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FREEDOM OF INFORMATION (FOI) SUMMARY
FOR
SEVOFLO™ (sevoflurane)
ANESTHETIC INJECTION FOR DOGS
NADA 141-103

Sponsored by:

Abbott Laboratories
Animal Health Products
1401 Sheridan Road
North Chicago, IL 60064

NADA 141-103

FOIS-1

SEVOFLO™

FREEDOM OF INFORMATION (FOI) SUMMARY

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

A. NADA Number: NADA 141-103

B. Sponsor: Abbott Laboratories
Animal Health Products
140 1 Sheridan Road
North Chicago, IL 60064-4000

C. Generic Name: Sevoflurane

D. Trade Name: SevoFlo™

E. Marketing Status: Rx

2. INDICATIONS FOR USE:

SevoFlo™ is indicated for induction and maintenance of general anesthesia in dogs.

3. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGES:

SevoFlo™ is a volatile gas inhalant anesthetic agent. It is available for use in 250 mL bottles.

DOSAGE AND ADMINISTRATION:

Inspired Concentration: The delivered concentration of SevoFlo™ should be known. Since the depth of anesthesia may be altered easily and rapidly, only vaporizers producing predictable percentage concentrations of sevoflurane should be used. Sevoflurane should be vaporized using a precision vaporizer specifically calibrated for sevoflurane. Sevoflurane contains no stabilizer. Nothing in the drug product alters calibration or operation of these vaporizers. The administration of general anesthesia must be individualized based on the patient's response.

Premedication: No specific premedication is either indicated or contraindicated with sevoflurane. The necessity for and choice of premedication is left to the discretion of the veterinarian. Preanesthetic doses for premedicants may be lower than the label directions for their use as a single medication'.

Induction: For mask induction using sevoflurane, inspired concentrations of 5 to 7% sevoflurane with oxygen are employed to induce surgical anesthesia in the healthy dog. These concentrations can be expected to produce surgical anesthesia in 3 to 14 minutes. The use of premedicants does not affect the concentration of sevoflurane required for induction.

Maintenance: SevoFlo™ has been evaluated for maintenance anesthesia following mask induction using sevoflurane or following injectable induction agents. The concentration of vapor necessary to maintain anesthesia is much less than that required to induce it.

Surgical levels of anesthesia in the healthy dog may be maintained with inhaled concentrations of 3.7-4.0% sevoflurane in oxygen in the absence of **premedication** and 3.3-3.6% in the presence of **premedication**. The use of injectable induction agents without **premedication** has little effect on the concentrations of sevoflurane required for maintenance. Anesthetic regimens that include opioid, alpha-, agonist, benzodiazepine or phenothiazine premedication will allow the use of lower sevoflurane maintenance concentrations.

4. EFFECTIVENESS:

The safety and effectiveness of sevoflurane in clinical use, as well as the appropriate doses, were determined in four studies.

A. Dosage Rationale:

1) Comparison of MAC and the Rate of Rise of Alveolar Concentration of Sevoflurane with Halothane and Isoflurane in the Dog. Anesthesiology. 68: 435-437, 1988.

STUDY PERSONNEL

Study Investigators

T. Kazama and K. Ikeda
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STUDY OBJECTIVES

This study was designed to determine the respective anesthetic requirements (minimum alveolar concentration, MAC) of sevoflurane, **isoflurane** and halothane in dogs and to determine the rate of rise of the alveolar concentration when a constant inspired concentration of each of these anesthetics was administered.

STUDY DESIGN

Forty (40) dogs were used to determine MAC: 18 for sevoflurane; 10 for isoflurane and 12 for halothane. Twelve (12) dogs were used to determine the rate of rise of end-tidal anesthetic concentration toward the inspired anesthetic concentration (F_a/F_i) under controlled ventilation. The order of anesthetic administration was randomized. Results were analyzed using a Student's t-test.

MAC is defined as that alveolar concentration at which 50% of healthy patients fail to respond to noxious stimuli. Multiples of MAC are used as a guide for surgical levels of anesthesia (% concentrations), which are typically 1.3 to 1.5 times the MAC value.

MATERIALS AND METHODS

Animals

Number: 40

Breed: Mongrel

Weight: 7.5 - 15.0 kg

Anesthetic Procedures

MAC Determination: Anesthesia was induced by mask or sealed exposure chamber using either 5% sevoflurane, 4% isoflurane or 4% halothane in oxygen. All dogs underwent endotracheal intubation with cuffed tubes, and end-tidal carbon dioxide was maintained at 30-35 mm Hg. Ventilation was controlled. A predetermined end-tidal anesthetic concentration was maintained for 20-40 minutes and then the animal's tail was clamped. The concentration midway between the highest concentration which allowed purposeful movement and the lowest concentration which prevented purposeful movement was taken as 1 MAC.

RESULTS

The MAC equivalents for each anesthetic agent were determined to be (mean \pm standard deviation (SD)):

| | |
|-------------|--------------------|
| sevoflurane | $2.36 \pm 0.46\%$ |
| isoflurane | $1.39 \pm 0.25 \%$ |
| halothane | $0.89 \pm 0.20\%$ |

The rate of rise of alveolar concentration toward that of the inspired concentration (F_a/F_i) was faster for sevoflurane than for either halothane or isoflurane.

Washout times were as follows (mean \pm SD):

| | |
|-------------|---------------------|
| sevoflurane | 48 ± 11 minutes |
| isoflurane | 52 ± 13 minutes |
| halothane | 72 ± 9 minutes |

CONCLUSION:

Sevoflurane's MAC equivalent of $2.36 \pm 0.46\%$ (mean \pm standard deviation (SD)) was used as the basis for further evaluation.

2) Sevoflurane Anesthesia in a Crossover Study with Isoflurane**Study Investigators/Sites**

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STUDY DATES September 21 - October 31, 1994

STUDY OBJECTIVES

The objective of this study was to evaluate sevoflurane for the induction, maintenance and recovery from anesthesia in adult dogs in a crossover study with isoflurane.

STUDY DESIGN

A total of 16 dogs (4 males and 4 females at each site) were randomized in a two-period crossover design so that four dogs at each site (2 males and 2 females) received isoflurane in the first period and sevoflurane in the second period (Sequence 1). The treatment order was reversed for the other four dogs (Sequence 2) at each site. There was a washout of at least seven days between each of the periods.

MATERIALS AND METHODS**Animals**

Number: 16

Breed: purpose-bred Beagles

Age: 9 to 24 months

Weight: 7.7 - 15.5 kg

Sex: 4 males and 4 females at two sites

Anesthetic Procedures

Following acclimation of the animal to the anesthetic mask with 100% oxygen, anesthesia was induced by increasing the vaporizer delivered concentration (VDC) at 15 second intervals from 0.5 to 2.0 MAC in increments of 0.5 MAC. In the dog, MAC is 2.36% for sevoflurane (Kazama *et al.*, 1985) and 1.28% for isoflurane (Steffey and Howland, 1977). The setting of 2.0 MAC was maintained until depth of anesthesia allowed for endotracheal intubation. The animals were allowed to breathe spontaneously at an oxygen flow of 1 L/minute maintained throughout 30 minutes of maintenance anesthesia. At the end of 30 minutes of maintenance anesthesia, the vaporizer was turned to 0% and oxygen flow rate increased to 4 L/minute until the animal was extubated. A positive response to the tail clamp, applied at 1 minute intervals during recovery, was used to indicate the end of anesthesia.

Variables Measured or Observed

Anesthetic Dose: Vaporizer settings and inspired and expired anesthetic concentrations were recorded throughout anesthesia.

Anesthesia: Induction and recovery times were recorded. Subjective assessments of the ease of induction and recovery were made by the investigator.

Physiological: Hemoglobin oxygen saturation, respiratory rate, pulse rate, indirect systolic, diastolic and mean arterial blood pressure and rectal temperature were recorded throughout the anesthetic period.

RESULTS AND DISCUSSION

Induction

The mean time to loss of palpebral reflex, time to negative tail clamp response and time to intubation are shown for sevoflurane in the table below. The subjective assessment of ease of induction is also included in the table.

| Treatment Group | <i>Time to Loss of Palpebral Reflex</i> | <i>Time to Negative Tail Clamp Response</i> | <i>Time to Intubation</i> | <i>Quality of Induction</i> | | | |
|-----------------|---|---|---------------------------|-----------------------------|------|------|------|
| | min Mean (Range) | min Mean (Range) | min Mean (Range) | Excel | Good | Fair | Poor |
| sevoflurane | 4.7 (4.0-7.0) | 4.0 (2.0-7.0) | 5.7 (3.0-9.0) | 10 | 5 | 1 | 0 |

Recovery

Recovery data are summarized in the table below:

| <i>Treatment Group</i> | <i>Time to Extubation min Mean (Range)</i> | <i>Time to Sternal Recumbency min Mean (Range)</i> | <i>Quality of Recovery</i> | | |
|------------------------|--|--|----------------------------|-------------|-------------|
| | | | <i>Excel</i> | <i>Good</i> | <i>Fair</i> |
| | | | <i>N</i> | <i>N</i> | <i>N</i> |
| sevoflurane | 6.4 (3.0-14.2) | 8.0 (4.0-14.2) | 12 | 3 | 1 |

The following table combines the variables of quality of induction and quality of recovery for sevoflurane anesthesia.

| | Recovery Excellent | Good | Fair | Total |
|---------------------|--------------------|---------|--------|-----------|
| Induction Excellent | 8 | 2 | 0 | 10 (63%) |
| Good | 3 | 1 | 1 | 5 (31%) |
| Fair | 1 | 0 | 0 | 1 (6%) |
| Poor | 0 | 0 | 0 | 0 (0%) |
| Total | 12 (75%) | 3 (19%) | 1 (6%) | 16 (100%) |

Physiological Effects

Tail clamp responses were negative throughout maintenance anesthesia. Apnea occurred sporadically in both treatment groups with a total of 16 of the 20 instances occurring within the first 5 minutes of the maintenance phase.

