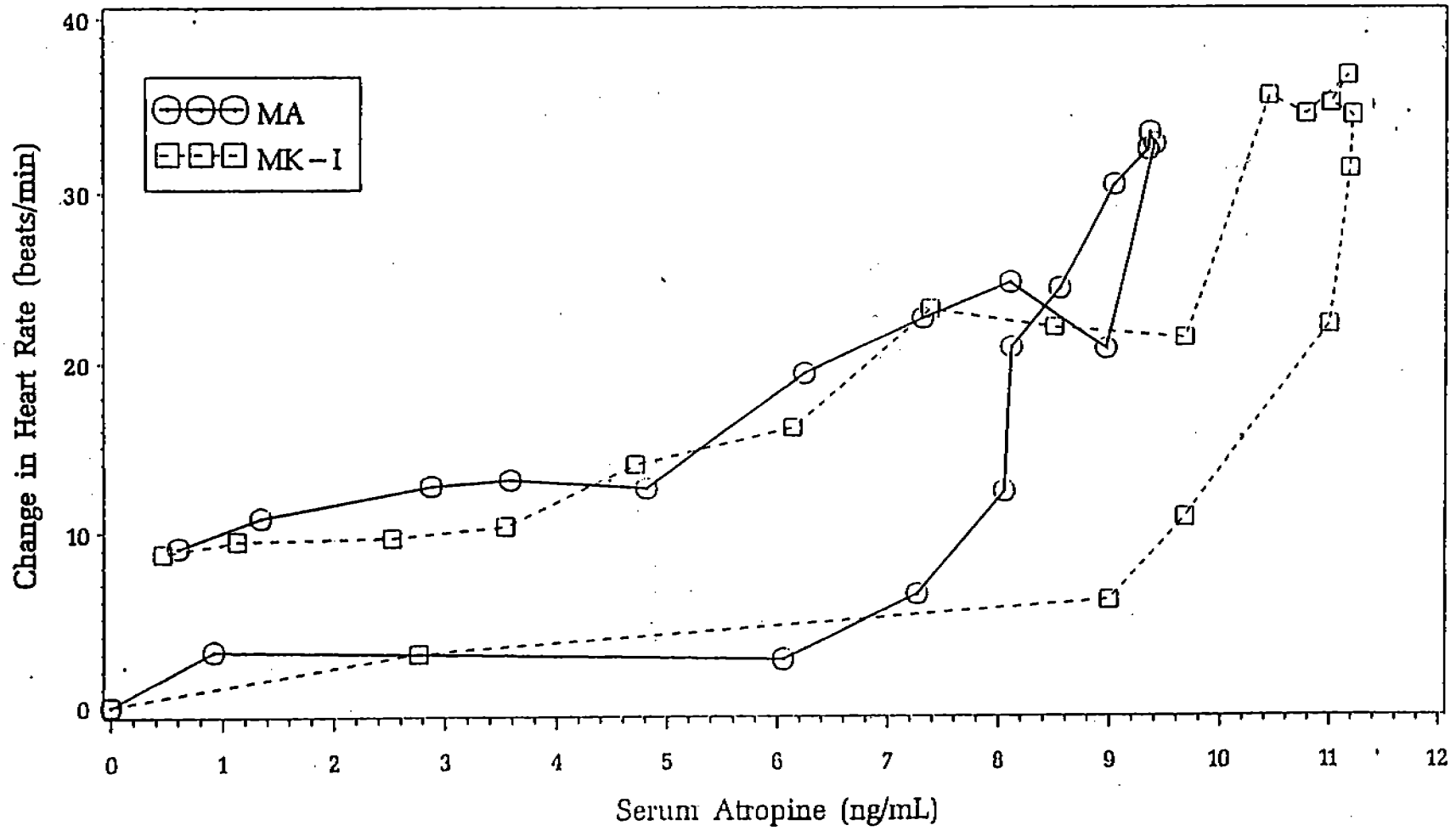
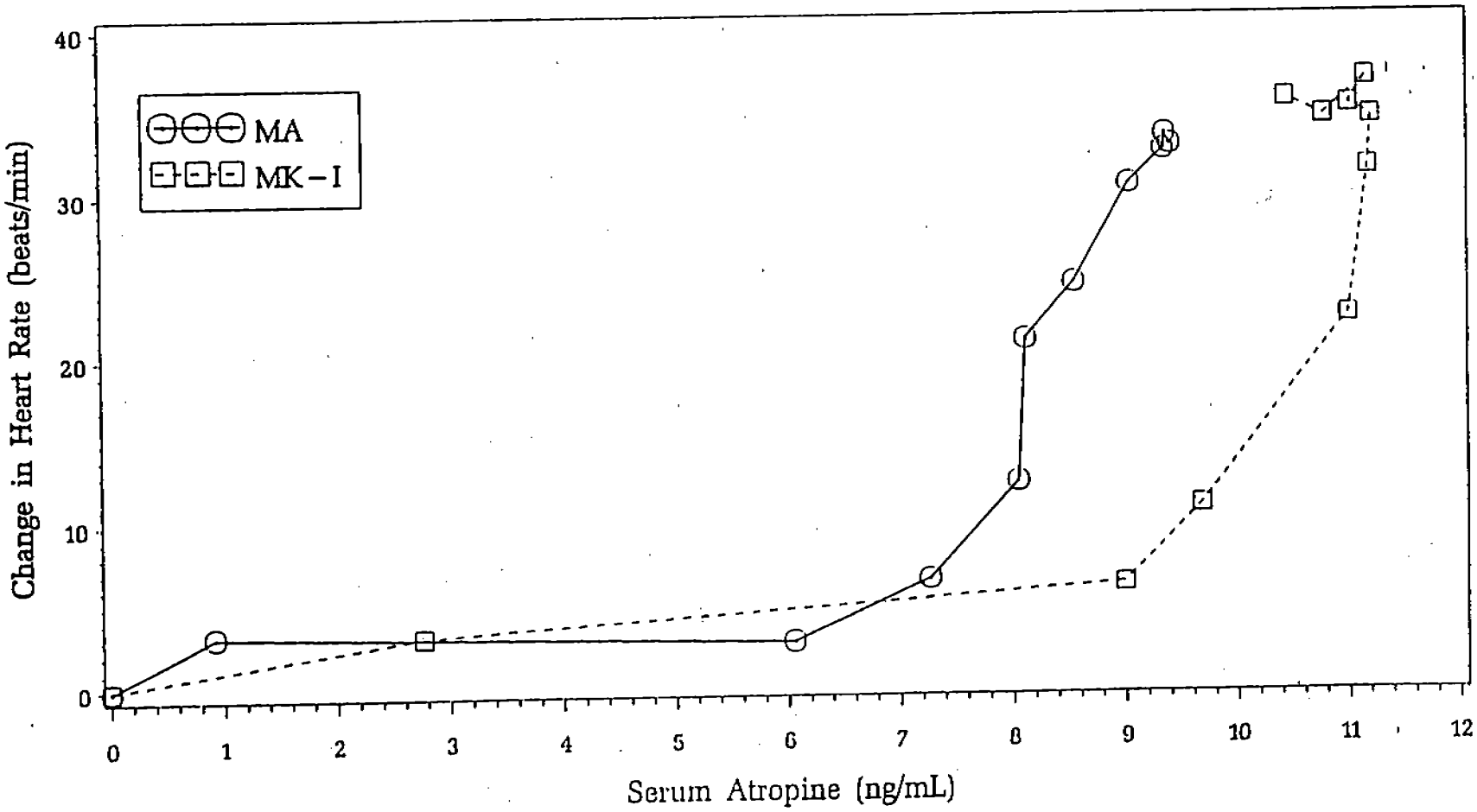


Figure 8a

Comparative Bioavailability of Atropine and 2-PAM Auto-injector Systems

Figure 8-B: Mean Change in Heart Rate (beats/min) vs. Mean Serum Atropine (ng/mL)
For Values Over 0-60 Minutes
n = 22



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Study #2

Title: A study assessing comparative availability of atropine and pralidoxime chloride administered by two different auto-injector' delivery systems in healthy volunteers.

Products

Test: Atropine alkaloid 2.09 mg/0.7 mL (equivalent to 2.51 mg atropine sulfate) and pralidoxime chloride (2-PAM), 600 mg, multichambered auto-injector delivery system (MA). Manufacturer: Meridian Medical Technologies.

Reference: Atropine alkaloid 1.67 mg/0.7 mL (equivalent to 2 mg atropine sulfate) and pralidoxime chloride (2-PAM), 600 mg, Mark-I auto-injector delivery system (MK-I); Manufacturer [redacted] (Meridian Medical Technologies).

ObJective

The objective of this study was to determine the absorption characteristics and establish the comparative bioavailability of atropine and pralidoxime chloride (2-PAM) as delivered by a multichambered (MA) auto-injector delivery system (IDMA-III) with the MARK-I (MK-I) auto-injector delivery system.

Study Design

Twenty-four healthy subjects (12 males and 12 females) were enrolled in this two-treatment crossover study in two groups. The subjects received a single intramuscular injection of atropine (equivalent to 2.51 mg atropine sulfate) and pralidoxime chloride 600 mg or atropine (equivalent to 2 mg atropine sulfate) and 600 mg pralidoxime chloride, on two occasions, separated by a wash-out period of at least 48 hours. Subjects fasted for ten hours before and six hours after each dose. Twelve mL venous blood samples were obtained at 20 time points from predose (0 hour) until 12 hours postdose (720 minutes). Blood

samples were separated into serum samples for assay of atropine, and plasma samples for assay of pralidoxime. Pharmacokinetic parameters such as Areas under the concentration-time curve from time zero to infinity $AUC_{(0\text{-Infinity})}$, the maximum drug concentration (C_{max}), the time to maximum drug concentration (T_{max}), and half-life ($T_{1/2}$) were estimated. The effect of gender on the pharmacokinetics of atropine and pralidoxime was also evaluated.

Results

All twenty-four subjects completed the study. During the conduct of the study, 23 of the 24 subjects experienced adverse events.

Atropine:

There were statistically significant differences (α=0.05) in mean concentrations from 10 to 720 minutes after dosing. Atropine concentrations after the multichambered device were up to 19% higher during the first 30 minutes and up to 53% higher at later time points, than the MK-I device.

The $AUC_{(0\text{-Infinity})}$ for the test was about 29% higher than the reference (MK-1) product. This is not surprising since the amount of atropine in the test formulation was 25% higher than the reference formulation. The C_{max} and the half-life between the test and the reference products were comparable. The T_{max} of the test product was about 10 minutes longer than the reference product (Table 4) (Figure 9). It should be noted that based on the equimolar dose of atropine, the AUC between the test and the reference product was comparable.

Pralidoxime:

Pralidoxime concentrations after the multichambered device were statistically significantly ($\alpha = 0.05$) lower than the pralidoxime concentrations after the MK-I device at 120, 150, 180, 360 and 540 minutes after dosing. The differences were less than 20% until 360 minutes when pralidoxime concentrations could no longer be measured in many of the subjects.

The C_{max} of pralidoxime for the test product was about 15% higher than the reference (MK-1) product. The $AUC_{(0\text{-Infinity})}$, the half-life and the T_{max} between the test and the reference products were comparable (Table 4) (Figure 12).

