

## ĒTHRANE (enflurane, USP)

### Liquid For Inhalation

#### R<sub>x</sub> only

### DESCRIPTION

ĒTHRANE (enflurane, USP), a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether (CHF2OCF2CHFC1). The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (in mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P_{\text{vap}} = A + B/T$$
$$A = 7.967$$
$$B = -1678.4$$
$$T = ^\circ\text{C} + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20°C is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C.

Enflurane is a clear, colorless, stable liquid whose purity exceeds 99.9% (area percent by gas chromatography). No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary even in the presence of ultraviolet light. Enflurane is stable to strong base, does not decompose in contact with soda lime (at normal operating temperatures), and does not react with aluminum, tin, brass, iron or copper. The partition coefficients of enflurane at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

### CLINICAL PHARMACOLOGY

ĒTHRANE (enflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is 1.68% in pure oxygen, 0.57 in 70% nitrous oxide, 30% oxygen, and 1.17 in 30% nitrous oxide, 70% oxygen.

Induction of and recovery from anesthesia with enflurane are rapid. Enflurane has a mild, sweet odor. Enflurane may provide a mild stimulus to salivation or tracheobronchial secretions. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia can be changed rapidly by changing the inspired enflurane concentration. Enflurane reduces ventilation as depth of anesthesia increases. High PaCO<sub>2</sub> levels can be obtained at deeper levels of anesthesia if ventilation is not supported. Enflurane provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce

corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine-containing solutions during enflurane anesthesia. Enflurane anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with enflurane and injected with epinephrine-containing solutions to achieve hemostasis in a highly vascular area (transsphenoidal surgery), up to 2 micrograms per kilogram (2 µg/kg) of epinephrine may be injected subcutaneously over a 10 minute period in patients judged to have ordinary tolerance to epinephrine administration. This would represent up to 14 mL of 1:100,000 epinephrine-containing solution (10 µg/mL), or the equivalent quantity, in a 70 kilogram patient. This may be repeated up to 3 times per hour (total 42 mL per hour). The concomitant administration of lidocaine enhances the safety of the use of epinephrine during enflurane anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operations at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with enflurane. **THE NON-DEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED.** In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1.0 to 1.5 mg of pancuronium will produce a 90% or greater depression of twitch height. Neostigmine does not reverse the direct effect of enflurane.

Enflurane 0.25 to 1.0% (average 0.5%) provides analgesia equal to that produced by 30 to 60% (average 40%) nitrous oxide for vaginal delivery. With either agent, patients remain awake, cooperative and oriented. Maternal blood losses are comparable. These clinical approaches produce normal Apgar scores. Serial neurobehavioral testing of the newborn during the first 24 hours of life reveals that neither enflurane nor nitrous oxide analgesia is associated with obvious neurobehavioral alterations. Neither enflurane nor nitrous oxide when used for obstetrical analgesia alters BUN, creatinine, uric acid or osmolality. The only difference in the use of these two agents for obstetrical analgesia appears to be higher inspired oxygen concentration that may be used with enflurane.

Analgetic doses of enflurane, up to approximately 1.0%, do not significantly depress the rate or force of uterine contraction during labor and delivery. A slowing of the rate of uterine contraction and a diminution of the force of uterine contraction is noted between the administration of 1.0 to 2.0% delivered enflurane; concentrations somewhere between 2.0 and 3.0% delivered enflurane may abolish uterine contractions. Enflurane displaces the myometrial response curve to oxytocin so that at lower concentrations of enflurane oxytocin will restore uterine contractions; however, as the

dose of enflurane progresses (somewhere between 1.5 and 3.0% delivered enflurane) the response to oxytocin is diminished and then abolished. Uterine bleeding may be increased when enflurane is used in higher concentrations for vaginal delivery or to facilitate delivery by Cesarean section; however, this has not been demonstrated within the recommended dosage range (see **DOSAGE AND ADMINISTRATION** section). Mean estimated blood loss in patients anesthetized for therapeutic termination of pregnancy with 1.0% enflurane in 70% nitrous oxide with oxygen is approximately twice that noted following therapeutic termination of pregnancy performed with the use of a local anesthetic technique (40 mL versus 20 mL).