Respiration rate declined during the first 5 minutes of maintenance and was relatively stable thereafter with both anesthetics. Mean pulse rate was relatively stable throughout maintenance for both anesthetics. Systolic, diastolic and mean blood pressure declined somewhat with both inhalants during the first 10 minutes of maintenance.

Oxygen saturation of hemoglobin averaged approximately 95% for both groups throughout maintenance. Body temperature was virtually identical for both agents.

CONCLUSION:

The induction and maintenance dosages and recovery characteristics of sevoflurane anesthesia in adult dogs were characterized during the study.

B. Effectiveness: Compatibility of Sevoflurane with Injectable Induction and Preanesthetic Agents

For safety reasons, general anesthesia with sevoflurane when used in conjunction with various preanesthetic and induction agents was evaluated. Some of these agents are not approved for these uses in dogs.

Study Investigator

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STUDY DATES: June 6 - August 18, 1995

STUDY OBJECTIVES

The objectives of this study were to assess the compatibility and dose requirements of sevoflurane in dogs when used in conjunction with preanesthetic and injectable induction agents typical of canine anesthesia.

STUDY DESIGN

This study consisted of two experiments, both represented by four treatment groups studied in two 4 X 4 Latin Square arrangements. In Experiment 1, the effects of various induction agents (either sevoflurane by mask or an injectable agent) followed by sevoflurane maintenance were evaluated. In Experiment 2, the effects of preanesthetic agents in combination with thiopental induction and sevoflurane maintenance were evaluated.

A group (4 of each sex) of adult, purpose-bred Beagle dogs was selected at random from a pool of 18 dogs (9 males, 9 females) for Experiment 1. A second group of 8 dogs (4 of each sex) were selected at random for Experiment 2 from the pool of remaining dogs. Each dog was anesthetized four times with at least a two-week washout between treatments.

EXPERIMENT 1- INDUCTION/MAINTENANCE REGIMENS

| Treatment Group | Preanesthetic | Induction | Maintenance |
|-----------------|---------------|--|-------------|
| 1 | None | Sevoflurane | Sevoflurane |
| 2 | None | Thiopental (25 mg/kg IV) | Sevoflurane |
| 3 | None | Propofol (6.6 mg/kg IV) | Sevoflurane |
| 4 | None | Ketamine/Diazepam (5.0/0.25 mg/kg IV) | Sevoflurane |

EXPERIMENT 2- PREMEDICATION/INDUCTION/MAINTENANCE REGIMENS

| Treatment Group | Preanesthetic | Induction (dosed to effect) | Maintenance |
|-----------------|--|--------------------------------|-------------|
| 5 | Acepromazine (0.1 mg/kg IM) | Thiopental | Sevoflurane |
| 6 | Xylazine (0.2 mg/kg IM) | Thiopental | Sevoflurane |
| 7 | Butorphanol/ Acepromazine (0.1/0.05 mg/kg IM) | Thiopental | Sevoflurane |
| 8 | Oxymorphone/ Acepromazine (0.05/0.05 mg/kg IM) | Thiopental | Sevoflurane |

Descriptive statistics (means, SD, etc) were used to evaluate the various combinations of premedications and /or induction agents.

MATERIALS AND METHODS**Animals**

Number: 16

Breed: purpose-bred Beagles

Weight: 11.4 - 18.2 kg

Sex: 8 males and 8 females

Anesthetic Procedures

Induction with Sevoflurane

Using a face mask, the concentration of sevoflurane was set to 0.5 MAC (1.1%) at an oxygen flow rate of 2 L/min and increased at 0.5 MAC intervals each 15 seconds. The last vaporizer setting was maintained until the animal was sufficiently anesthetized to facilitate endotracheal intubation, and the oxygen flow rate was reduced to 1 L/minute.

Induction with Injectable Agents/Premedicants

Intravenous injection agents were administered via a pre-placed catheter. Premedicants were administered intramuscularly 20 minutes prior to induction.

Maintenance with Sevoflurane

Following intubation, an endotracheal tube was connected to the circle anesthesia system and the vaporizer setting adjusted to establish surgical anesthesia at 1.4 - 1.6 MAC end-tidal concentration (approximately 3.3 - 3.7%) for Groups 1 - 4 and approximately 1.2 MAC end-tidal concentration (approximately 2.8 to 3.0%) for Groups 5 - 8 with an oxygen flow rate of 1 L/minute.

Variables Measured or Observed

Anesthetic Dose: Sevoflurane vaporizer concentration and inspired and expired sevoflurane were measured throughout anesthesia.

Anesthesia Events: Induction and recovery times were recorded.

Physiological: Respiration rate, systolic, diastolic and mean blood pressures, pulse, rectal temperature, hemoglobin oxygenation saturation, ECG, and expired carbon dioxide were recorded throughout anesthesia. Incidence and duration of apnea were recorded, along with other adverse reactions.

RESULTS AND DISCUSSION

Anesthetic Events and Dose Requirements

The time to intubation following administration of the induction agent is summarized in the following table. Predictably, induction with injectable agents was more rapid than mask induction with sevoflurane, which took an average of 10.3 minutes. The presence of premedication had little impact on the intubation time, since times for Groups 5 - 8 were generally similar to those for Group 2.

The use of induction agents tended to decrease only slightly the overall sevoflurane requirements for maintenance (see table), whereas the presence of premedication decreased these requirements by 18-31% (dose sparing effect).

Recovery times in groups induced with thiopental tended to be longer. The use of acepromazine/oxymorphone appeared to further increase recovery times. The shortest

recovery times were observed in the sevoflurane mask induction group, where the mean time to sternal recumbency was achieved in 13.5 minutes and standing in 15.9 minutes.

| Anesthetic Event Times/Dose Requirements | | | | |
|---|---|---|---|--------------------------------|
| Treatment Group | Induction Agents or Premedicants | Time to Intubation (min.) mean (range) | Time to Sternal Recumbency (min.) mean (range) | MAC Hours* mean (range) |
| 1 | None | 10.25 (7.5-13.0) | 13.48 (11.28-18.50) | 1.46 (1.37-1.54) |
| 2 | Thiopental | (1.0-2.0) | 30.45 (19.12-54.68) | 1.39 (1.33-1.45) |
| 3 | Propofol | 2.0 (1.0-3.0) | 16.50 (12.25-21.88) | 1.37 (1.29-1.47) |
| 4 | Ketamine/ Diazepam | 2.5 (1.0-5.0) | 18.27 (13.55-24.42) | 1.43 (1.36-1.54) |
| 5 | Thiopental/ Acepromazine | 1.63 (1.0-2.0) | 29.13 (15.87-54.17) | 1.19 (1.11-1.24) |
| 6 | Thiopental/ Xylazine | 1.13 (1.0-2.0) | 22.17 (14.78-32.10) | 1.16 (1.10-1.30) |
| 7 | Thiopental/ Butorphanol/ Acepromazine | 1.0 (1.0-1.0) | 32.08 (14.42-43.67) | 1.06 (0.93-1.20) |
| 8 | Thiopental/ Oxymorphone/ Acepromazine | 1.38 (1.0-2.0) | 65.73 (31.25-167.18) | 1.01 (0.71-1.16) |

*MAC Hours = sevoflurane maintenance requirements (time-weighted sevoflurane end-tidal concentration/60 minutes/2.3 6% [MAC])

Physiologic Responses

The administration of sevoflurane resulted in the reduction of respiration rate relative to baseline or induction respiration rate. All other treatment combinations resulted in a reduction in respiration rate during maintenance compared to sevoflurane alone.

Systolic blood pressure was generally reduced in animals mask-induced with sevoflurane, compared to pretreatment levels. The hypotensive effects of sevoflurane and the various induction agents did not appear to be additive. Results for all treatment groups were within acceptable ranges for anesthesia and were generally stable throughout the 60 minute maintenance period. Mean and diastolic blood pressure was reduced by each medication (sevoflurane, induction agents and premedicants) relative to pretreatment values.

Sevoflurane induction and maintenance had a minimal impact on pulse rate, which tended to decrease only slightly over time during the maintenance period.

Rectal temperature was decreased by the administration of each drug (sevoflurane, induction agents and premedicants), compared to pretreatment values. Hemoglobin oxygen saturation was not greatly affected during sevoflurane maintenance and remained at acceptable levels throughout the maintenance period. Expired carbon dioxide values tended to decrease slightly during the maintenance period and were similar among the treatment groups (mean values ranged from 45.5 - 53.8%). An exception was the acepromazine/oxymorphone group in which means ranged from 53.8 - 59.8% during the maintenance period, reflecting the greater cardiorespiratory depression observed with this pretreatment compared to other groups.