Table 4

Pharmacokinetic parameters of atropine and pralidoxime following the administration of two different auto-injector delivery systems in healthy volunteers

Parameters	Test: multichambered	Reference: MK-1
Atropine:		
C_{max} (ng/mL)	12.8 ± 3.2	11.2 ± 3.1
T_{max} (mins)	30.9 ± 30.2	20.9 ± 19.6
$T_{1/2}$ (mins)	146.3 ± 17.8	137.5 ± 18.2
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	3187 ± 486	2469 ± 435
Pralidoxime:		
C_{max} (µg/mL)	6.8 ± 2.8	5.9 ± 1.4
T_{max} (mins)	27.6 ± 14.6	24.4 ± 14.1
$T_{1/2}$ (mins)	125.2 ± 65.8	147.4 ± 76.0
$AUC_{(0\text{-inf})}$ (µg*hr/mL)	1006 ± 247	1084 ± 337

The 90% confidence interval for log transformed data indicated that the C_{max} for both atropine and pralidoxime was within the limits of bioequivalence criteria, but the $AUC_{(0\text{-inf})}$ for atropine failed to meet this criteria (Table 5). This is expected as the amount of atropine dose is 25% higher for the test as compared to the reference formulation.

TABLE 5

The confidence intervals for atropine and pralidoxime following the administration of two different auto-injector delivery systems in healthy volunteers

Analyte	**C_{max} (90% CI)**	**AUC (90% CI)**
Atropine	1.08 - 1.23	1.27 - 1.35
Pralidoxime	1.02 - 1.22	0.87 - 1.00

Gender effect:

For atropine, both the C_{max} and the $AUC_{(0\text{-inf})}$ were 15% higher in females than males for both the reference and the test products. The half-life of atropine was slightly longer in males than females (17 to 22 minutes) (Table 6) (Figures 10-11).

For the test pralidoxime, the $AUC_{(0\text{-inf})}$ was comparable between males and females but the C_{max} was 36% higher in females than males. The half-life of pralidoxime was approximately 45 minutes longer in males than females. For the reference pralidoxime, the $AUC_{(0\text{-inf})}$ and C_{max} were 9% and 28% higher in females than males with a comparable half-life between two genders (Table 6) (Figures 13-14).

Table 6

Effect of gender on the pharmacokinetics of atropine and pralidoxime following the administration of two different auto-injector delivery systems in healthy volunteers

Parameters	Test: multichambered		Reference: MK-1	
	Female	Male	Female	Male
Atropine:				
C_{max} (ng/mL)	13.7 ± 0.5	11.9 ± 0.5	12.1 ± 0.5	10.3 ± 0.5
T_{max} (mins)	38.7 ± 6.5	23.1 ± 6.5	26.3 ± 6.5	15.4 ± 6.5
$T_{1/2}$ (mins)	136 ± 3	157 ± 3	130 ± 3	147 ± 4
$AUC_{(0\text{-inf})}$ (ng*hr/mL)	3412 ± 58	2962 ± 58	2631 ± 58	2262 ± 64
Pralidoxime:				
C_{max} (µg/mL)	7.8 ± 0.5	5.8 ± 0.5	6.7 ± 0.5	5.2 ± 0.5
T_{max} (mins)	23.2 ± 2.7	31.9 ± 2.7	20.2 ± 2.7	28.6 ± 2.7
$T_{1/2}$ (mins)	106 ± 17	153 ± 19	149 ± 19	157 ± 17
$AUC_{(0\text{-inf})}$ (µg*hr/mL)	1021 ± 57	1001 ± 62	1151 ± 62	1054 ± 57

Conclusion

The multichambered device delivered about 30% more atropine than did the MK-1 device. The multichambered device and the MK-I device delivered equivalent amounts of pralidoxime. This accurately represents the 25% greater atropine content in the multichambered device. The females appear to have higher atropine concentrations than males when delivered from either of the devices.

Pharmacodynamics of Atropine

Heart rate was measured throughout this study to provide data for the description of the pharmacological effect of atropine and for exploration of the relationship between effect and atropine concentration. The elevation in heart rate of healthy volunteers was compared after a single intramuscular dose of atropine and pralidoxime chloride from the two different auto-injector delivery systems. The subjects received atropine (equivalent to 2.51 mg atropine sulfate) and 600 mg pralidoxime chloride (2-PAM) delivered by a multichambered (MA) auto-injector delivery system, and atropine (equivalent to 2 mg atropine sulfate) and 600 mg pralidoxime chloride, as delivered by the MK-I auto-injector delivery system.

Methods

Heart rate was measured three times before dosing and 19 times after each dose at 1, 3, 6, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, 240, 300, 360, 540 and 720 minutes. The subjects were placed in a supine position and remained supine for six hours after drug administration. The pharmacological effect of atropine was characterized by calculating the maximum change in heart rate (E_{max}), the time of maximum effect (T_{Emax}), the effect corresponding to the time of the maximum atropine concentration (E_{Cmax}), and the area(s) under the effect curve (AUEC).

Results

All twenty-four subjects completed the study. Based on the arithmetic means of the change in heart rate from baseline, heart rate was significantly increased from 10 to 720 minutes for the multichambered auto-injector (MA) device and from 3 to 720 minutes for the MK-I auto-injector device. The maximum effects were an increase of 50 beats/minute at 31 minutes for the MA device and an increase of 48 beats/minute at 36 minutes for the MK-I device (statistically not significant). The effect at the time of maximum atropine concentration was an increase of 32.9 beats/minute after the MA device and an increase of 28.8 beats/minutes after the MK-I device (statistically not significant) (Table 7) (Figure 15).

For males, the mean heart rate was significantly increased from 3 to 720 minutes for the MA device and from 6 to 720 minutes for the MK-I device. The maximum change was an increase of 44 beats/minute at 35 minutes for the MA device and 43 beats/minute at 46 minutes for the MK-I device. For males, the analysis of variance for the increase in heart rate at the time of the maximum atropine concentration revealed no statistically significant difference between the MA and MK-I devices.

For females, the mean heart rate was significantly increased from 6 to 360 minutes for the MA device and from 6 to 240 minutes for the MK-I device. The maximum change was an increase of 55 beats/minute at 27 minutes for the MA product and an increase of 52 beats/minute at 26 minutes for the MK-I product. The analysis of variance for the increase in heart rate at the time of the maximum atropine concentration revealed no statistically significant difference between the MA and MK-I devices.

The analysis of variance of the effect at the time of the maximum atropine concentration revealed a statistically significant (α=0.05) gender difference with female subjects exhibiting a larger increase in heart rate than male subjects. At the time of maximum atropine concentration after the MA device the increase in heart rate was 41 beats/minute for females and 25 beats/minute for males. For females, the maximum increase in heart rate occurred 27 minutes after the MA device and before the time of maximum atropine

concentration (39 minutes). For males, the maximum increase in heart rate occured 35 minutes after the MA device and after the time of maximum atropine concentration (23 minutes).

At the time of maximum atropine concentration after the MK-I device the increase in heart rate was 37 beats/minute for females and 20 beats/minute for males. For females, the maximum increase in heart rate occurred 26 minutes after the MK-I device and at the time of maximum atropine concentration (39 minutes). For males, the maximum increase in heart rate occured at 46 minutes after the MK-I device and after the time of maximum atropine concentration (15 minutes).

Table 7

Pharmacodynamic parameters of atropine following the administration of two different auto-injector delivery systems in healthy volunteers

Parameters	Test: multichambered	Reference: MK-1
$AUEC_{(0\text{-}720\ min)}$	11479 ± 6679	10159 ± 7853
E_{max} (beats/min)	49.79 ± 13.99	47.63 ± 15.90
TE_{max} (min)	30.83 ± 15.79	36.04 ± 26.66
EC_{max} (beats/min)	32 .9 ± 21.9	28.8 ± 22.6

Unit of AUEC is in beats.
E_{max} = maximum change in heart rate or maximum effect
T_{Emax} = time of maximum effect
E_{Cmax} = effect at C_{max} concentration.

Concentration-Effect Relationship:

The plot of mean change in heart rate vs mean atropine concentration at each time point revealed counter-clockwise hysteresis after both the MA and MK-I devices (Figure 16). There appears to be a steep increase in heart rate from 4 beats/minute to 40 beats/minute when atropine concentrations rise above 8 ng/mL. This is independent of the difference in

maximum concentration reached from the two devices (11 ng/ml, for the multichambered device and 9 ng/ml, for the Mark I device). As atropine concentrations drop heart rate does not decrease to predose rates as quickly. In the presence of hysteresis, however, no attempt was taken by the Sponsor to collapse the hysteresis by the use of effect compartment. The plot of change in heart rate vs atropine concentration at each time point for individual subjects also revealed counter-clockwise hysteresis.

The hysteresis may be an indication of a delayed effect but looking at the individual data (time of C_{max} and the maximum effect or maximum change in heart rate), the following observations were noted:

Thirteen subjects in whom the maximum effect occurred after C_{max}

Seven subjects in whom the maximum effect occurred before C_{max}

Three subjects in whom the maximum effect occurred around C_{max}

In one subjects the heart rate was lower than the baseline heart rate after C_{max}.

Therefore, it is difficult to conclude that the effect produced by atropine is delayed or immediate. Overall, administration of atropine has resulted in increase in heart rate which may not be of any clinical significance.

Conclusion

The atropine/pralidoxime injections resulted in increased heart rates when administered by either device. Though IDMA III contains 25% more atropine than MK-I, the maximum increase in heart rate by both devices was comparable.