## Pharmacokinetics

Biotransformation of enflurane in man results in low peak levels of serum fluoride averaging 15  $\mu\text{mol/L}$ . These levels are well below the 50  $\mu\text{mol/L}$  threshold level which can produce minimal renal damage in normal subjects. However, patients chronically ingesting isoniazid or other hydrazine-containing compounds may metabolize greater amounts of enflurane. Although no significant renal dysfunction has been found thus far in such patients, peak serum fluoride levels can exceed 50  $\mu\text{mol/L}$ , particularly when anesthesia goes beyond 2 MAC hours. Depression of lymphocyte transformation does not follow prolonged enflurane anesthesia in man in the absence of surgery. Thus enflurane does not depress this aspect of the immune response.

## INDICATIONS AND USAGE

ĒTHRANE (enflurane, USP) may be used for induction and maintenance of general anesthesia. Enflurane may be used to provide analgesia for vaginal delivery. Low concentrations of enflurane (see **DOSAGE AND ADMINISTRATION**) may also be used to supplement other general anesthetic agents during delivery by Cesarean section. Higher concentrations of enflurane may produce uterine relaxation and an increase in uterine bleeding.

## CONTRAINDICATIONS

Seizure disorders (see **WARNINGS**).

Known sensitivity to ĒTHRANE (enflurane, USP) or other halogenated anesthetics.

Known or suspected genetic susceptibility to malignant hyperthermia.

## WARNINGS

### Perioperative Hyperkalemia

Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne

muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatinine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

## **Malignant Hyperthermia**

In susceptible individuals, enflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. The syndrome of malignant hyperthermia secondary to enflurane appears to be rare; by March 1980, 35 cases had been reported in North America for an approximate incidence of 1:725,000 enflurane anesthetics.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of CO<sub>2</sub> absorption system (hot cannister). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangement. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

Increasing depth of anesthesia with ETHRANE (enflurane, USP) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or “jerks” of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentrations usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged enflurane anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory exchange can serve as a guide to depth of anesthesia. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

When previous exposure to a halogenated anesthetic is known to have been followed by evidence of unexplained hepatic dysfunction, consideration should be given to use of an agent other than enflurane.

## **PRECAUTIONS**

### **General**

ĒTHRANE (enflurane, USP) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by the drug.

ĒTHRANE (enflurane, USP), like some other inhalational anesthetics, can react with desiccated carbon dioxide (CO<sub>2</sub>) absorbents to produce carbon monoxide which may result in elevated levels of carboxyhemoglobin in some patients. Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO<sub>2</sub> absorber cannister at high flow rates over many hours or days. When a clinician suspects that CO<sub>2</sub> absorbent may be desiccated, it should be replaced before the administration of ĒTHRANE (enflurane, USP).

### **Information to Patients**

Enflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 to 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for several days following administration.

### **Laboratory Tests**

Bromsulphthalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients.

### **Drug Interactions**

The action of nondepolarizing relaxants is augmented by enflurane. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of enflurane than when halothane or nitrous oxide with a balanced technique are used.

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## Carcinogenesis/Mutagenesis

Swiss ICR mice were given enflurane to determine whether such exposure might induce neoplasia. Enflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice who were given the same background gases, but not the anesthetic.

Exposure of mice to 20 hours of 1.2% enflurane causes a small (about 1/2 of 1.0%) but statistically significant increase in sperm abnormalities. In contrast to these results, *in vitro* approaches to the study of mutagenesis (Ames test, sister chromatid exchange test, and the 8-azaguanine system) have not shown a mutagenic effect of enflurane.

## Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to enflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

## Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when enflurane is administered to a nursing woman.