Adverse reactions

The most frequently observed adverse reaction was apnea during induction or anesthetic adjustment periods. The average duration of apnea during induction in the various treatment groups is summarized below:

| Summary of Apnea Incidence | | | | |
|----------------------------|----------------------------------|---|---------------------|--------------|
| Group | Induction Agents or Premedicants | No. of Dogs Affected (Total no. in each group is 8) | Mean Duration (min) | Range |
| 1 | None | 2 | 10:06 | 6:17 – 13:51 |
| 2 | Thio | 4 | 4:30 | 1:16 – 11:00 |
| 3 | Prop | 5 | 10:48 | 0:30 – 28:00 |
| 4 | Ket/Diaz | 2 | 1:18 | 1:07 – 1:26 |
| 5 | Thio/Ace | 2 | 1:30 | 0:30 – 2:30 |
| 6 | Thio/Xyl | 2 | 23:00 | 1:00 – 45:00 |
| 7* | Thio/But/Ace | 6 | 3:44* | 1:05 – 6:40* |
| 8 | Thio/Oxy/Ace | 3 | 28:18 | 1:20 – 53:30 |

*No end point time was recorded for one animal; average and range are based on five animals with complete data.

Results for other adverse reactions are summarized in the table below:

| Summary of Adverse Reactions Observed | | | | |
|---------------------------------------|----------------------------------|---------------------|----------|-------------------|
| Treatment Group | Induction Agents or Premedicants | Effect | No. Dogs | Anesthesia Phase* |
| | None | Reverse sneeze | 6 | R |
| 2 | Thiopental | Irregular breathing | 1 | M |
| | | Low heart rate | 1 | M |
| | | I Reverse sneeze | 5 | R |
| 3 | Propofol | Rebreathing | 1 | M |
| | | Reverse sneeze | 4 | R |
| 4 | Ket/ Diaz | Whine | 1 | R |
| | | Reverse sneeze | 3 | R |
| 5 | Thio/ Ace | Panting | 1 | I |
| | | Reverse sneeze | 4 | R |
| 6 | Thio/ Xylaz | Panting | 2 | I |
| | | Shaking | 1 | R |
| | | Reverse sneeze | 3 | R |
| 7 | Thio/ But/ Ace | Panting | 2 | |
| | | Shaking | 1 | R |
| | | Low heart rate | 1 | I |
| | | Nystagmus | 1 | R |
| | | Reverse sneeze | 3 | R |
| 8 | Thio/ Oxy/ Ace | Vomiting | 3 | P |
| | | Panting | 1 | I |
| | | Shaking | 1 | I |
| | | Heavy salivation | 1 | M |
| | | Low heart rate | 1 | R |
| | | Reverse sneeze | 1 | R |

*I = induction, M = maintenance, R = recovery

There were no serious and/or unexpected adverse reactions noted during the course of the study.

CONCLUSION:

Sevoflurane was compatible and effective with the premedicants and induction agents used in the study. The presence of premedication had little impact on induction time. Injectable induction agents had little impact on sevoflurane maintenance requirements; however, premedication decreased sevoflurane maintenance requirements by 18 - 31% (dose sparing effect).

C. Effectiveness Study III: Clinical Trial

For safety reasons, general anesthesia with sevoflurane when used in conjunction with various preanesthetic and induction agents was evaluated. Some of these agents are not approved for these uses in dogs.

Study Investigators

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STUDY DATES October 25, 1995 - February 20, 1996

STUDY OBJECTIVES

The objective of this study was to evaluate the clinical safety and effectiveness of sevoflurane for induction and maintenance of anesthesia in dogs.

STUDY DESIGN

This multi-site clinical study encompassed three clinical sites and included a variety of surgical and non-surgical procedures varying in duration and complexity. The animals were not randomly assigned to treatment since physical status and the nature of the medical procedure usually determined the most appropriate anesthetic protocol to be used. The effects of the drug were evaluated without a separate control group, as provided under 21 CFR 5 14.11 1(a)(5)(ii) (a)(2)(iii).

Treatment groups are provided in the following table. All dogs received sevoflurane for maintenance. Treatment groups 1-4 represented typical premedication and induction regimens. In treatment group 5, preanesthesia was optional; however, animals were mask-induced with sevoflurane. In group 6, both pretreatment and induction agents were optional.

Administration of a preanesthetic anticholinergic (atropine or glycopyrrolate) was optional for all treatment groups,

| Treatment Group | Premedication Drug(s) | Induction Drug | Number of Dogs |
|-----------------|----------------------------|----------------|----------------|
| 1 | oxymorphone | thiopental | 39 |
| 2 | acepromazine & oxymorphone | thiopental | 30 |
| 3 | butorphanol & xylazine | thiopental | 29 |
| 4 | opioid | propofol | 33 |
| 5 | optional* | sevoflurane | 30 |
| 6 | optional* | optional* | 35 |
| Total | | | 196 |

*Drug selection and dosage were left to the discretion of the attending anesthesiologist

MATERIALS AND METHODS

Animals

The study included any client-owned animal of ASA (American Society of Anesthesiologists) status I, II or III (see Lumb and Jones, ed. Veterinary Anesthesia. Williams and Wilkins, Baltimore, p. 22. 1996) requiring general anesthesia for elective or emergency surgical or non-surgical procedures that would fit one of the treatment groups. Medical conditions resulting in patient health status classification of ASA IV or ASA V were excluded. Patients that had received an investigational drug or had been enrolled in an investigational drug study within 30 days prior to admission to this study were also excluded. No limitation was placed on breed, age or gender of the patient. Details of enrollment are provided below:

Number: 196

A protocol amendment dated November 30, 1995, revised adverse reaction reporting. Sixty-eight dogs were included in the study prior to implementing the protocol amendment. The initial 68 dogs were not evenly distributed across all treatment groups; the table on adverse reactions (see results below) was derived from 128 dogs included in the study after the amendment was implemented.

Breed: The most common breeds were Labrador Retriever (n=16), Sighthound (n=10), Australian Cattle Dog (n=6) and German Shepherd (n=6). The remaining breeds were Mixed (n=76) and numerous others (n=82). Sighthounds included eight Greyhounds, one Italian Greyhound and one Whippet.

Age: The mean patient age was 3.1 years with a range of 2 months to 14 years.

Weight: Mean patient body weight was 20.2 kg and ranged from 1.5 to 77.0 kg.

Sex: There were 80 intact males, 10 castrated males, 72 intact females and 34 spayed female patients, respectively, in the study.

Health Status: Sixty-six percent (66%) of the patients were assigned an ASA health status classification of I, followed by 29% ASA classification II and 10 patients (5%) ASA classification III (essentially healthy dogs). Only five patients were considered to be in a compromised health condition by the investigators.

Surgical Procedures: The procedures performed could be placed into one of ten categories: circumcostal gastropexy (2.5%), cruciate repair (2.5%), dental exam/treatment (6.6%), castration (27.5%), castration and minor procedure (3.1%), ovariectomy (26.5%), ovariectomy and minor procedure (2.5%), orthopedic/fracture (3.6%), orthopedic/non-fracture (5.6%) and other (19.4%).

Anesthetic Procedures

Premedicants: Atropine or glycopyrrolate were optional for all treatment groups and were given in forty-nine percent (96/196) of the patients. Administration of preanesthetics was performed according to the clinical practice standards of each test facility. Generally, preanesthetic drugs were given 15 to 20 minutes prior to induction of anesthesia.

Induction with Sevoflurane

Using a face mask, the vaporizer was set to deliver a concentration of 4 to 7% and adjusted until the animal was sufficiently anesthetized to facilitate endotracheal intubation. Dose ranges of all premedicants, when used as part of the masked sevoflurane induction regimen, are provided in the following table.

| <i>Preanesthetic</i> | <i>Sevoflurane Induction</i> | |
|----------------------|---|-----------------|
| | <i>Dose of First/Second Preanesthetic</i> | <i>N Routes</i> |
| | <i>Mean (Range) (mg/kg)</i> | |
| Oxymorphone | 0.010 (0.05-0.11) | 6 IM, SC |
| Butorphanol | 0.022 | 1 IM |
| Morphine | 0.52 (0.44-0.68) | 6 IM |

| | | | |
|----------------------------|-----------------------------------|---|---------------|
| Acepromazine/Oxymorphone | 0.05 (0.03-0.10)/0.09 (0.05-0.10) | 6 | IM, SC/IM, SC |
| Acepromazine/Butorphanol | 0.04 (0.02-0.06)/0.26 (0.20-0.41) | 6 | IM/IM |
| Acepromazine/Morphine | 0.06/1.10 | 1 | IM/IM |
| Acepromazine/Buprenorphine | 0.02/0.02 | 1 | IM/IM |
| Xylazine/Butorphanol | 0.30/0.49 | 1 | IM/IM |
| Xylazine/Morphine | 0.25/0.5 | 1 | IM/IM |
| Diazepam/Buprenorphine | 0.22/0.0 | 1 | IV/IM |

Sevoflurane Maintenance Regimens Using Induction with Injectable Agents

Administration of injectable anesthetics (thiopental, propofol, or ketamine/diazepam) was performed according to the clinical practice standards of each test facility. Doses which were sufficient to allow intubation depended on the premedication regimen. The dogs were connected to an anesthetic system containing the vaporized inhalant anesthetic, sevoflurane, immediately after intubation. Dose ranges of all premedicants, when used with injectable induction agents followed by sevoflurane maintenance, are provided in the following table.