Fig 9

Figure 2 .1: Mean Atropine Serum Levels (Semi-log Scale)
For All Subjects (N = 24)
#141-02-11280

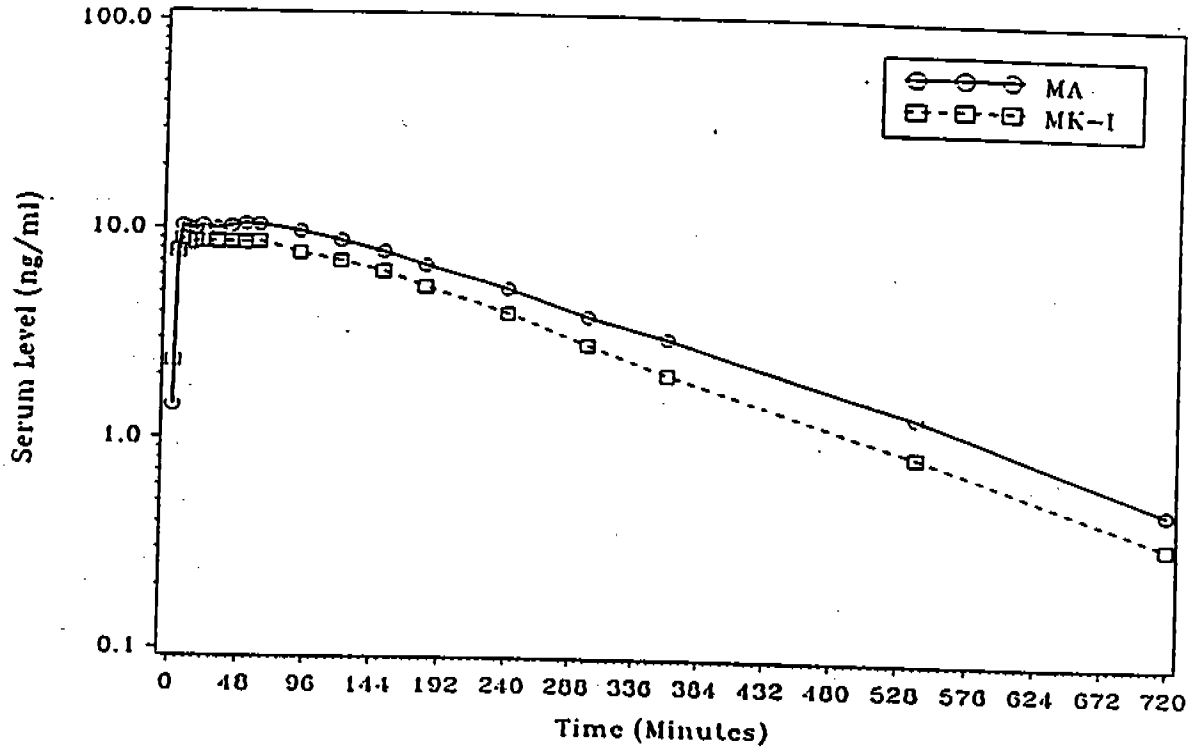

Figure 2 .2: Mean Atropine Serum Levels (Semi-log Scale)
For All Subjects (N = 24)
#141-02-11280

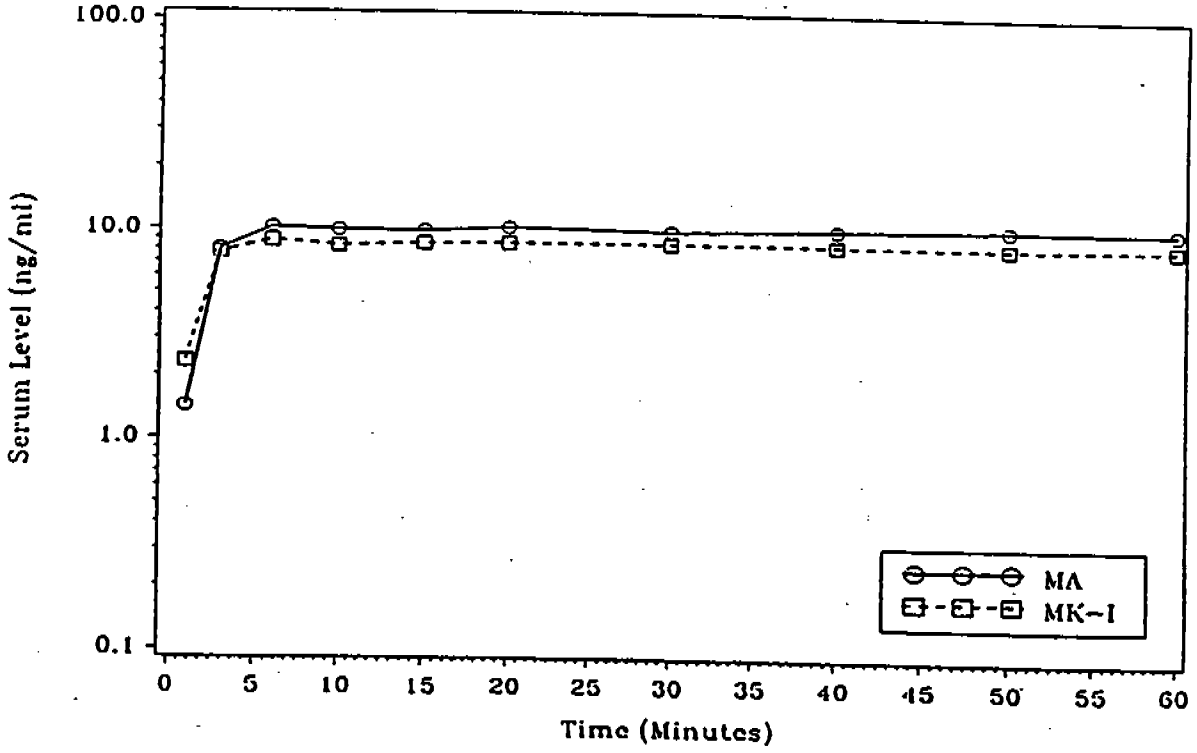

Figure 10

Figure 8 .1: Mean Atropine Serum Levels (Semi-log Scale)
For Delivery System = MA (N = 12)
#141-02-11280

Males and females

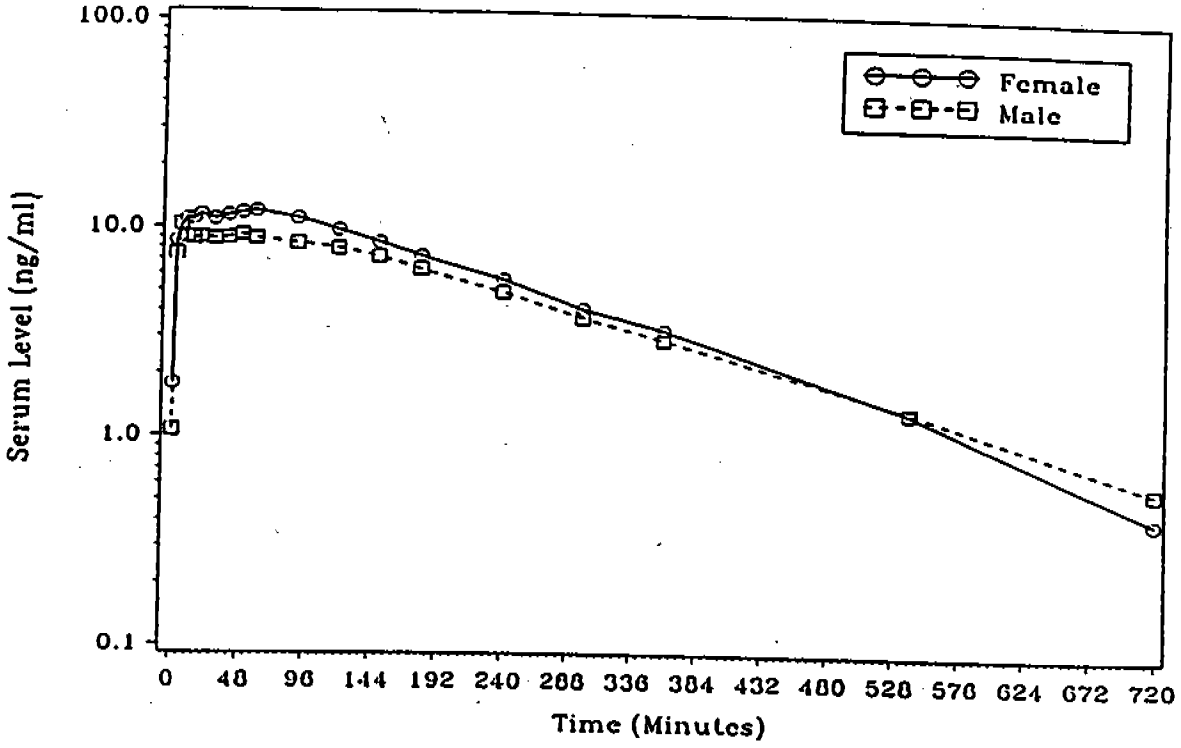

Figure 8 .2: Mean Atropine Serum Levels (Semi-log Scale)
For Delivery System = MA (N = 12)
#141-02-11280

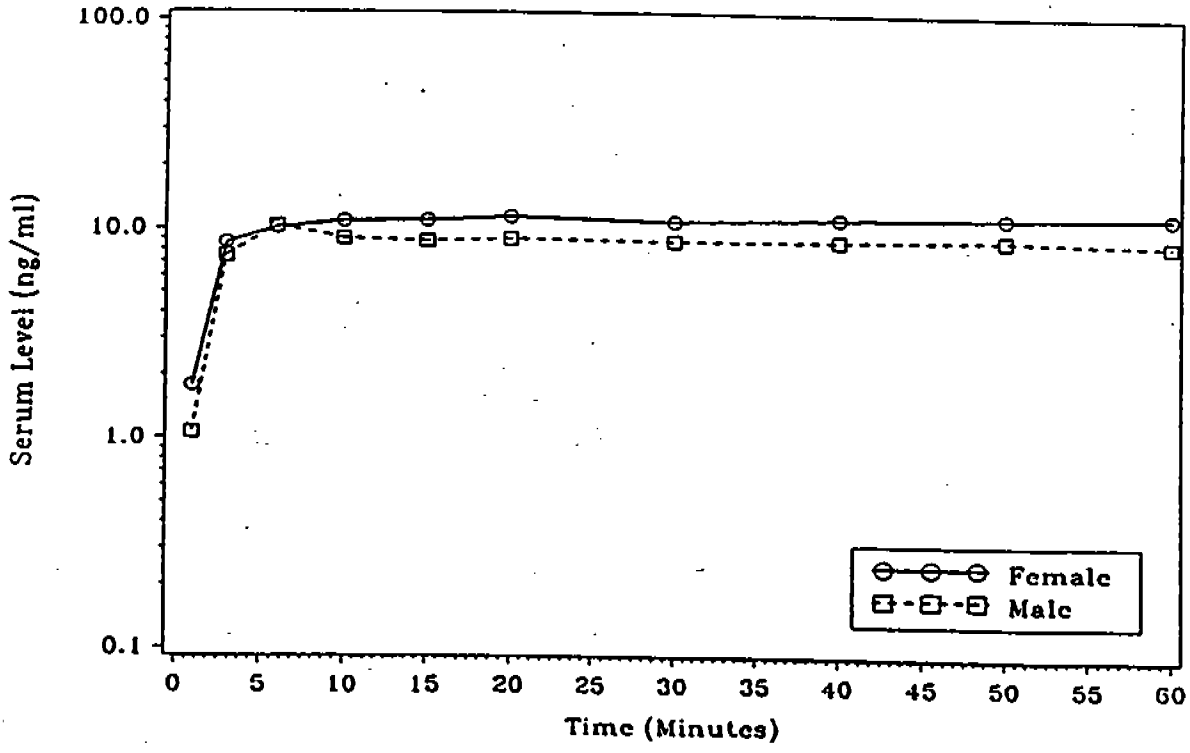

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Figure 11

Figure 9 .1: Mean Atropine Serum Levels
For Delivery System = MK-I (N = 12)
#141-02-11280

