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Comparison of MAC and the Rate of Rise of Alveolar Concentration of Sevoflurane with Halothane and Isoflurane in the Dog

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The anesthetic requirements for sevoflurane, isoflurane, and halothane were determined in mongrel dogs. The MACs (minimum alveolar concentration) of sevoflurane, isoflurane, and halothane were 2.36 ± 0.46% (n = 18), 1.39 ± 0.25% (n = 10), and 0.89 ± 0.20% (n = 12), respectively (mean ± SD). In agreement with sevoflurane's low blood/gas partition coefficient (0.6), the rate of rise of alveolar concentration toward that inspired (F_A/F_I) for sevoflurane was significantly faster than that for either halothane or isoflurane. Thirty seconds after breathing a constant inspired concentration F_A/F_I was 0.75 for sevoflurane, which was 2.96 times higher than that with halothane (0.25 ± 0.02) and 1.29 times higher than that with isoflurane (0.6 ± 0.05). Induction with sevoflurane was smooth, with no struggling nor excessive salivation. (Key words: Anesthetics, volatile: halothane; isoflurane; sevoflurane. Pharmacokinetics: F_A/F_I ratio; induction time. Pharmacology: minimum alveolar concentration.)

SEVOFLURANE (CH_2F-O-$CH(CF_3)_2$), fluoromethyl-1,1,1,3,3,3-hexafluoro-2-propyl ether) is a promising new, nonflammable inhalational anesthetic agent. Induction and emergence from anesthesia are very rapid, as a consequence of low blood solubility (blood-gas partition coefficient 0.6 ± 0.07).[1-3] The present studies were conducted to determine the respective anesthetic requirements of sevoflurane, isoflurane, and halothane in dogs, and to determine the rate of rise of the alveolar concentration when a constant inspired concentration of these anesthetics was breathed.

Materials and Methods

MAC

Forty unmedicated mongrel dogs (7.5–15.0 kg) were studied to determine MAC (minimum alveolar concentration) values. Anesthesia was induced, respectively, with 5% sevoflurane, 4% isoflurane, or 4% halothane in oxygen, using a standard dog mask or a sealed exposure chamber (about 600 l). After induction, the tracheas were intubated with cuffed endotracheal tubes without using any other drugs. End-tidal carbon dioxide was maintained at 30–35 mmHg measured with a Datex® end-tidal CO_2 monitor. Ventilation was controlled using a piston ventilator with a non-rebreathing valve (Harvard® pump equipped with a reservoir bag on the intake to ensure constant flow through the vaporizer). Arterial blood samples were obtained from femoral arteries prior to tail clamping. The end-tidal anesthetic concentration was measured with the Engstrom® gas analyzer (EMMA®), calibrated using a mass spectrometer, which in turn was previously calibrated with tanks containing a known concentration of sevoflurane. A heat and moisture exchanger (Engstrom® humidifier, modified to decrease the volume) was added between the analyzer transducer and the endotracheal tube to avoid the effect of humidity on the transducer. Before each measurement of anesthetic concentration, the heat and moisture exchanger was replaced with a fresh one. Rectal temperature was continuously monitored and was maintained at 36.5–38.0° C using heated blankets. MAC values for the three anesthetics were determined according to previously established technique.[4] The predetermined end-tidal anesthetic concentration was held constant for 20–40 min. A positive response to tail clamping was considered to be gross purposeful muscular movement, usually of the head or extremities. Head movements did not include a twitch or grimace, but only a jerking or twisting motion. Coughing, swallowing, or chewing were not considered positive. The concentration midway between the highest concentration which allowed and the lowest which prevented movements was determined as 1.0 MAC for that dog.