Induction with Injectable Agents

| <i>Preanesthetic</i> | <i>Dose First/Second Preanesthetic Mean (Range) (mg/kg)</i> | <i>N</i> | <i>Routes</i> |
|----------------------------|---|----------|----------------|
| Acepromazine | 0.06 (0.04-0.09) | 8 | IM, SC |
| Oxymorphone | 0.010 (0.05-0.23) | 49 | IM, SC |
| Butorphanol | 0.27 (0.1 g-0.44) | 13 | IM, SC |
| Morphine | 0.72 (0.49- 1.20) | 12 | IM |
| Acepromazine/Oxymorphone | 0.04 (0.02-0.10)/0.09 (0.05-0.20) | 32 | IM,SC/IM,SC,IV |
| Acepromazine/Butorphanol | 0.05 (0.04-0.06)/0.21 (0.20-0.22) | 3 | IM, SC/IM, SC |
| Acepromazine/Morphine | 0.05 (0.05-0.05)/0.80 (0.05-1.10) | 2 | IM/IM |
| Acepromazine/Buprenorphine | 0.05/0.02 | 1 | IM/IM |
| Xylazine/Butorphanol | 0.38 (0.21-0.55)/0.35 (0.20-0.55) | 33 | IM, SC/IM, SC |
| Xylazine/Morphine | 0.43 (0.25-0.55)/0.50 (0.47-0.55) | 11 | IM/IM |

Maintenance with Sevoflurane

Following intubation, an endotracheal tube was connected to the circle anesthesia system and the vaporizer setting adjusted to establish surgical anesthesia. Anesthesia was maintained using a rebreathing (i.e., circle) or non-rebreathing (i.e., Bain) anesthetic delivery system at a minimum oxygen flow rate of 0.5 L/minute, and a vaporizer setting adjusted to maintain an appropriate depth of anesthesia. A precision out-of-circle vaporizer was used for anesthetic vaporization with all systems and an in-circle carbon dioxide absorbent was used in the rebreathing systems. In general, the animals were allowed to breathe spontaneously during the procedure and the vaporizer settings were adjusted to maintain a surgical depth of anesthesia.

Variables Measured or Observed

Anesthetic Dose: Vaporizer concentrations and flow rates were recorded at the beginning of maintenance and at each change to their levels.

Anesthetic Response: The investigator assigned a subjective evaluation to the induction, maintenance and recovery from anesthesia. Induction and recovery times were recorded.

Physiological: Arterial blood pressure (BP), respiratory rate (RR), core body temperature, end-tidal carbon dioxide and percent oxygen hemoglobin saturation were recorded at specified times before and during the procedure. The investigator recorded all adverse reactions observed throughout the study for specified time intervals. Particular attention was paid to, but not limited to, cardiorespiratory, musculoskeletal, gastrointestinal, central nervous system, ocular and behavioral phenomena. Frequency and duration of apnea were documented.

RESULTS

Anesthetic Dose, Event Times and Quality

Induction

Thirty animals were mask-induced with sevoflurane. The sevoflurane concentration required to induce the patients ranged from 4 to 7% volume with an average of 4.88%. These data were recorded from delivery concentrations indicated on the vaporizer dial settings. Of the four mask-induced animals receiving "Fair" or "Poor" ratings of induction quality, all were anesthetized with a vaporizer concentration of 4% sevoflurane. Therefore, a concentration of 5-7% is preferable for induction with sevoflurane in healthy dogs.

The mean time to intubation was faster for the injectable induction drugs thiopental and propofol (1.1 to 1.6 minutes) compared to sevoflurane (see the following table). Times to intubation ranged from 0.2 to 8 minutes for thiopental and propofol and 3 to 14 minutes for mask induction with sevoflurane.

Investigator quality scores are also provided in the table below. The higher quality scores for the injectable induction drugs, as opposed to mask induction, are expected since they produce a faster increase in anesthetic blood levels.

| <i>Treat- ment Group</i> | <i>Pretreatment/ Induction Agent</i> | <i>Mean Time to Intubation min (Range)</i> | <i>Quality of Induction</i> | | | | | <i>Total N</i> |
|----------------------------------|---|--|-----------------------------|-------------------|-------------------|-------------------|------------------|--------------------|
| | | | <i>Excel N</i> | <i>Good N</i> | <i>Fair N</i> | <i>Poor N</i> | <i>NA* N</i> | |
| 1 | oxymorphone/ thiopental | 1.6 (0-6-6.0) | 25 | 12 | 2 | 0 | 0 | 39 |
| 2 | acepromazine and oxymorphone/ thiopental | 1.6 (0.5-8.0) | 22 | 6 | 1 | 0 | 1 | 30 |
| 3 | butorphanol and xylazine/ thiopental | 1.1 (0.6-2.0) | 25 | 3 | 0 | 0 | 1 | 29 |
| 4 | opioid/propofol | 1.5 (0.2-4.0) | 27 | 4 | 2 | 0 | 0 | 33 |
| 5 | optional/ sevoflurane | 7.3 (3.0-14.0) | 23 | 3 | 3 | 1 | 0 | 30 |
| 6 | optional/ optional | 1.7 (0.6-3.0) | 30 | 3 | 1 | 0 | 1 | 35 |
| Total | | | 152 | 31 | 9 | 1 | 3 | 196 |

*Induction scores not available

Maintenance:

The average maintenance time was 111.7 minutes in all groups combined, ranging from 16 to 424 minutes (see following table). The average concentrations were slightly higher than in the compatibility study probably reflecting the presence of surgical stimulation, which would increase anesthetic requirements. An expected general lowering of vaporizer concentrations was noted as the anesthesia progressed. No differences in doses were observed based on the premedication and induction agent usage.

Investigator ratings of maintenance quality are also provided in the table:

| Treatment Group | Pretreatment/ Induction Agents | Mean Vap. Conc. During First 30 Min(Vol %) (Range) | Mean O ₂ Flow Rate During First 30 Min (L/min) (Range) | Mean Duration of Maintenance (min) (Range) | <u>Quality of Maintenance</u> | | | | |
|-----------------|--|--|---|--|-------------------------------|-----------|------------|-----------|------------|
| | | | | | Excel N | Good N | Fair NN | Poor N | Total N |
| 1 | oxymorphone/ thiopental | 3.46 (2.6-4.2) | 0.97 (0.5-2.3) | 104.1 (16-247) | 20 | 15 | 3 | 1 | 39 |
| 2 | acepromazine & oxymorphone /thiopental | 3.31 (2.5-4.1) | 1.07 (0.7-2.3) | 136.7 (44-275) | 19 | 8 | 3 | 0 | 30 |
| 3 | butorphanol and xylazine/ thiopental | 3.31 (2.0-4.0) | 0.99 (0.5-1.8) | 104.2 (42-175) | 20 | 2 | 3 | 4 | 29 |
| 4 | opioid/propofol | 3.63 (2.5-5.1) | 1.13 (0.5-1.9) | 129.1 (3 7-424) | 14 | 14 | 4 | 1 | 33 |
| 5 | optional/ sevoflurane | 3.35 (2.5-4.5) | 1.31 (0.7-3.0) | 94.5 (20-306) | 19 | 8 | 1 | 2 | 30 |
| 6 | optional/ optional | 3.44 (1.6-4.7) | 1.13 (0.5-3.0) | 103.0 (25-315) | 25 | 5 | 4 | 1 | 35 |
| Total | | | | | 117 | 52 | 18 | 9 | 196 |

Recovery: Over all 6 treatment groups, the mean recovery time to extubation was 8.3 minutes (range = 1 to 36 minutes). Mean times to extubation for preanesthetic/induction agents ranged from 5.3 minutes for sevoflurane with one preanesthetic to 9.6 minutes using thiopental with one preanesthetic.

Mean times and ranges to sternal recovery and standing recovery by induction agent:

| Induction Agent | Mean Time to Sternal (min) | Mean Time to Standing (min) | No. of Dogs |
|-------------------|----------------------------|-----------------------------|-------------|
| thiopental | 21.5 (3.5-135) | 41.7 (8.2-249) | 108 |
| propofol | 15.7 (2.2-91.1) | 35.5 (5.0-211.1) | 40 |
| sevoflurane | 11.2 (3.2-55.9) | 24.9 (3.7-114.0) | 29 |
| diazepam/ketamine | 8.2 (5.3-15.0) | 26.2 (9.6-40.1) | 4 |

The times to extubation, sternal recumbency and standing recovery were longer for dogs that received two preanesthetics compared to one, prior to thiopental induction, These times were shorter and similar for sevoflurane and propofol induced dogs.