Males and females

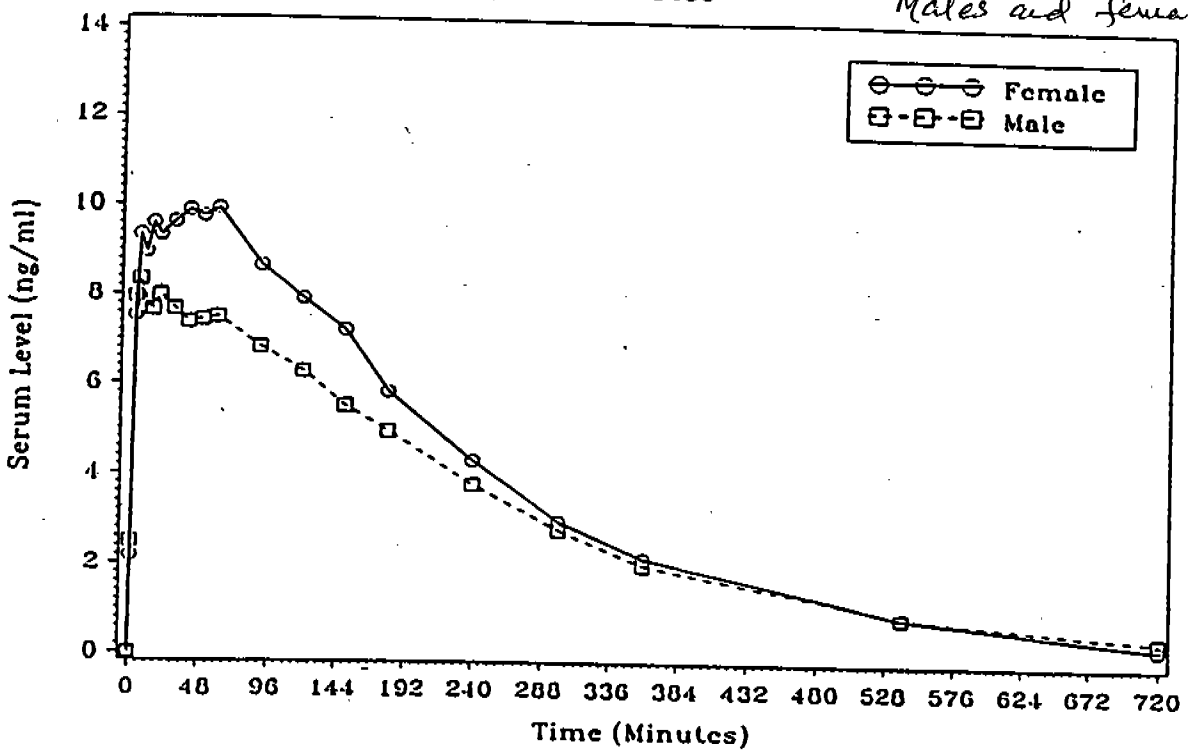

Figure 9 .2: Mean Atropine Serum Levels
For Delivery System = MK-I (N = 12)
#141-02-11280

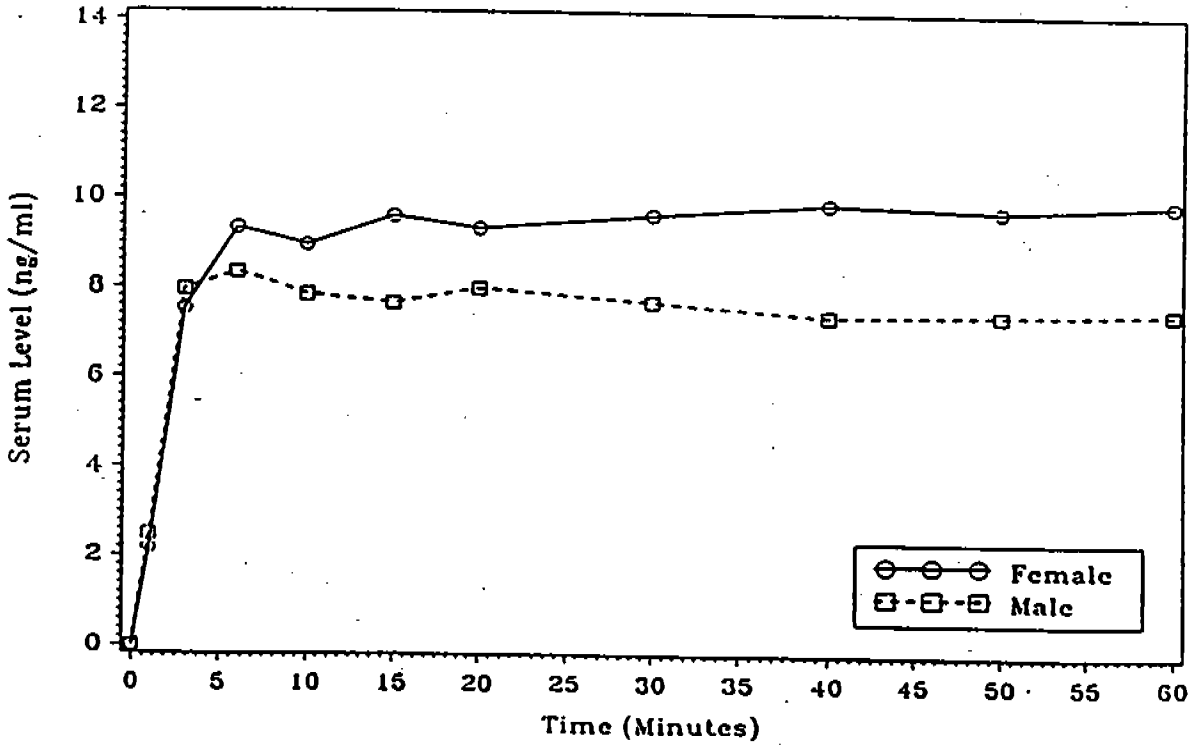

Figure 12

Figure 12 .1: Mean Pralidoxime Plasma Levels (Semi-log Scale)
For All Subjects (N = 24)
#141-02-11280

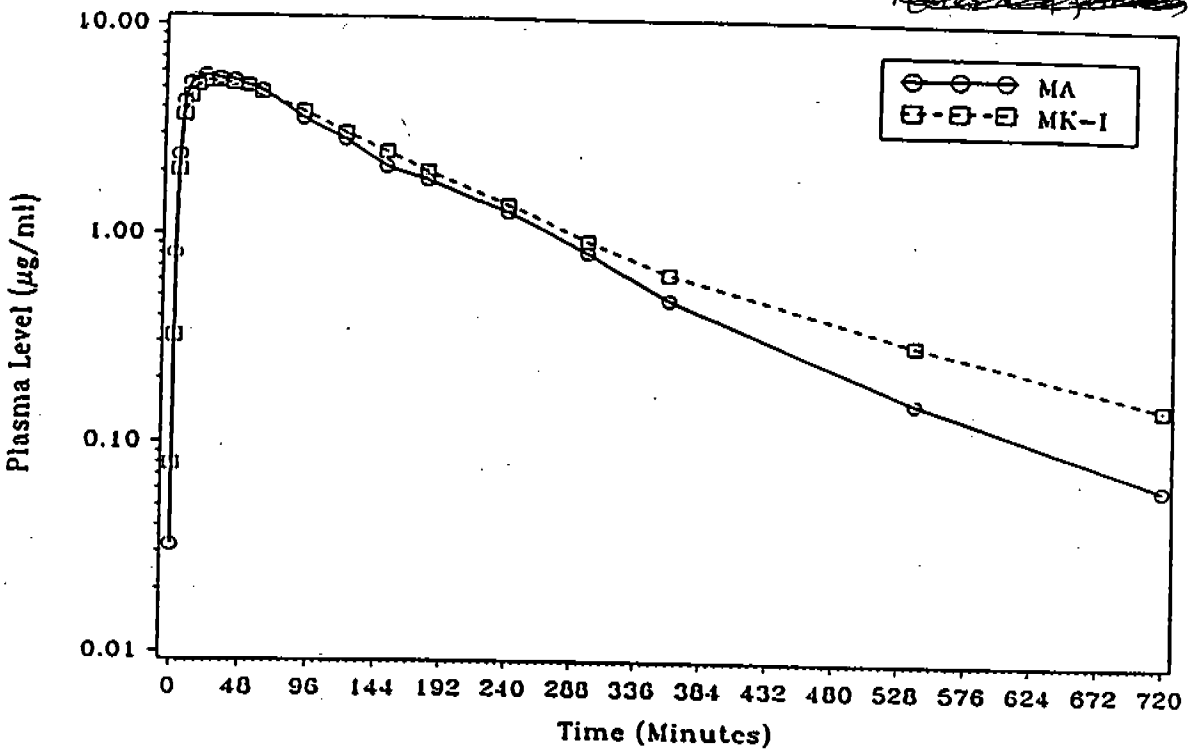

Figure 12 .2: Mean Pralidoxime Plasma Levels (Semi-log Scale)
For All Subjects (N = 24)
#141-02-11280

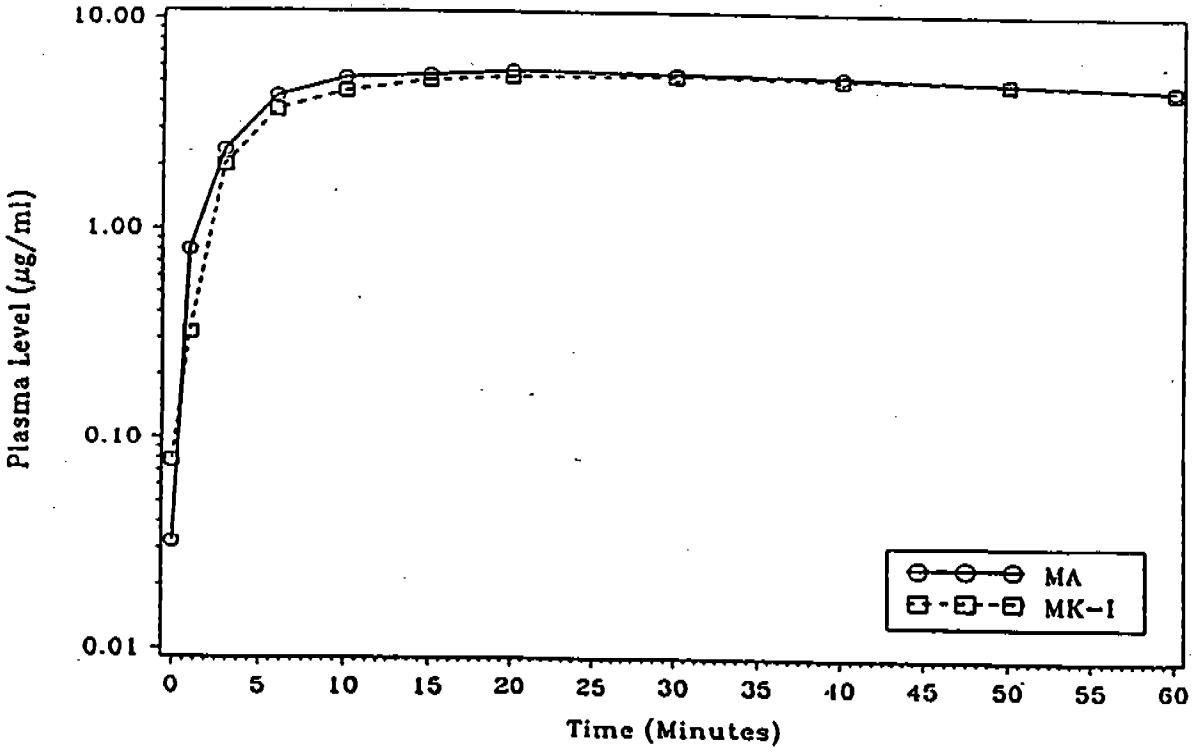

Figure 13

Figure 18 .1: Mean Pralidoxime Plasma Levels (Semi-log Scale)
For Delivery System = MA (N = 12)
#141-02-11280