The Rate of Rise of End-Tidal Anesthetic Concentration

The rate of rise of end-tidal anesthetic concentration toward the inspired anesthetic concentration (F_A/F_I) was determined in dogs during controlled ventilation. In 12 unmedicated mongrel dogs (7.5–14.0 kg), anesthesia was induced with ketamine 5–7 mg/kg iv, and the trachea was intubated after pancuronium 0.2 mg/kg iv. Anesthesia was maintained with ketamine not exceeding 10–20 mg/kg iv, and with pancuronium

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TABLE 1. MAC and Corresponding Blood-gas Values Prior to Tail-clamping (Mean ± SD)

	Sevoflurane N = 18	Isoflurane N = 10	Halothane N = 12
Body weight (kg)	11.1 ± 2.0	10.5 ± 2.8	11.0 ± 2.1
MAC (percent)	2.36 ± 0.46	1.39 ± 0.25	0.89 ± 0.20
Pa_{O_2} (mmHg)	450 ± 98	423 ± 110	415 ± 75
Pa_{CO_2} (mmHg)	34 ± 6	36 ± 7	35 ± 5
*p*Ha	7.43 ± 0.08	7.41 ± 0.06	7.41 ± 0.05
Base excess (mEq/L)	−1.0 ± 0.8	−2.0 ± 0.9	−1.5 ± 0.6

0.3 mg/kg iv. The dogs were mechanically ventilated with oxygen for 20–40 min for stabilization and to set the end-tidal carbon dioxide at 30–35 mmHg. After stabilization, the dogs' airways were connected to a mechanical ventilator and breathing circuit which had been filled with one of the three inhalational anesthetics, sevoflurane, isoflurane, and halothane, at a concentration equal to 1.5 MAC. The expired and inspired anesthetic concentrations were recorded breath by breath for 20 min, at which time the inspired anesthetic concentration was reduced to zero. It took 40–60 min for end-exhaled concentration to decrease to less than 0.05%, at which time a second of the three anesthetics was administered as above. Following elimination of the second anesthetic, the third was administered again at an inspired concentration equal to 1.5 MAC. Tidal volume (150–250 ml) and respiratory rate (10–15 per min) were not changed throughout these measurements. The order in which the three inhalational anesthetics were tested in each dog was randomized. The results were analyzed with Student's *t* test.

Results

Induction with sevoflurane was rapid when 5% sevoflurane was inhaled and the dogs could not remain upright for more than several breaths. MAC values and corresponding blood-gas values are shown in table 1.

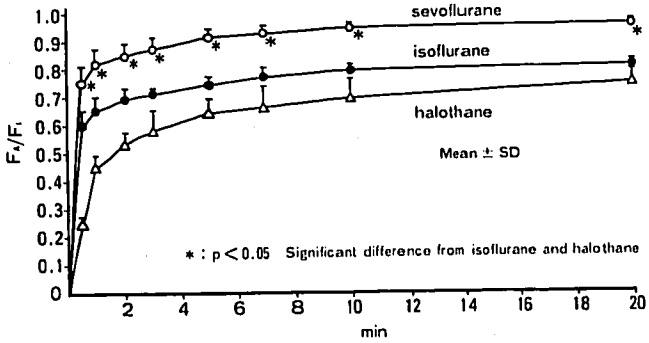

FIG. 1. The rate of rise of F_A/F_I with sevoflurane (open circle) was higher than that with halothane (open triangle) and isoflurane (closed circle), especially in the early stage of induction.

The rates of rise of alveolar concentration toward the inspired concentration for sevoflurane, isoflurane, and halothane are shown in figure 1. The washout time of sevoflurane, isoflurane, and halothane were 48 ± 11, 52 ± 13, and 72 ± 9 min, respectively. The F_A/F_I ratio for sevoflurane already rose 0.75 ± 0.06 at 30 s, compared with 0.60 ± 0.05 for isoflurane and 0.25 ± 0.02 for halothane (fig. 1, table 2).