Data for recovery parameters are provided in the following table. Investigator ratings of recovery quality are also provided in the table:

| Treatment Group | Pretreatment/ Induction Agent | Mean Time to Extubation | Mean Time to Sternal Recumbency | Quality of Recovery | | | | | |
|-----------------|---|-------------------------|---------------------------------|---------------------|-----------|-----------|-----------|----------|------------|
| | | min (Range) | min (Range) | Excel N | Good N | Fair N | Poor N | NA* N | Total N |
| 1 | oxymorphone/ thiopental | 9.7 (3-19) | 24.7 (5-135) | 21 | 13 | 4 | 1 | 0 | 39 |
| 2 | acepromazine and oxymorphone/ thiopental | 7.9 (1-18) | 23.9 (4-55) | 22 | 8 | 0 | 0 | 0 | 30 |
| 3 | butorphanol and xylazine/ thiopental | 8.7 (4-19) | 14.3 (4-45) | 23 | 5 | 1 | 0 | 0 | 29 |
| 4 | opioid/propofol | 7.9 (1-18) | 16.4 (2-91) | 27 | 5 | 1 | 0 | 0 | 33 |
| 5 | optional/ sevoflurane | 6.8 (1-17) | 11.2 (3-56) | 25 | 2 | 0 | 2 | 1 | 30 |
| 6 | optional/ optional | 7.5 (3-19) | 17.1 (5-50) | 26 | 7 | 1 | 1 | 0 | 35 |
| Total | | | | 144 | 40 | 7 | 4 | 1 | 196 |

*Quality of recovery scores not available

Physiological Effects

Respiration rates and pulse were reduced during sevoflurane maintenance relative to baseline levels. Nine patients received atropine for bradycardia; seven patients received glycopyrrolate. In all cases, the bradycardia was managed during anesthesia by the investigators and was without post-anesthesia consequences. Decreased blood pressure was also associated with sevoflurane maintenance: at least one recording of hypotension (<60 mm Hg) occurred in over half of the patients. In all cases, the hypotension was treated at the discretion of the anesthesiologist and no dogs were removed from the study or suffered morbidity or mortality attributable to hypotension. Sevoflurane produced expected respiratory depression and respiratory rate responses to surgical stimulation.

Mean values and ranges for heart and respiration rate and mean blood pressure during 30 to 60 minutes of maintenance are presented in the following table:

| <i>Treatment Group</i> | <i>Treatment</i> | <i>Pulse beats per minute during 30-60 minutes of maintenance (mean)</i> | <i>Respiration Rate breaths per minute during 30-60 minutes of maintenance (mean)</i> | <i>Blood Pressure mm Hg during 30- 60 minutes of maintenance (mean)</i> | <i>N</i> |
|------------------------|--|--|---|---|----------|
| 1 | oxymorphone/ thiopental | 107.6 (68.3-168.4) | 14.3 (3.2-41.3) | 83.2 (46.2-120.7) | 37 |
| 2 | acepromazine & oxymorphone/ thiopental | 107.8 (62.8-172.3) | 11.7 (5.5-43.7) | 76.6 (61.2-113.4) | 30 |
| 3 | butorphanol & xylazine/ thiopental | 95.7 (63.2-124.7) | 12.3 (6.2-25.5) | 91.3 (62.8-124.8) | 27 |
| 4 | opioid/propofol | 98.0 (45.0-134.9) | 20.6 (3.8-84.0) | 80.8 (48.5-116.6) | 33 |
| 5 | optional/ sevoflurane | 107.8 (70.2-142.2) | 23.1 (6.2-98.8) | 74.2 (51.7-102.3) | 28 |
| 6 | optional/ optional | 110.4 (58.5-160.5) | 14.9 (5.2-57.3) | 81.5 (51.0-121.2) | 34 |

A total of 4301 five-minute interval blood pressure readings were taken during the study. Ten percent were recorded at < 60 mm Hg, usually during the early maintenance anesthesia period.

| HYPOTENSION | Thiopental Induction | Sevoflurane Induction | Propofol Induction |
|---|---------------------------------|----------------------------------|-------------------------------|
| n = 196 total no. of dogs* | n = 118 | n = 30 | n = 43 |
| % dogs with at least one BP recording < 60 mm Hg | 47% | 67% | 60% |
| % dogs with more than one BP recording < 60 mm Hg | 33.9% | 50% | 39.5% |

*Of the total 196 dogs, 4 received diazepam/ketamine and 1 received no premedication. These 5 dogs were not included in the table; all 5 dogs had at least one BP recording < 60 mm Hg.

Adverse Reactions:

Adverse reactions were consistently reported using an adverse event form in 128 of the total number of 196 dogs included in the study. The incidence of adverse reactions for this subset of dogs follows:

| Adverse Reaction | Number of Dogs n = 128* | Percent of 128 |
|-------------------------------------|------------------------------------|---------------------------|
| hypotension | 72 | 56.25% |
| tachypnea | 67 | 52.34% |
| muscle tenseness | 56 | 43.75% |
| excitation | 40 | 31.25% |
| apnea | 24 | 18.75% |
| muscle fasciculation | 23 | 17.97% |
| emesis | 13 | 10.16% |
| paddling | 11 | 8.59% |
| retching | 9 | 7.03% |
| salivation | 7 | 5.47% |
| cyanosis | 3 | 2.34% |
| premature ventricular contraction | 2 | 1.56% |
| excess cardiorespiratory depression | 2 | 1.56% |
| labored breathing | 1 | 0.78% |
| coughing | 1 | 0.78% |
| testicular retraction | 1 | 0.78% |

***This total does not include the 68 animals included in the study prior to the protocol amendment dated November 30, 1995. The amendment revised adverse reaction reporting.**

The most frequently reported adverse reaction during the maintenance period was hypotension, followed by tachypnea, muscle tenseness, excitation, apnea, muscle fasciculations and emesis. Other adverse reactions occurred in less than 10% of the animals.

One serious adverse reaction was evaluated in this study. Severe hypotension was suspected, although not confirmed due to equipment problems. The clinical signs of hypotension resolved when the inhaled sevoflurane concentration was reduced, ventilation was controlled and IV fluids were administered.

Special Groups

Sighthounds

There were ten (10) sighthounds included in the study. Five were induced with propofol (Group 4) and 5 with sevoflurane (Group 5). Most of the quality scores for induction,

maintenance and recovery were excellent and only two of the 30 scores were Fair (no Poor ratings). Sevoflurane mask induction in these animals was accomplished with inhaled gas concentrations ranging from 5 to 6% volume. Sevoflurane maintenance concentrations during the first 30 minutes of maintenance ranged from 3.00 to 3.89% volume, compared to a mean for all patients of 3.42% volume. The average recovery time (sternal recumbency) for sighthounds was 14.7 minutes and was similar to averages of 16.4 and 11.2 minutes for Groups 4 and 5, respectively. Thus, in this study, there was no indication of extended recovery times following anesthesia that may be associated with Sighthounds. All variables corresponding to dose level, physiologic response, and quality of induction, maintenance and recovery were comparable between the Sighthounds and the main study population.

The percent incidence of adverse reactions such as emesis, tachypnea and excitation in Sighthounds was greater than the overall population. Many of the adverse reactions were, however, associated with the preanesthetic period. Six of ten of the sighthounds were **premedicated** with morphine and four of these animals exhibited emesis. Since vomiting is a **common** adverse reaction of morphine (Plumb, 1995) and the other effects were observed in a number of animals in this study, no particular adverse reactions associated with sevoflurane were identified in sighthounds.

CONCLUSION:

Sevoflurane was demonstrated to be safe and effective for dogs when used for induction and maintenance of anesthesia in a clinical setting.

5. TARGET ANIMAL SAFETY

The safety of **sevoflurane** was demonstrated in four studies.

A. Two Week (30 Hour) Toxicity Study

STUDY LOCATION

Travenol Laboratories
Morton Grove, IL

STUDY DATES Final report: 1969

STUDY OBJECTIVE

The purpose of this study was to determine the effect of extended (ten 3-hour periods of anesthesia within 2 weeks) exposure to sevoflurane on dogs compared to the positive control, halothane.

STUDY DESIGN

Dogs were assigned to 2 groups of 8 dogs (4 dogs/sex) and treated with either sevoflurane or halothane. Half of the dogs were mechanically ventilated; the other half breathed spontaneously. Dogs were exposed for 3 hours/day, 5 days/week for 2 weeks, for a total of 30 hours.

Determination of Arrhythmogenic Potency

During the final (tenth) anesthesia episode, cardiac sensitization potential was determined as a response to increasing doses of epinephrine. Following a single intravenous injection of 1 mg/kg atropine sulfate, anesthetized dogs were treated with doses of 0.25, 0.5, 1, 2, 4, 8, 16 and 32 mcg/kg epinephrine in increasing doses or until ventricular fibrillation occurred. Atrial blood pressure was allowed to return to normal between doses of epinephrine. Cardiac responses were evaluated with respect to nature and severity.

Immediately following the sensitization evaluations, dogs were euthanized with pentobarbital and subjected to gross and microscopic necropsy.

A comparison of hematology and clinical chemistry results prior to exposure and after nine sevoflurane exposures was performed.

MATERIALS AND METHODS

Animals

Number: 16

Breed: purebred Beagles

Age: young adult

Weight: 7.5 - 14.2 kg

Sex: 4 males and 4 females per treatment group

Anesthetic Procedures

Animals were mask-induced with 5 - 8% sevoflurane or 5% halothane in oxygen delivered from an Ohio anesthetic machine using a pediatric circle with soda lime carbon dioxide absorber (Sodasorb indicator grade, high moisture, 4 - 8 mesh) and a 1 liter rebreathing bag. The flow rate was 500 mL/min. Following induction, an endotracheal tube was inserted, and animals were maintained at a surgical plane of anesthesia for 3 hours (2.5 - 3.5% for halothane in most cases, and 4 - 5% with sevoflurane).