Males and females

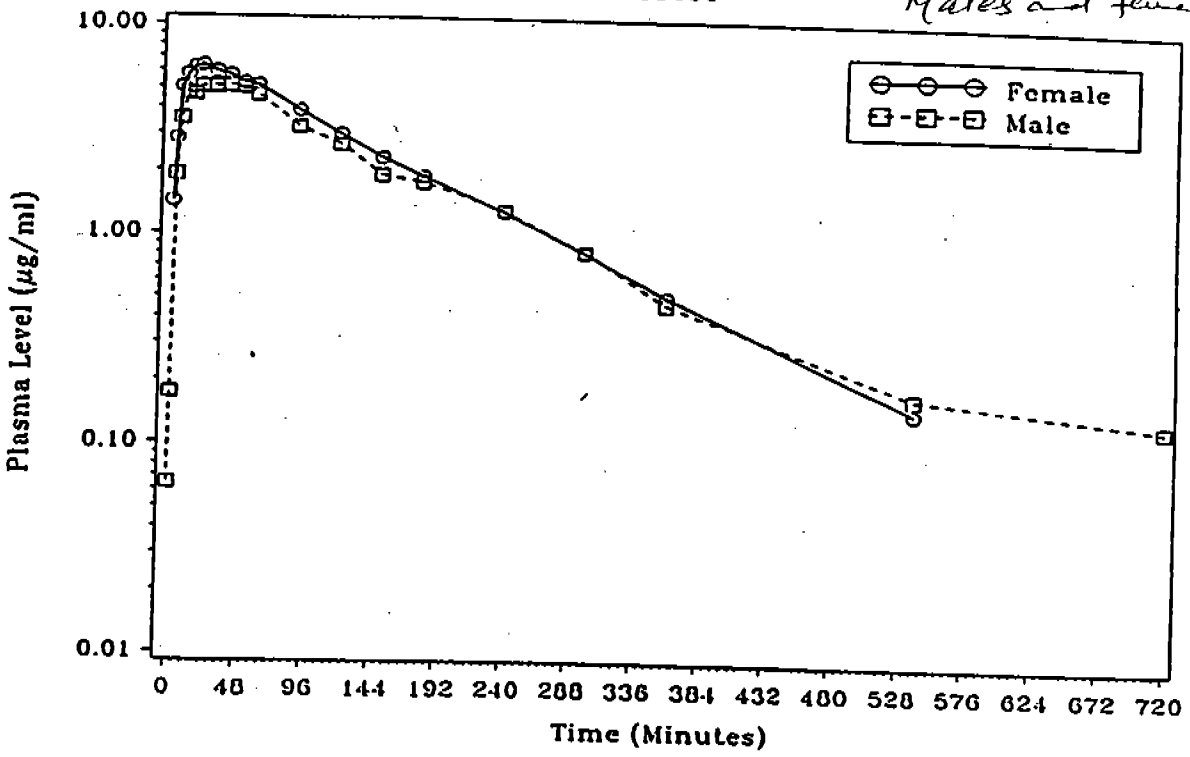

Figure 18 .2: Mean Pralidoxime Plasma Levels (Semi-log Scale)
For Delivery System = MA (N = 12)
#141-02-11280

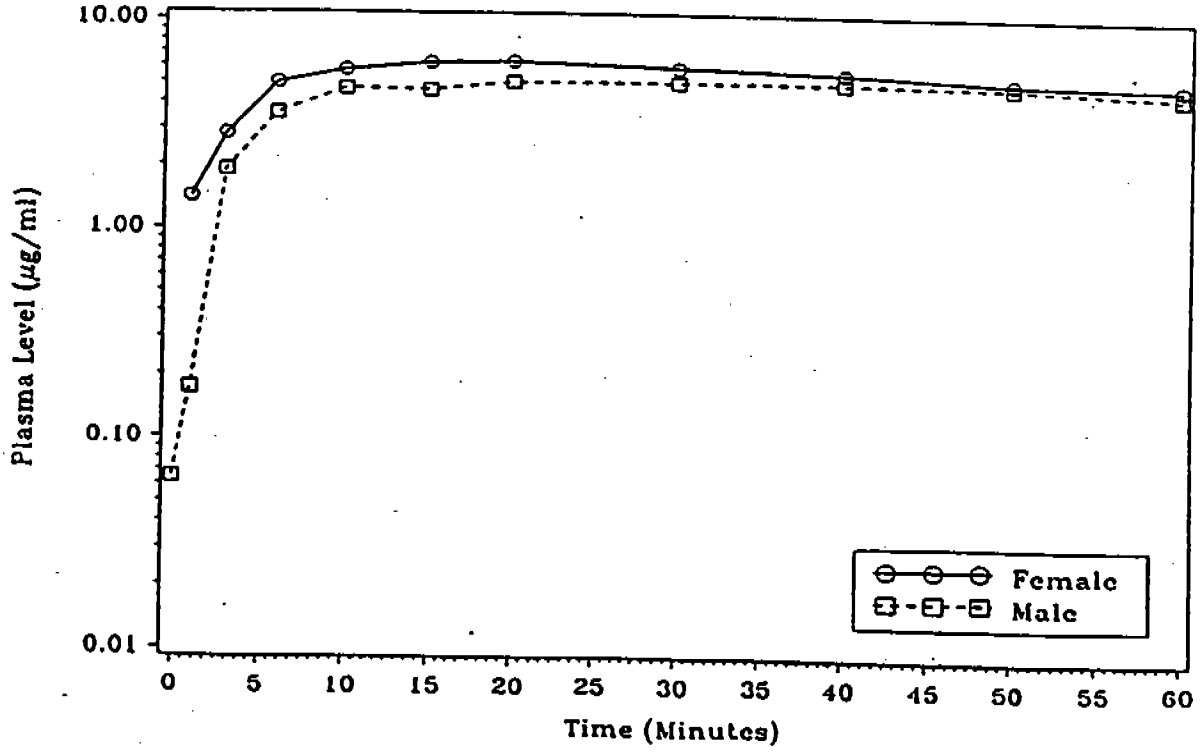

Figure 14

2 44

Figure 20 .1: Mean Pralidoxime Plasma Levels (Semi-log Scale)
For Delivery System = MK-I (N = 12)
#141-02-11280

males and females

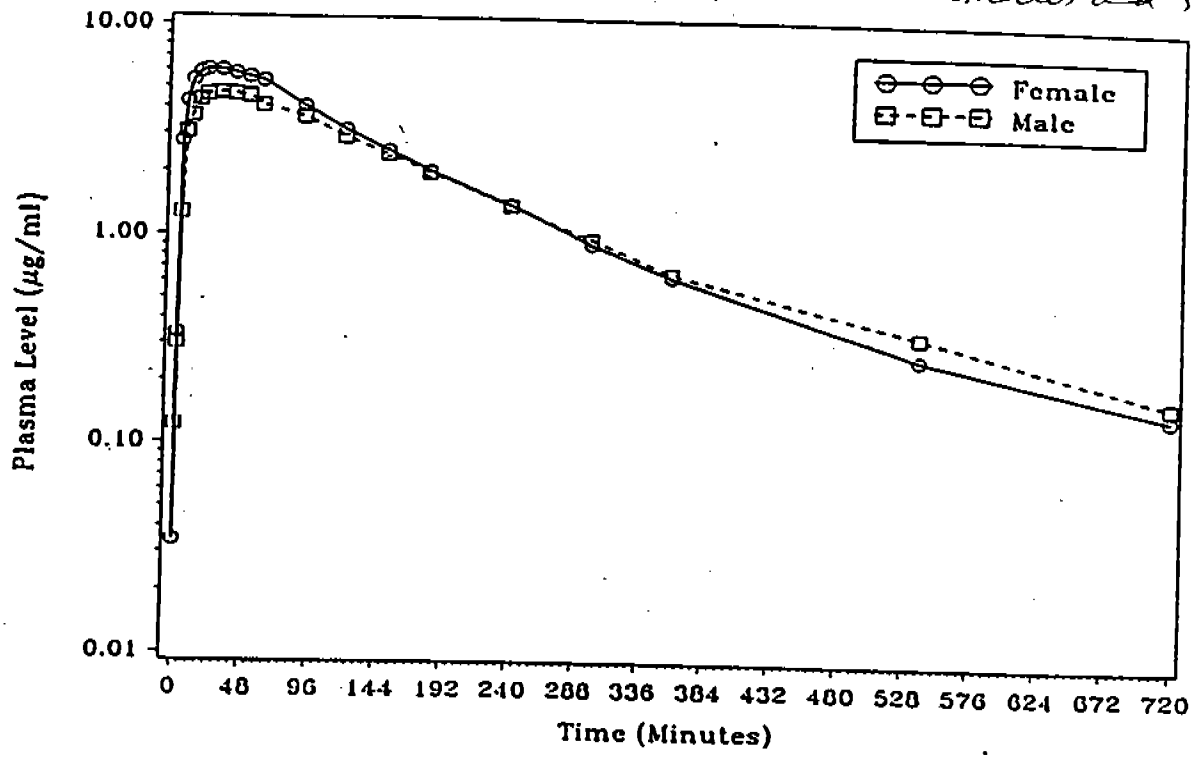

Figure 20 .2: Mean Pralidoxime Plasma Levels (Semi-log Scale)
For Delivery System = MK-I (N = 12)
#141-02-11280