Discussion

Based on the relationship derived from the equation oil/gas partition coefficient times MAC values equals a constant,[5] we would expect sevoflurane MAC to be approximately four and two times that for halothane and isoflurane, respectively, in contrast to the three and 1.5 times that we found. The reasons for these differences are not readily apparent, although the halothane and isoflurane MAC values are slightly higher than those published by other authors.[6–8]

TABLE 2. The Rate of Rise of End-tidal Anesthetic Concentration Toward that Inspired (F_A/F_I Ratio)

	Time (Min)							
	0.5	1.0	2.0	3.0	5.0	7.0	10	20
Sevoflurane	0.75 ± 0.06	0.82 ± 0.05	0.85 ± 0.04	0.87 ± 0.04	0.91 ± 0.03	0.92 ± 0.03	0.93 ± 0.02	0.94 ± 0.02
Isoflurane	0.60 ± 0.05	0.65 ± 0.05	0.69 ± 0.04	0.71 ± 0.04	0.73 ± 0.05	0.76 ± 0.04	0.78 ± 0.03	0.79 ± 0.03
Halothane	0.25 ± 0.02	0.45 ± 0.04	0.50 ± 0.04	0.58 ± 0.05	0.64 ± 0.04	0.66 ± 0.05	0.69 ± 0.05	0.74 ± 0.03
$\frac{F_A/F_I \text{ sevo}}{F_A/F_I \text{ isof}}$	1.29 ± 0.11	1.26 ± 0.10	1.20 ± 0.11	1.22 ± 0.07	1.23 ± 0.05	1.19 ± 0.06	1.19 ± 0.06	1.19 ± 0.05
$\frac{F_A/F_I \text{ sevo}}{F_A/F_I \text{ halo}}$	2.96 ± 0.38	1.83 ± 0.14	1.59 ± 0.08	1.51 ± 1.36	1.41 ± 0.08	1.39 ± 0.11	1.35 ± 0.09	1.25 ± 0.07
$\frac{F_A/F_I \text{ isof}}{F_A/F_I \text{ halo}}$	2.45 ± 0.35	1.46 ± 0.15	1.28 ± 0.13	1.24 ± 0.12	1.15 ± 0.08	1.16 ± 0.11	1.13 ± 0.10	1.07 ± 0.06
N	12	12	12	12	12	12	12	12

Mean ± SD.

The blood-gas partition coefficient of 0.59 is lower than that for any of the commonly used volatile anesthetics, and should result in rapid rate of rise of alveolar concentration toward that inspired, as was shown in these studies. The rate of rise of F_A/F_I with sevoflurane was higher than that with halothane and isoflurane, especially in the early stage of induction. We conclude that sevoflurane possesses desirable physical characteristics associated with both a sufficiently high anesthetic potency and a rapid rate of induction of anesthesia, which warrant further investigation of this anesthetic.

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References

1. Cook TL, Beppu J, Hitt BA, Kosek JC, Mazze RI: A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats. Anesth Analg 54:829–835, 1975
2. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI: Renal effects and metabolism of sevoflurane in Fischer 344 rats. ANESTHESIOLOGY 43:70–77, 1975
3. Wallin RF, Regan BM, Napoli MD, Stern IJ: Sevoflurane: A new inhalational anesthetic agent. Anesth Analg 54:758–766, 1975
4. Eger EI II, Saidman LJ, Brandstater B: Minimum alveolar anesthetic concentration: A standard of anesthetic potency. ANESTHESIOLOGY 26:756–763, 1965
5. Steward A, Allott PR, Cowles AL, Mapleson WW: Solubility coefficients for inhaled anesthetics for water, oil and biological media. Br J Anaesth 45:282–293, 1973
6. Eger EI II, Saidman LJ, Brandstater B: Temperature dependence of halothane and cyclopropane anesthesia in dogs: Correlation with some theories of anesthetic action. ANESTHESIOLOGY 26:764–770, 1965
7. Regan MF, Eger EI II: Effect of hypothermia in dogs on anesthetizing and apneic doses of inhalation agents. Determination of the anesthetic index (apnea/MAC). ANESTHESIOLOGY 28:689–700, 1967
8. Steffey EP, Howland D: Isoflurane potency in the dog and cat. Am J Vet Res 38:1833–1836, 1977