Controlled respiration was achieved using a Harvard model 6 13 Respiration Pump. Respiratory rate was set at 16 - 20 per minute and the tidal volume was established for each dog during the first exposure to provide a PaCO₂ of < 40 ton and maintain the pH of arterial blood at 7.4.

Variables Observed or Measured

Anesthesia: Anesthetic depth was evaluated throughout anesthesia. Anesthetic induction and recovery times were recorded.

Physiological: Clinical observations were performed daily before and after anesthesia. Food and water consumption were observed, and body weight was measured daily. Appearance of feces was inspected daily.

During the first and last exposures, direct femoral blood pressure was measured at 15 minute intervals. Femoral arterial blood samples were withdrawn at 30 minutes for blood gas analysis (pH, PaO₂, PaCO₂). Electrocardiograms, respiratory rate, electroencephalograms and body temperature were continuously monitored.

Blood samples were drawn for baseline hematology and clinical chemistry, immediately prior to the first exposure, and immediately prior to the tenth anesthesia for hematology and clinical chemistry analysis. Immediately after the first induction, urine samples were drawn via catheter for urinalysis. At the same time, liver biopsy samples were taken for microscopic examination.

RESULTS

Clinical Observations During Anesthesia

Mask induction with sevoflurane produced less struggling and was more rapid than with halothane. Induction was achieved in 5 - 15 minutes with sevoflurane and 15 - 30 minutes with halothane. The anesthetic depth during induction was lighter with sevoflurane than with halothane, and sometimes insufficient to place the endotracheal tube at the first attempt. Apnea was not observed with either agent.

Respiration was depressed to a greater extent by sevoflurane (3 to 28 respirations/minute) than by halothane (4 to 54 respirations/minute). Mean rectal temperatures decreased throughout surgery.

No adverse reactions were observed during anesthesia, and the animals' response to induction did not change with the number of anesthetic episodes. No significant changes were observed in the ECG patterns. Bradycardia requiring treatment with atropine (< 70 beats per minute) occurred more frequently in the halothane group than in the sevoflurane group. Blood pressure measured on the first and tenth exposure days were within normal limits with both anesthetic agents.

Cardiac Sensitization Potential

All dogs anesthetized with halothane developed ventricular fibrillation at doses of 4 to 32 mcg/kg epinephrine. None of the dogs receiving sevoflurane developed ventricular fibrillation; however, 5 of 8 dogs developed runs of premature ventricular contractions at epinephrine doses of 2 to 32 mcg/kg. The numerical scores for cardiac sensitization potential were 27.1 (ranging from 16 to 40) for halothane and 7.25 (ranging from 0 to 43)

for sevoflurane. In the study, sevoflurane was less likely to sensitize the heart to ventricular arrhythmias subsequent to the administration of epinephrine compared to halothane.

Clinical Pathology

No changes of clinical significance in hematology or serum chemistry were identified. Transient elevations in ALP were noted in some dogs of both treatment groups and mild vacuolization of liver parenchymal cells were found during necropsy. It is probable that changes in ALP were due to the administration of the anesthetics. No differences in clinical pathology were observed with respect to controlled versus spontaneous respiration. No changes associated with sevoflurane treatment were observed in urinalysis or gross necropsy.

Compound A:

Under worst-case exposure conditions known to be associated with the production of Compound A (low flow rate, high moisture and temperature in the presence of soda lime), toxicity to the kidney was not observed after a total of 30 hours of sevoflurane exposure. In rats, the toxicity is characterized by necrosis of the convoluted tubule and tubular epithelial hyperplasia. Sevoflurane treated dogs exhibited no evidence of degenerative or hyperplastic changes in the tubular elements of the kidney.

CONCLUSION:

Sevoflurane caused anesthetic effects similar to other halogenated anesthetic agents when healthy dogs were exposed for 3 hours/day, 5 days/week for 2 weeks for a total of 30 hours. No serious adverse reactions were observed during the study.

B. Acute Toxicity Study

STUDY PERSONNEL

Study Investigators

E.B. Thompson

F.T. Galysh

B. Abbink

R. Romero

W.E. Williams

B. Haszar

Travenol Laboratories

Morton Grove, IL

STUDY DATES Final report dated 1969

STUDY OBJECTIVE

To examine the effects of sevoflurane and halothane at various concentrations on arterial blood pressure (BP) and spontaneous heart rate (HR) in dogs.

Phase I:

Twenty-three healthy adult mongrel dogs were divided into four groups and anesthetized twice (once with halothane and once with sevoflurane) for one hour using a closed system at the following doses:

| Sevoflurane | Halothane | No. dogs |
|-------------|-----------|----------|
| 2% | 1% | 6 |
| 4% | 2% | 6 |
| 6% | 3% | 6 |
| 8% | 4% | 5 |

Results:

Four dogs died of excessive respiratory depression during anesthesia:

| Anesthetic | No. of Dogs | Dose | Time of Death |
|-------------|-------------|------|----------------------------|
| halothane | 1 (of 5) | 4% | 45 min after exposure |
| sevoflurane | 3 (of 5) | 8% | 20 min 40 min 60 min |

Phase II:

An additional investigation followed using four dogs that received higher doses:

| Anesthetic | No. Dogs | Dose |
|-------------|----------|------|
| halothane | 1 | 4% |
| sevoflurane | 1 | 6% |
| sevoflurane | 2 | 8% |

Results:

- Dog #1: Halothane 4%: This dog survived (recovery time 20 minutes). No evidence of respiratory acidosis and no long term adverse reactions due to anesthesia.
- Dog #2: Sevoflurane 6%: This dog survived with no long term anesthetic adverse reactions. Mild respiratory acidosis occurred during anesthesia; recovery time 6 minutes.
- Dog #3: Sevoflurane 8%: This dog died at 53 minutes from severe respiratory acidosis.
- Dog #4: Sevoflurane 8%: This dog made a sluggish recovery after 20 minutes. Neurological signs were noted 8 - 12 hours after recovery (ataxia, loss of righting reflex, clonic convulsions, unilateral miotic pupil, dilated retinal vessels). Death occurred 18 hours after anesthesia. Necropsy findings were unremarkable.

CONCLUSION:

The study indicates that dogs can survive one hour exposures up to 6% sevoflurane (proposed label maintenance dose is up to 4.0%). Acute death during anesthesia is due to respiratory depression and acidosis.

C. Liver Toxicity Study

STUDY PERSONNEL

Study Investigator

R. Nagata

Shin Nippon Biomedical Laboratories

243 8 Miyanoura

Yoshida, Kogoshima 89 1- 13, Japan

STUDY DATES August 25 - October 6, 1989

STUDY OBJECTIVE

The purpose of this study was to determine the hepatotoxic potential of sevoflurane exposure in dogs.

STUDY DESIGN

Dogs (four/group) were acclimated to the testing facility and randomized into three (3) groups for treatment with sevoflurane, halothane or enflurane. Animals were exposed to 1.8 MAC sevoflurane (4.2%), halothane (1.6%) or enflurane (3.7%) for 1 hour. Physiological parameters and clinical pathology were evaluated.

MATERIALS AND METHODS

Animals

| | |
|----------------|--------------|
| <u>Number:</u> | 12 |
| <u>Breed*:</u> | Beagles |
| <u>Age:</u> | 7- 10 months |
| <u>Weight:</u> | 8.9-10.7 kg |
| <u>Sex:</u> | Males |

Anesthetic Procedure

Sevoflurane was administered by face mask using a vaporizer for small animals at a flow rate of 5 L/minute. The dogs were artificially ventilated at 12 breaths per minute.

Variables Measured or Observed

Anesthetic: Anesthetic concentrations were analyzed by gas chromatography.

Anesthesia: Recovery times were recorded.

Physiological: Observations were made frequently during the exposure period, then at 12 hours and daily for 3 days post-exposure. Diastolic and systolic blood pressures were measured immediately before and 30 minutes after the initiation of treatment, at the cessation of dosing and 1, 2 and 3 hours post-exposure. Blood samples were drawn immediately prior to and after dosing, and 3, 6, 8, 10, 12, 24, 48 and 72 hours after dosing for hematology and blood chemistry analysis. At 72 hours after dosing, the animals were sacrificed and a gross pathological examination conducted. Liver weights were measured and liver samples examined for microscopic pathology.

RESULTS

No signs of toxicity were observed during the exposure period or the 72 hour observation period. Average recovery times in minutes were 9.5 (ranging from 4 - 18 minutes), 20.3 (10 - 35 minutes) and 59.8 (10 minutes - 3 hours) for sevoflurane, enflurane and halothane, respectively. Decreased blood pressure was observed following treatment with all three agents, the mean pressure being reduced by 48.9, 50.7 and 3 1.7% in sevoflurane, enflurane and halothane groups, respectively at 30 minutes post-exposure.