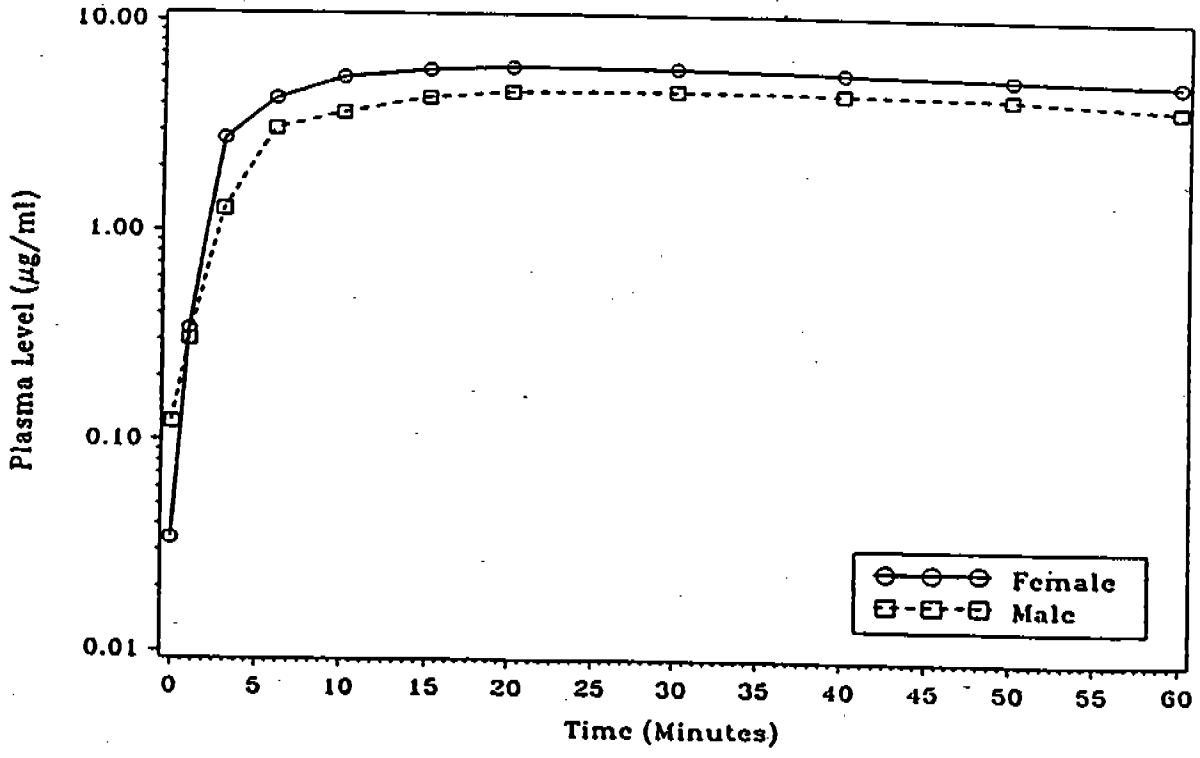

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Figure 15

Figure 21 .1: Mean Change in Heart Rate (beats/min)
N = 24

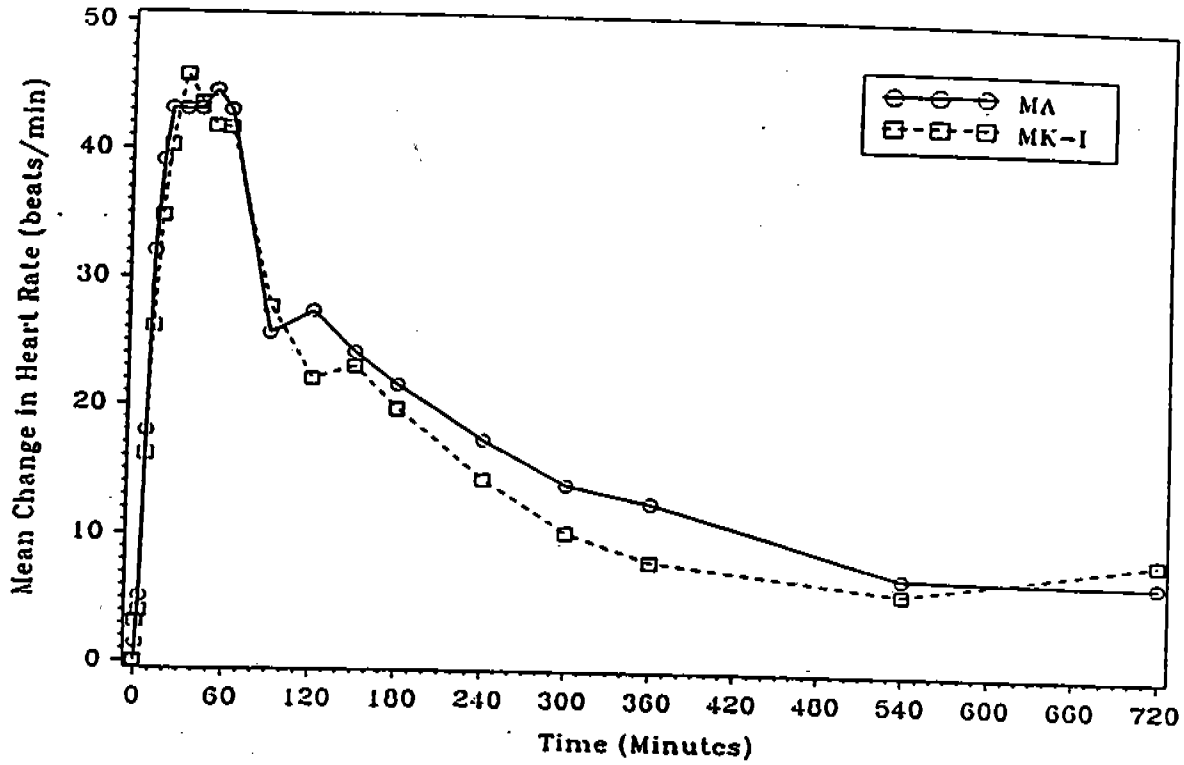


Figure 21 .2: Mean Change in Heart Rate (beats/min) Over 0-60 Minutes
N = 24

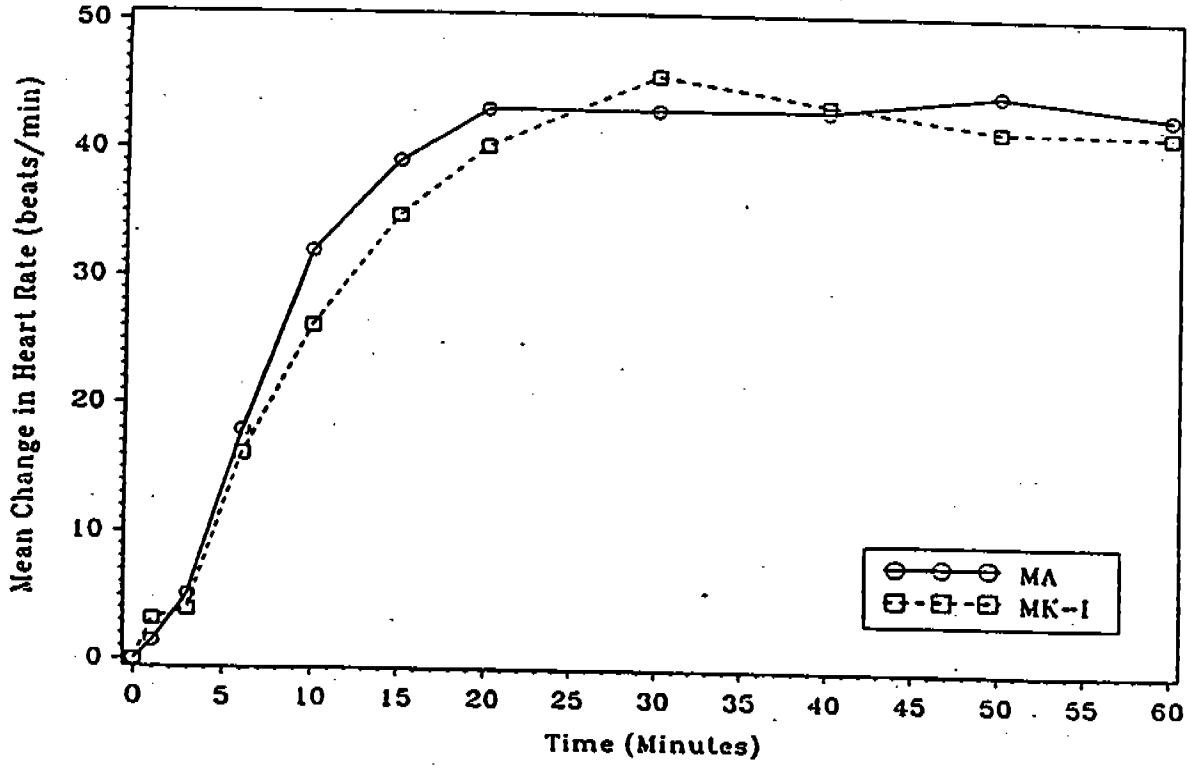


Figure 16

Figure 22 .1: Mean Change in Heart Rate (beats/min)
N = 24

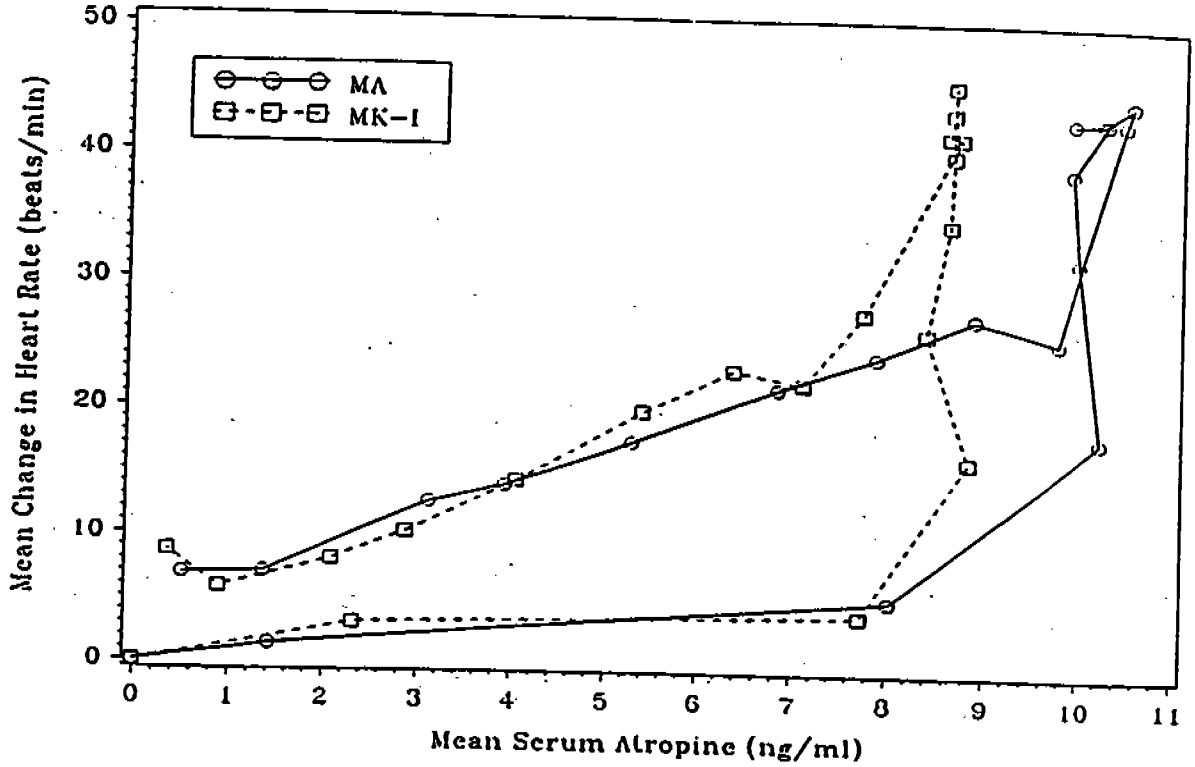
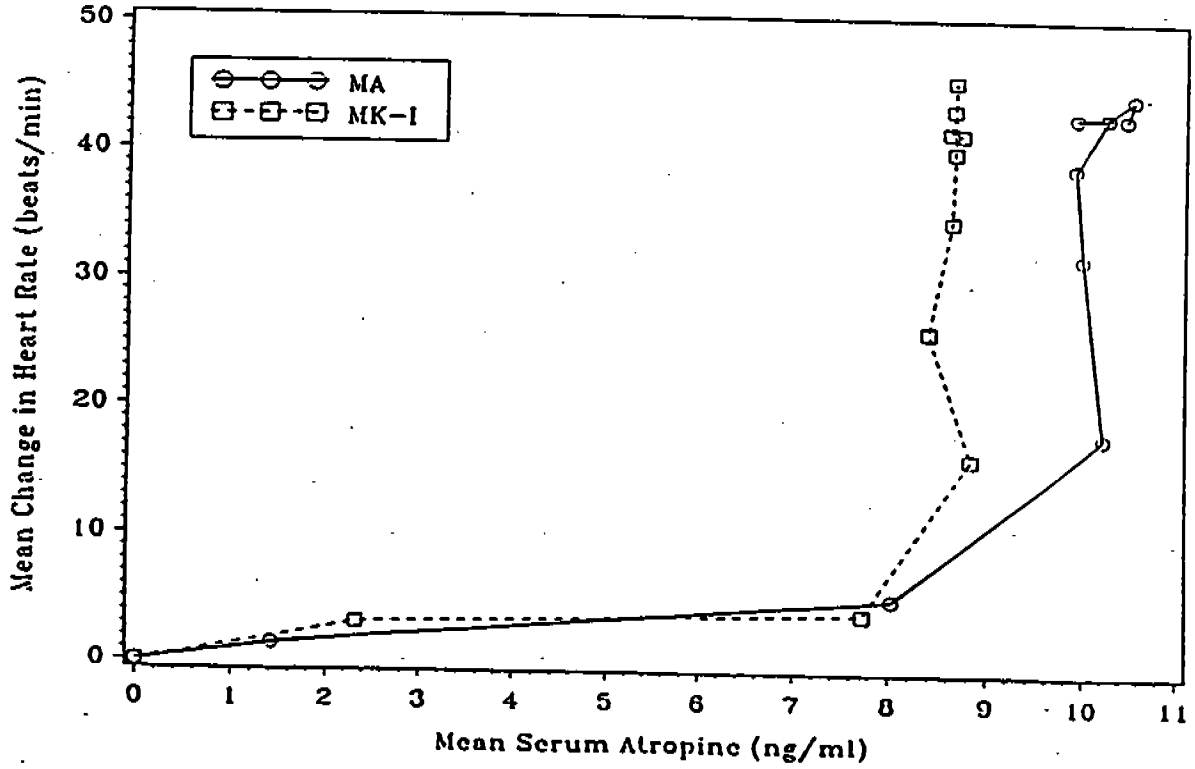