## ADVERSE REACTIONS

1. Malignant hyperthermia (see **WARNINGS**).
2. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane, USP) anesthesia, or light levels with hypocapnia.
3. Hypotension, respiratory depression, and hypoxia have been reported.
4. Arrhythmias, shivering, nausea and vomiting have been reported.
5. Elevation of the white blood count has been observed.
6. Mild, moderate and severe liver injury, including hepatic failure, may rarely follow anesthesia with enflurane. Serum transaminases may be increased and histologic evidence of injury may be found. The histologic changes are neither unique nor consistent. In several of these cases, it has not been possible to exclude enflurane as the cause or as a contributing cause to liver injury. The incidence of unexplained hepatotoxicity following the administration of enflurane is unknown, but it appears to be rare and not dose related.

ĒTHRANE (enflurane, USP) has also been associated with perioperative hyperkalemia (see **WARNINGS**).

### Post-Marketing Events

The following adverse events have been identified during post-approval use of ĒTHRANE (enflurane, USP). Due to the spontaneous nature of these reports, the actual incidence and relationship of ĒTHRANE (enflurane, USP) to these events cannot be established with certainty.

*Cardiac Disorders:* Cardiac arrest

*Hepatobiliary Disorders:* Hepatic necrosis, Hepatic failure

## **OVERDOSAGE**

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

## **DOSAGE AND ADMINISTRATION**

The concentration of ĒTHRANE (enflurane, USP) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- a. vaporizers calibrated specifically for enflurane;
- b. vaporizers from which delivered flows can easily and readily be calculated.

## **Preanesthetic Medication**

Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by enflurane and that enflurane does not alter heart rate. The use of anticholinergic drugs is a matter of choice.

## **Surgical Anesthesia**

Induction may be achieved using enflurane alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the enflurane mixture. In general, inspired concentrations of 2.0 to 4.5% enflurane produce surgical anesthesia in 7 to 10 minutes.



## Maintenance

Surgical levels of anesthesia may be maintained with 0.5 to 3.0% enflurane. Maintenance concentrations should not exceed 3.0%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35 to 45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of enflurane concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

## Analgesia

Enflurane 0.25 to 1.0% provides analgesia for vaginal delivery equal to that produced by 30 to 60% nitrous oxide. These concentrations normally do not produce amnesia. See also the information on the effects of enflurane on uterine contraction contained in the **CLINICAL PHARMACOLOGY** section.

## Cesarean Section

Enflurane should ordinarily be administered in the concentration range of 0.5 to 1.0% to supplement other general anesthetics. See also the information on the effects of enflurane on uterine contraction contained in the **CLINICAL PHARMACOLOGY** section.

## HOW SUPPLIED

ĒTHRANE (enflurane, USP) is packaged in 125 and 250 mL amber-colored bottles.

125 mL — NDC 10019-350-50

250 mL — NDC 10019-350-60

## Safety and Handling

### Occupational Caution

There is no specific work exposure limit established for ĒTHRANE (enflurane, USP). However, the National Institute for Occupational Safety and Health Administration (NIOSH) recommends that no worker should be exposed at ceiling concentrations greater than 2 ppm of any halogenated anesthetic agent over a sampling period not to exceed one hour.



The predicted effects of acute overexposure by inhalation of ËTHRANE (enflurane, USP) include headache, dizziness or (in extreme cases) unconsciousness. There are no documented adverse effects of chronic exposure to halogenated anesthetic vapors (Waste Anesthetic Gases or WAGs) in the workplace. Although results of some epidemiological studies suggest a link between exposure to halogenated anesthetics and increased health problems (particularly spontaneous abortion), the relationship is not conclusive. Since exposure to WAGs is one possible factor in the findings for these studies, operating room personnel, and pregnant women in particular, should minimize exposure. Precautions include adequate general ventilation in the operating room, the use of a well-designed and well-maintained scavenging system, work practices to minimize leaks and spills while the anesthetic agent is in use, and routine equipment maintenance to minimize leaks.

## Storage

**Store at room temperature 15°-30°C (59°-86°F).** Enflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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***Baxter***

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