Hematological changes were limited to a decrease in Hb, PCV and RBC's at the cessation of dosing, which was reversed by 6 hours after dosing. Also, there was a decrease in white blood cells noted with all three agents at the cessation of dosing. Increases in white blood cells were observed at the 8, 10, 12 and 24 hour intervals with sevoflurane, and at the 6 hour interval with enflurane and halothane. The decreases were believed to be associated with an increase in blood plasma (dilution effect) in connection with the decrease in blood pressure (renin/angiotensin/aldosterone system). Since blood cell counts had returned to baseline values by the 72 hour interval, they were not thought to be associated with toxicity.

Changes in several biochemical markers associated with hepatic toxicity were observed following treatment with all three agents (AST, ALT, LDH, ALP, bilirubin). In general the changes were slight and most were reversible (except ALP) within 48 - 72 hours. Effects on liver enzymes were comparable among the three anesthetics, and no toxicological changes unique to sevoflurane were identified.

Liver weights showed no differences among treatment groups; the mean for sevoflurane was greater than that for halothane or enflurane. No significant treatment related changes were observed at necropsy.

CONCLUSION:

No toxicological changes unique to sevoflurane were identified.

D. Sevoflurane Fluoride Toxicity Study in Dogs

STUDY PERSONNEL

Study Investigators

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S. Lynch

M. D. Napoli

E. F. Woods

Travenol Laboratories

Morton Grove, IL

STUDY DATES Final report completed February 10, 1978

STUDY OBJECTIVE

The purpose of this study was to evaluate sevoflurane metabolism, including fluoride ion production and elimination, during maintenance anesthesia in dogs.

STUDY DESIGN

Four mongrel dogs (3 males, 1 female) were exposed (face mask) for 3 hours to 3% sevoflurane. Twenty-four hour samples of blood, urine and feces were taken at 1, 2, 7 or 8 and 14 or 15 days post-anesthesia. The entire experiment was then repeated, with animals exposed to 4% sevoflurane. Sampling continued for 7 days post-anesthesia. One month after anesthesia with 4% sevoflurane, animals were sacrificed and subjected to gross necropsy. Tissues were retained for microscopic evaluation. Clinical chemistry and hematology data were evaluated; however, the interpretation of this information is limited based on the small number of animals.

MATERIALS AND METHODS

Animals

Number: 4

Breed: Mongrel

Weight: 12-16 kg

Sex: 3 males and 1 female

Anesthetic Procedures

Animals were exposed for 3 hours to 3% and 4% sevoflurane in oxygen via a face mask in an open system without soda lime at a flow rate of 500 ml/minute.

Variables Measured or Observed

Anesthetic: Induction and recovery times were recorded.

Physiological: Twenty-four hour samples of blood, urine and feces were taken at 1, 2, 7 or 8 and 14 or 15 days post-anesthesia. Blood samples were subjected to hematology, clinical chemistry and inorganic fluoride determination; urine and feces were collected at baseline and were analyzed for inorganic fluoride. Respiration rate, heart rate, and arterial blood pressure were measured throughout the anesthetic period. Blood samples for pCO₂, pO₂, pH and PCV as well as urine samples for inorganic fluoride (from sevoflurane metabolites HFIP and HFIP glucuronide) determinations were also taken throughout anesthesia.

RESULTS

Clinical/Toxicological Evaluations

Surgical anesthesia was achieved within 4 - 7 minutes. Recoveries were uneventful and occurred within 3 - 9 minutes. Heart rate and respiration rate were generally similar in animals anesthetized with either 3% or 4% sevoflurane.

No changes in hematologic and clinical chemistry which could be attributed to sevoflurane were observed. Two dogs exhibited high CPK values at 24 and 48 hours post-anesthesia, however, these values returned to normal at seven days post-treatment. No treatment-related changes were observed in tissues.

Metabolism Evaluations

Elimination of sevoflurane from all four dogs was essentially complete within 24 hours of anesthesia. Pulmonary desaturation data from one dog indicated that approximately 45% of the absorbed sevoflurane dose was eliminated through the lungs within two hours after anesthesia, confirming that most of the anesthetic dose is rapidly cleared through the lungs.

The inorganic fluoride concentrations in the serum of the dogs anesthetized with sevoflurane were significantly increased relative to pre-exposure concentrations.

Fluoride ion concentrations are influenced by the duration of anesthesia and the concentration of sevoflurane.

During anesthesia with 4% sevoflurane, mean inorganic fluoride concentration increased during the anesthetic period to a maximum of 20.0 ± 4.8 $\mu\text{mole/L}$ at 3 hours. The mean serum inorganic fluoride concentration fell to 11.5 ± 4.8 $\mu\text{mole/L}$ by 1.3 hours into the post anesthetic period and had returned to normal values by 24 hours after anesthesia. The serum inorganic fluoride concentration following 3 hours of exposure to 3% sevoflurane was 18.5 $\mu\text{mole/L}$. These serum fluoride levels were not associated with renal toxicity in the four dogs.

The urinary excretion of inorganic fluoride by the dogs was also significantly increased following sevoflurane exposure. By 48 hours, the inorganic fluoride excretion rate had returned to the pre-exposure level. There was no increase in the fecal fluoride excretion following exposure of the dogs to sevoflurane.

A metabolite of sevoflurane, HFIP, was found in the urine of treated animals as a glucuronide conjugate, averaging 36 - 56 $\mu\text{moles/hr}$ during exposure and declining rapidly. Based on the urinary excretion data for HFIP glucuronide following exposure to 4% sevoflurane, this represents approximately 2.5% of the total sevoflurane uptake. Considering that a significant portion of the inorganic fluoride is retained in bone, the urinary excretion data suggest that HFIP would account for a major portion of the metabolism of sevoflurane in the dog. The elimination of the metabolite was essentially complete by 48 hours after exposure to sevoflurane.

CONCLUSION:

Most of the sevoflurane anesthetic dose is rapidly cleared through the lungs. Inorganic fluoride concentrations in the serum of the dogs anesthetized with sevoflurane significantly increased relative to pre-exposure concentrations. The elimination of the metabolite was essentially complete by 48 hours after exposure to sevoflurane. Serum fluoride levels were not associated with renal toxicity.

6. HUMAN SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is labeled for use in dogs which are non-food animals.

Labeling contains adequate cautions to provide adequate ventilation in the operating rooms and animal recovery areas in order to prevent the accumulation of anesthetic vapors. An "800" number is provided by the sponsor for the provision of Material Safety Data Sheets (MSDS).

7. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 5 12 of the Federal Food, Drug, and Cosmetic Act and Section 5 14.111 of the implementing regulations. It demonstrates that **SevoFlo™** (sevoflurane) Inhalation Anesthetic, when used under labeled conditions of use in dogs, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical in the administration of a drug that provides induction and maintenance of general anesthesia.

Under Section 5 12(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this original approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

8. REFERENCES

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Martis, L., Lynch, S., Napoli, M.D. and Woods, E.F. Biotransformation of Sevoflurane in dogs and rats. *Anesthesia and Analgesia* 60: 186- 19 1, 198 1.

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Steffey, E.P. and Howland D. Isoflurane Potency in the Dog and Cat. *Am. J. Vet. Research* 37(2): 127-131, 1977.

LABELING

Bottle label

Carton label

Package Insert

N141103 E0002
OK approval

| Proof A B C D E F (J) | |
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| CAPD ART Prepared by HPD Graphics Studio | |
| LIST NO. | 5458-04-01 |
| COMM. NO. | 58-1537 version b |
| LABEL EDITOR | Naue |
| DATE PREPARED | 8/2/99 |
| DRAWING NUMBER | DB5706-03 |
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|  | Abbott 293 |
|  | Black |



Store at room temperature
15° to 30°C (59° to 86°F).

IMPORTANT: Read
accompanying product
information for directions
pertaining to use of
SevoFlo™ (sevoflurane).

Contains sevoflurane
250 mL

Caution: Operating rooms
and animal recovery areas
should be provided with
adequate ventilation to
prevent the accumulation of
anesthetic vapors.

List 5458-04-01


SevoFlo™
sevoflurane

**Nonflammable, Nonexplosive
Inhalation Anesthetic
250 mL**

For Use in Dogs
Caution: Federal law restricts this drug to use by or
on the order of a licensed veterinarian.

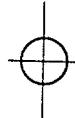
SevoFlo™ is a trademark of Abbott
Laboratories.

NADA No. 141-103, Approved by FDA

Manufactured by:
 Abbott Laboratories
North Chicago, IL 60064, USA

Under license from
Maruishi Pharmaceutical Co., LTD
2-3-5, Fushimi-Machi, Chuo-Ku,
Osaka, Japan

58-1537-2/R1



Sevoflurane is nonflammable and nonexplosive as defined by the requirements of International Electrotechnical Commission 601-2-13

Sevoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water. Sevoflurane is stable when stored under normal room lighting condition according to instructions.

HOW SUPPLIED:

SevoFlo™ (sevoflurane) is packaged in amber colored bottles containing 250 mL sevoflurane, List 5458, NDC # 0074-5458-02.

STORAGE CONDITIONS:

Store at room temperature 15°C-30°C (59°F-86°F).

INDICATIONS:

SevoFlo™ is indicated for induction and maintenance of general anesthesia in dogs.