Figure 22 .2: Mean Change in Heart Rate (beats/min) Over 0-60 Minutes
N = 24



Labeling Comments

The Sponsor is requested to incorporate the following pharmacokinetic informations in their labeling under pharmacokinetics section (page #4):

Atropine: This information can be inserted after the first paragraph:

The C_{max}, T_{max}, and $T_{1/2}$ of atropine following 2.09 mg atropine sulfate given intramuscularly by multichambered delivery system was 13 ± 3 ng/mL, 31 ± 30 minutes, and 2.4 ± 0.3 hours, respectively. The protein binding of atropine is 14 to 22% in plasma. There are gender differences in the pharmacokinetics of atropine. The $AUC_{(0\text{-inf})}$ and C_{max} were 15% higher in females than males. The half-life of atropine is slightly shorter (approximately 20 minutes) in females than males.

Pralidoxime: This information can be inserted after the first paragraph:

The C_{max}, T_{max}, and $T_{1/2}$ of pralidoxime following 600 mg pralidoxime given intramuscularly by multichambered delivery system was 7 ± 3 ng/mL, 28 ± 15 minutes, and 2 ± 1 hours, respectively. The C_{max} of pralidoxime was about 36% higher in females than males but the AUC was comparable between the two genders.

Recommendation:

The pharmacokinetics and pharmacodynamics of atropine and pralidoxime are comparable between IDMA II and MK-I device. Though IDMA III contains 25% more atropine than MK-I which resulted in a 29% increase in the AUC of IDMA III than MK-I, the maximum increase in heart rate between the two devices are comparable. This submission from pharmacokinetics and biopharmaceutics point of view is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Iftekhar Mahmood, Ph.D. /S/ 5/2/2000

RD/FT initialed by Raman Baweja, Ph.D. /S/ 5/3/2000

Division of Pharmaceutical Evaluation I

Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-175, HFD-120, HFD-860 (Mahmood, Baweja, Mehta), HFD-340 (Viswanathan), CDR-Biopharm (for Drug-Files) and FOI (HFD-19) files.

DRAFT

REVIEW AND EVALUATION OF CLINICAL DATA

NDA	21-175
Sponsor:	Department of the Army, Office of the Surgeon General
Drug:	"ATNAA" Antidote Treatment - Nerve Agent, Auto-Injector (atropine/pralidoxime chloride auto-injector)
Proposed Indication:	Treatment of poisoning by nerve agents having anticholinesterase activity
Material Submitted:	Volumes 1-27 (NDA 21-175)
Correspondence Date:	12/06/99
Reviewer:	Joel Freiman, MD
Date Review Completed:	05/30/00

Background

Administrative History

The U.S. Army Office of the Surgeon General has submitted a New Drug Application (NDA 21-175) for the Antidote Treatment - Nerve Agent, Auto-Injector (ATNAA). The ATNAA will deliver atropine (2.1 mg in 0.7 ml) and pralidoxime chloride (600 mg in 2 ml) from a single needle multi-chambered auto-injector (MA). Currently, these antidotes are available as two separate auto-injectors (AtroPen®, NDA 17-106) and ComboPen®, NDA 18-986) which individually deliver 1.67 atropine and 600 mg pralidoxime, respectively. The ATNAA was developed to facilitate the rapid delivery of these antidotes in a combat situation by military personnel.

Indication

The ATNAA delivers injectable solutions of atropine and pralidoxime chloride for intramuscular use in the treatment of poisoning by nerve agents having anticholinesterase activity.

Proposed Directions for Use

The **Dosage and Administration** section of the proposed label reads as follows:

> For optimal reactivation of organophosphorous-inhibited cholinestrerase, the ATNNA should be administered as soon as possible after [redacted]
>
> The ATNAA should be self- or buddy-administered by military personnel after donning protective mask and hood at the first sign of a chemical attack, and only if some or all of the following mild symptoms of nerve agent exposure are present:

- Bradycardia

2. If you encounter a service member suffering from severe signs of nerve agent poisoning, render the following aid:

   a) Mask the casualty, if necessary. Do not fasten the hood.

   b) Administer in rapid succession, ——— ATNAAs into the casualty's lateral thigh muscle or buttocks. **Note:** Use the casualty's own ATNAAs when providing aid. Do not use your own injectors on a casualty. If you do, you may not have any antidote available when needed for self-aid.

Human Pharmacokinetic Considerations

In the course of developing an MA several designs were evaluated. The Improved Dispersion Multi-Chambered Auto-Injector III (IDMA-III) represents the final design and the one which is the subject of this application. The IDMA-III sequentially delivers 2.1 mg of atropine in a 0.7 ml solution and 600 mg pralidoxime in a 2 ml solution. Two features of the IDMA-III should be noted, the atropine dose was increased by 25 percent and the needle size decreased to 23 gauge (relative to the Mark-I NAAK). These modifications were made in order to achieve similar atropine and pralidoxime concentrations to those from sequential administration of the Mark-I NAAK auto-injectors.

Summary of Study (141-02-1180) Pertinent to Bioavailability

Study 141-02-11280 examined the bioavailability of atropine and pralidoxime administered by the IDMA-III compared to the MK-I NAAK. This was a two-treatment crossover study enrolling 24 subjects (12 males and 12 females). All subjects completed the study. A complete and detailed review of this comparative bioavailability study was conducted by Dr. Iftekhar Mahmood, OCPB and is briefly summarized below.

Results

Atropine:

The C_{max} and $T_{1/2}$ between the IDMA-III and MK-I was comparable (Table 1). The T_{max} of the IDMA-III occurred 10 minutes later than the MK-I. The $AUC_{(0\text{-infinity})}$ of the IDMA-III was 29% higher than that of the MK-I.

Pralidoxime:

The T_{max}, $T_{1/2}$, and $AUC_{(0\text{-infinity})}$ between the IDMA-III and MK-I were comparable (Table 1). The C_{max} of the IDMA-III was 15% higher than that of the MK-I.

Table 1. Bioavailability of Atropine and Pralidoxime Administered by Two Different Auto-Injector Delivery Systems in 24 Healthy Volunteers

Parameters **Atropine**	**IDMA-III**	**MK-I NAAK**
C_{max} (ng/mL)	12.8 ± 3.2	11.2 ± 3.1
T_{max} (mins)	30.9 ± 30.2	20.9 ± 19.6
$T_{1/2}$ (mins)	146.3 ± 17.8	137.5 ± 18.2
AUC (0-inf)	3187 ± 486	2469 ± 435
Pralidoxime		
C_{max} (ng/mL)	6.8 ± 2.8	5.9 ± 1.4
T_{max} (mins)	27.6 ± 14.6	24.4 ± 14.1
$T_{1/2}$ (mins)	125.2 ± 65.8	147.4 ± 76.0
AUC (0-inf)	1006 ± 247	1084 ± 337

Adverse Events

Twenty-three of the 24 subjects experienced an adverse event. Adverse events experienced by subjects are summarized in the sponsor's table below. The sponsor reports that all events were rated as mild with the exception of one moderate episode of tachycardia following MK-I administration and one episode of dry mouth following IDMA-III administration.

Table 2. Incidence of Adverse Events Following IDMA-III and MK-I Administration (24 Subjects)

Adverse Event	**IDMA-III**	**MK-I NAAK**
Increased Heart Rate	23	20
Dry Mouth	11	13
Blurred Vision	3	4
Spots in Visual Field	2	1
Restlessness	1	1
Headache	0	1
Difficulty Voiding	1	2

Conclusion

The C_{max} for atropine and pralidoxime met the criteria for bioequivalence (90% CI of log transformed data 0.80 –1.25). The $AUC_{(0\text{-infinity})}$ for pralidoxime met the criteria for bioequivalence, however the $AUC_{(0\text{-infinity})}$ for atropine exceeded the bioequivalence criteria (90% CI of log transformed data 1.27 – 1.35).

The atropine T_{max} of the IDMA-III occurs later than that of the MK-I, however at no time is the actual concentration of atropine lower with the IDMA-III than with the MK-I.

The severity and frequency of adverse events were similar following IDMA-III and MK-I administration.

Comments

The 25% increase in atropine dosage of the IDMA-III compared to the MK-I resulted in a correspondingly higher $AUC_{(0\text{-infinity})}$ (29% higher). The increased level of atropine delivered by the IDMA-III was not associated with greater toxicity in the above bioavailability study.

In general increased levels of atropine produce a greater degree of protection against organophosphorus nerve agents. The total amount of atropine required in an individual patient will vary by the toxicity and exposure to the nerve agent. A standard pharmacology text[1] recommends that "Atropine should be given in doses sufficient to cross the blood brain barrier. Following an initial injection of 2 to 4 mg, given intravenously if possible, otherwise intramuscularly, 2 mg should be given every 5 to 10 minutes until muscarinic symptoms disappear, if they reappear, or until signs of atropine toxicity appear. More than 200 mg may be required on the first day. A mild degree of atropine block should be maintained for up to 48 hours." The dose of atropine delivered by the IDMA-III is consistent with these guidelines.

Recommendation

Based on the review of the data submitted the Antidote Treatment - Nerve Agent Auto-Injector (NDA 21-175) appears to be reasonably safe when used as indicated. In the opinion of this reviewer NDA 21-175 is approvable from a clinical standpoint.

/S/

Joel Freiman, MD
Division of Neuropharmacolical Drug Products

cc: NDA 21-175
HFD-120 File

[1] Goodman and Gillman, The *Pharmacologic Basis of Therapeutics, ninth edition, p. 170.*

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA AMENDMENT

Brand Name:	**ATNAA**
Generic Name:	**Atropine & Pralidoxine**
Sponsor:	**U.S. Army**
Indication:	**Nerve Agent Antidote**
NDA Number:	**21-175**
Original Receipt Date:	**8/15/01**
Review Author:	**Kevin A. Prohaska D.O.**
Review Completed:	**9/17/01**

Table of Contents

1. Review Sources

1.1 Materials from NDA Supplement

- NDA Amendment submission dated 8/15/01.

1.2 Related Reviews, Consults

The following individuals are participating in the review of this NDA supplement:

Discipline	Reviewer
Chemistry	Janusz Rzeszotarski Ph.D.
Pharmacology	Barry Rosloff Ph.D.
Biopharmacology	Iftekha Mahmood, Ph.D.
OPDRA	Naming Subcommittee
Devices	Von Nakayama

1.3 Other Reviews

Historical information regarding this NDA was obtained from Robbin Nighswander R.Ph., the Division File and DFS. Other reviews and letters that have been helpful in this review include the following:

Reviews/Letters	Author	Date
Action Memo	Russell Katz M.D.	6/5/2000
Approvable letter	Russell Katz M.D.	6/6/2000
Pharmacology Review	Barry Rosloff, Ph.D.	5/17/2000
CDRH Reviews	Von Nakyama	2/16/2000 4/26/2000
Project manager labeling review	Robbin Nighswander	5/18/2000.
Microbiology Review	David Hussong, Ph.D.	5/3/2000
Biopharmacology Review	Iftekhar Mahmood, Ph.D.	5/2/2000
Chemistry Reviews	J. Rzeszotarski, Ph.D.	4/10/2000 8/15/2001
Medical Review	Joel Freiman, MD	5/30/2000
OPDRA Review	Hye-Joo Kim, Ph.D.	8/20/2001

2. Background

On December 1, 1999, the Department of the Army submitted NDA 21-175, for the use of a multichamber autoinjector (Antidote Treatment-Nerve Agent), designed to deliver atropine first and then pralidoxime in a single injection to be delivered intramuscularly, as a treatment for organophosphate nerve agent poisoning. The original application was reviewed and an "approvable" letter, dated June 6, 2000 was sent to the sponsor. This submission contains the complete response to comments contained in that letter. This review will evaluate the sponsor's reply to the specific labeling questions outlined in the approvable letter dated June 6, 2000. The sponsor submits their response to labeling questions in section L1 through L4. The respective review disciplines will review responses addressed to CDRH, chemistry and pharmacology.

This NDA is for a change in the delivery system device and does not reflect a change in the active ingredients. There are no clinical studies involved with this NDA supplement. The two active agents, atropine and pralidoxine, are approved products and are presently supplied to soldiers as separate single-drug autoinjectors. Atropine is supplied as AtroPen® (NDA 17-106) and pralidoxime chloride is supplied as Pralidoxime Chloride Injection (Auto-Injector) (NDA 18-986). The new autoinjector proposed in this NDA is designed to deliver both active products in a single injection using an autoinjector with two separate prefilled chambers. The Army contends that the change in delivery system will facilitate ease of use under stressful battlefield conditions.

The previous NDA review team had concluded that the sponsor has effectively demonstrated the C_{MAX}'s for both atropine and pralidoxime when given by the proposed new dual-chamber autoinjector and by the two individual autoinjectors meet the standard criteria for equivalence. They also agreed that the AUC for pralidoxime meet the equivalence standard however the AUC for atropine was slightly outside the accepted confidence interval. This difference was attributed to the fact that the manufacturer "overfilled" the atropine chamber with 2.51 mg of atropine whereas the comparator single chamber atropine autoinjector contains 2.0 mg of atropine. The difference in dose was deemed necessary by the Army to ensure an equivalent C_{MAX}. The review team agreed that this slight difference had no clinical significance. Finally the T_{MAX} for atropine when using the dual chamber autoinjector is later than the T_{MAX} resulting form the single chamber autoinjector (31 minutes vs. 21 minutes). It was Dr. Freiman's opinion that this had little clinical relevance since the concentration of atropine using the dual chamber autoinjector was at no time lower than the concentration seen when using the single chamber autoinjector.

2.1 Indication

ATNAA containing atropine 2.1 mg and pralidoxime chloride 600 mg is indicated for treatment of poisoning by susceptible organophosphorous nerve agents having anticholinergic activity.

2.2 Administrative History

- On December 6, 1999 the US Army, Office of the Surgeon General, submitted a New Drug Application (NDA 21-175) for ATNAA.
- The original NDA submission was reviewed by Dr. Joel Frieman (medical reviewer, review dated 6/5/00), Dr. Mahmood (biopharmaceutical reviewer, review dated 5/3/00), and Dr. Nakayam (devices reviewer, review dated 2/16/00 and 4/26/00). Dr. Mahmood did a review of the DSI conclusions in his review dated 5/22/00.
- On June 6, 2000 an "approvable" letter was sent to the sponsor.
- On August 15, 2001 the sponsor responded to the June 6, 2000 approvable letter.

3. Response to Labeling Questions

The June 6, 2000 "approvable letter" contained four comments pertaining to labeling. In this section I will review the sponsor's response to the four comments

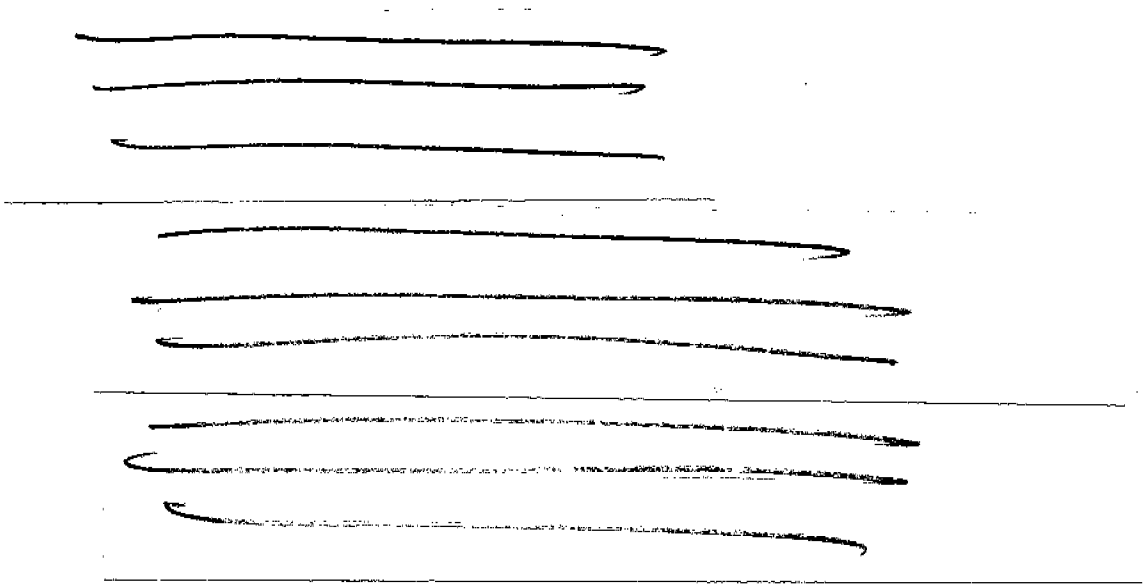
3.1 RX Only

The sponsor had originally requested that the "Rx only" statement be removed form their label since they thought it might be confusing to soldiers. The sponsor was informed that the Agency was not able to grant a waiver for the "Rx only" statement required under §503 (b)(4) of the Act. However they were informed that this statement was a minimum requirement and as such could be modified with clauses such as "Rx only, for self-administration by soldiers". The sponsor has decided to include the "Rx only" statement at the end of their package insert without modification.
Discussion: This change is acceptable.

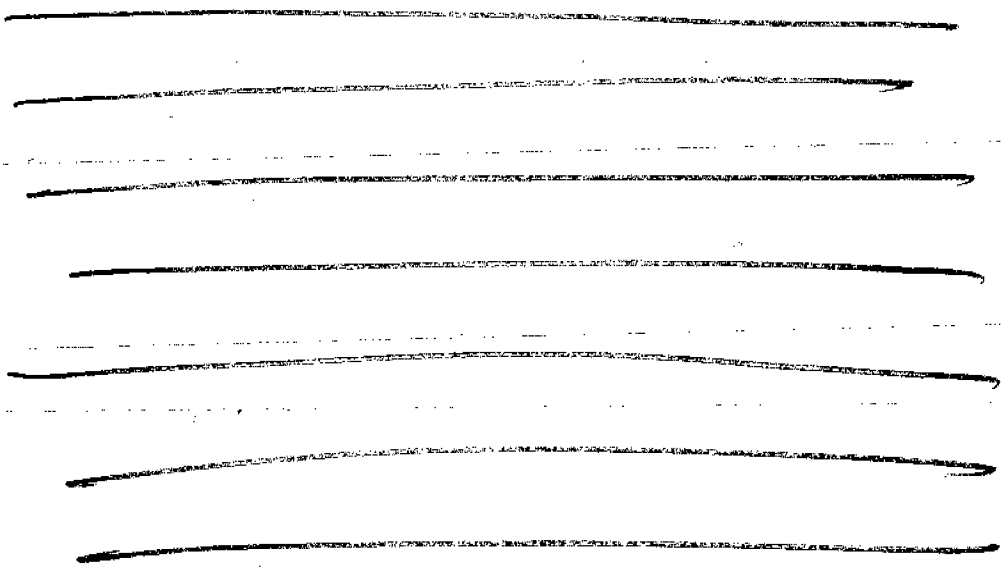
3.2 Carton/Container Labels

The sponsor was requested to supply a detailed description of all components of packaging, including the outer shipping containers and copies of pertinent labels to be used with this packaging. In response to this request the sponsor provides the following statement and generic labels:

- *"Labeled auto-injectors are to be packaged in a semi-transparent amber bag. Fifteen packaged auto-injectors will be placed into a cardboard interior shipper. Ten interior shippers will then be packed into a cardboard exterior shipper. Both interior and exterior shipper labels will be prepared at Meridian Medical Technologies. Examples of these shipper labels immediately follow."*



8 page(s) of revised draft labeling has been redacted from this portion of the review.



6. Recommendations

The sponsor should address the comments listed above.

Kevin Prohaska, D.O.
Medical Reviewer

J. Feeney, M.D. _____

cc: R. Katz M.D.
HFD-120
NDA 21-175 (N-AZ)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kevin Prohaska
10/3/01 02:01:00 PM
MEDICAL OFFICER

John Feeney
10/3/01 04:50:21 PM
MEDICAL OFFICER
concur