DOSE AND ADMINISTRATION:

Inspired Concentration: The delivered concentration of SevoFlo™ should be known since the depth of anesthesia may be altered easily and rapidly, only vaporizers producing predictable percentage concentrations of sevoflurane should be used. Sevoflurane should be vaporized using a precision vaporizer specifically calibrated for sevoflurane. Sevoflurane contains no stabilizer. Nothing in the drug product alters calibration or operation of these vaporizers. The administration of general anesthesia must be individualized based on the patient's response.

Premedication: No specific premedication is either indicated or contraindicated with sevoflurane. The necessity for and choice of premedication is left to the discretion of the veterinarian. Preanesthetic doses for premedicants may be lower than the label directions for their use as a single medication.¹

Induction: For 135% induction using sevoflurane, inspired concentrations of 5 to 7% sevoflurane alone with oxygen are employed to induce surgical anesthesia in the healthy dog. These concentrations can be expected to produce surgical anesthesia in 3 to 14 minutes. The use of premedicants does not affect the concentration of sevoflurane required for induction.

Maintenance: SevoFlo™ may be used for maintenance anesthesia following mask induction using sevoflurane or

following injectable induction agents. The concentration of vapor necessary to maintain anesthesia is much less than that required to induce it.

Surgical levels of anesthesia in the healthy dog may be maintained with inhaled concentrations of 3.7-4.0% sevoflurane in oxygen in the absence of premedication and 3.3-3.6% in the presence of premedication. The use of injectable induction agents without premedication has little effect on the concentrations of sevoflurane required for maintenance. Anesthetic regimens that include opioid, alpha-2 agonist, benzodiazepine or phenothiazine premedication will allow the use of lower sevoflurane maintenance concentrations.

CONTRAINDICATIONS:

SevoFlo™ is contraindicated in dogs with a known sensitivity to sevoflurane or other halogenated agents.

WARNINGS:

Sevoflurane is a profound respiratory depressant. **RESPIRATION MUST BE MONITORED CLOSELY IN THE DOG AND SUPPORTED WHEN NECESSARY WITH SUPPLEMENTAL OXYGEN AND/OR ASSISTED VENTILATION.**

In cases of severe cardiopulmonary depression, discontinue drug administration, ensure the existence of a patent airway and initiate assisted or controlled ventilation with pure oxygen. Cardiovascular depression should be treated with plasma expanders, pressor agents, antiarrhythmic agents or other techniques as appropriate for the observed abnormality.

Due to sevoflurane's low solubility in blood, increasing the concentration may result in rapid hemodynamic changes (dose dependent decreases in blood pressure) compared to other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be corrected by decreasing or discontinuing the inspired concentration of sevoflurane.

ADVERSE REACTIONS:

The most frequently reported adverse reactions during maintenance anesthesia were hypotension, followed by tachypnea, muscle tenseness, excitation, apnea, muscle fasciculations and emesis.

Inrequent adverse reactions include paddling, retching, salivation, cyanosis, premature ventricular contractions and excessive cardiopulmonary depression.

Transient elevations in liver function tests and white blood cell count may occur with sevoflurane, as with the use of other halogenated anesthetic agents.

PRECAUTIONS:

Halogenated volatile anesthetics can react with desiccated carbon dioxide (CO₂) absorbents to produce carbon monoxide (CO) that may result in elevated carboxyhemoglobin levels in some patients. To prevent this reaction, sevoflurane should not be passed through desiccated soda lime or barium hydroxide lime.

The use of some anesthetic regimens that include sevoflurane may result in bradycardia that is reversible with anticholinergics. Studies using sevoflurane anesthetic regimens that included atropine or glycopyrrolate as premedicants showed these anticholinergics to be compatible with sevoflurane in dogs.

During the maintenance of anesthesia, increasing the concentration of sevoflurane produces dose dependent decreases in blood pressure. Due to sevoflurane's low solubility in blood, these hemodynamic changes may occur more rapidly than with other volatile anesthetics. Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of sevoflurane. The low solubility of sevoflurane also facilitates rapid elimination by the lungs.

The use of sevoflurane in humans increases both the intensity and duration of neuromuscular blockades induced by nondespoliarizing muscle relaxants. The use of sevoflurane with nondespoliarizing muscle relaxants has not been evaluated in dogs.

Compromised or debilitated dogs: Doses may need adjustment for geriatric or debilitated dogs. Because clinical experience in administering sevoflurane to dogs with renal, hepatic and cardiovascular insufficiency is limited, its safety in these dogs has not been established.

Breeding dogs: The safety of sevoflurane in dogs used for breeding purposes, during pregnancy, or in lactating bitches, has not been evaluated.

Neonates: The safety of sevoflurane in young dogs (less than 12 weeks of age) has not been evaluated.

HUMAN SAFETY:

Not for human use. Keep out of reach of children.

Caution: Operating rooms and animal recovery areas should be provided with adequate ventilation to prevent the accumulation of anesthetic vapors.

There is no specific work exposure limit established for sevoflurane. However, the National Institute for Occupational Safety and Health has recommended an 8 hour time-weighted average limit of 2 ppm for halogenated anesthetic agents in general.

Direct exposure to eyes may result in mild irritation. If eye exposure occurs, flush with plenty of water for 15 minutes. Seek medical attention if irritation persists.

Symptoms of human overexposure (inhalation) to sevoflurane vapors include respiratory depression, hypotension, bradycardia, shivering, nausea and headache. If these symptoms occur, remove the individual from the source of exposure and seek medical attention.

The material safety data sheet (MSDS) contains more detailed occupational safety information. For customer service, adverse effects reporting, and/or a copy of the MSDS, call (800) 323-9997.

CLINICAL PHARMACOLOGY:

Sevoflurane is an inhalational anesthetic agent for induction and maintenance of general anesthesia. The Minimum Alveolar Concentration (MAC) of sevoflurane as determined in 18 dogs is 2.36%.² MAC is defined as that alveolar concentration at which 50% of healthy patients fail to respond to noxious stimuli. Multiples of MAC are used as a guide for surgical levels of anesthesia, which are typically 1.3 to 1.5 times the MAC value.

Because of the low solubility of sevoflurane in blood (blood/gas partition coefficient at 31°C = 0.63-0.69), a minimal amount of sevoflurane is required to be dissolved in the blood before the alveolar partial pressure is in equilibrium with the arterial partial pressure. During sevoflurane induction, there is a rapid increase in alveolar concentration toward the inspired concentration.

Sevoflurane produces only modest increases in cerebral blood flow and metabolic rate, and has little or no ability to potentiate seizures.³ Sevoflurane has a variable effect on heart rate, producing increases or decreases depending on experimental conditions.^{4,5} Sevoflurane produces dose-dependent decreases in mean arterial pressure, cardiac output and myocardial contraction.⁶ Among inhalation anesthetics, sevoflurane has low arrhythmogenic potential.⁷

Sevoflurane is chemically stable. No discernible occurs in the presence of strong acids or heat. Sevoflurane through direct contact with CO₂ absorbents (soda lime hydroxide lime) producing pentafluoroisopropyl ether (PFIE, C₃H₇F₅O), also known as Compound A. Amounts of pentafluoromethoxy isopropyl ether (PFME, C₃H₇F₅O), also known as Compound B.

Compound A:

The production of degradants in the anesthesia circuit (KOH and/or NaOH) forming an alkene (Compound A) and/or an alkene (Compound B).

Compound A is produced when sevoflurane interacts with barium hydroxide lime. Reaction with barium results in a greater production of Compound A reaction with soda lime. Its concentration in a circuit increases with increasing sevoflurane concentration and decreasing fresh gas flow rates. Sevoflurane soda lime has been shown to increase with temperature reaction of carbon dioxide with absorbents (e.g. temperature increase will be determined by the amount absorbed, which in turn will depend on fresh gas flow rate, anesthetic circuit system, metabolic status of the patient). Although Compound A is a dose-dependent nephrotoxin in rats, the mechanism of this is unknown. Two spontaneously breathing dogs under anesthesia showed increases in concentrations of Compound A when the oxygen flow rate was decreased at hourly 750 mL/min (36 and 18 ppm Compound A) to 250 mL/min (31 ppm) to 50 mL/min (61 and 48 ppm).⁸

Fluoride ion metabolism:

Sevoflurane is metabolized to hexafluoroisopropyl fluoride and inorganic fluoride and CO₂. Fluoride ion release is influenced by the duration of anesthesia and the amount of sevoflurane. Once formed, HFIP is rapidly excreted as glucuronic acid and eliminated as a urinary metabolite. The fluoride ion half-life was prolonged if renal impairment, but human clinical trials contain toxicity associated with elevated fluoride ion level which a dogs were exposed to 4% sevoflurane maximum serum fluoride concentrations of 17.0.

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List No. 5458-04-01

Contains sevoflurane 250 mL

IMPORTANT: Read accompanying product information for directions pertaining to use of SevoFlo™ (sevoflurane).

List No. 5458-04-01



Store at room temperature 15° to 30° (59° to 86°F).

Caution: Operating rooms and animal recovery areas should be provided with adequate ventilation to prevent the accumulation of anesthetic vapors.

Nonflammable,
Nonexplosive Inhalation
Anesthetic

NADA 141-103, Approved by FDA

250 mL

For Use in Dogs

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

SevoFlo™ is a trademark of Abbott laboratories.

Manufactured by:
Abbott Laboratories
North Chicago, IL 60064, USA

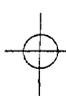
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