

## Minimum Alveolar Concentrations (MAC) of Halothane, Enflurane, and Isoflurane in Ferrets

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The minimum alveolar concentrations (MAC) of isoflurane, enflurane, and halothane were determined in adult male ferrets during controlled ventilation at normothermia (37° C). Mean ( $\pm$ SD) MAC values for isoflurane (n = 8), enflurane (n = 8), and halothane (n = 8) at 37° C were  $1.52 \pm 0.10\%$ ,  $1.99 \pm 0.18\%$ , and  $1.01 \pm 0.10\%$ , respectively. Halothane MAC was reduced by 26% in the presence of 70% N<sub>2</sub>O. At  $29.9 \pm 0.2^\circ$  C, the mean MAC value of halothane ( $0.85 \pm 0.11\%$ ) was 16% less than MAC at 37° C. The relative potencies of the halogenated anesthetics are of the same order as those reported for large animals and for humans. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane; nitrous oxide. Ferret. Potency: MAC. Temperature: hypothermia.)

THE FERRET HAS BECOME widely used as an experimental laboratory animal, especially for studies of cardiac physiology and pharmacology.<sup>1-4</sup> To validly compare influences of anesthetic agents at equipotent anesthetic concentrations on isolated cardiac muscle of a given species, one needs to know the minimum alveolar concentrations (MAC) of these anesthetics in that species. Since there is no information available on the relative anesthetic potency and MAC values of various anesthetic agents in the ferret, this study was undertaken to determine the MAC of halothane, enflurane, and isoflurane in ferrets. In addition, we determined the reduction in halothane MAC caused by the addition of 70% nitrous oxide.

### Materials and Methods

Each of eight adult (16-19 weeks of age) male ferrets (weighing 1,000-1,200 g) was anesthetized with isoflu-

rane in 100% oxygen in a transparent lucite box. The trachea was intubated with a cuffed endotracheal tube (3 mm ID), and the animals were ventilated with a Harvard controlled ventilator with 100% oxygen. Both tidal volume and respiratory rate were adjusted to maintain end-tidal CO<sub>2</sub> partial pressures within 22.5-37.5 mmHg. The right internal jugular vein and external carotid artery were cannulated by cutdown. Lactated Ringer's solution was continuously infused at a rate of  $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  via the venous catheter. Arterial blood pressure was continuously monitored by a Gould transducer and recorded on a Grass polygraph (model 78B). End-tidal concentrations of the anesthetics were measured intermittently with a mass spectrometer (Perkin-Elmer model 1100). The mass spectrometer was calibrated with the following gravimetrically prepared standards ( $\pm 0.02\%$ ): 10% CO<sub>2</sub>-90% O<sub>2</sub>, 50% N<sub>2</sub>O-50% O<sub>2</sub>, 1% halothane in N<sub>2</sub>, 1% isoflurane in N<sub>2</sub>, 1% enflurane in N<sub>2</sub> (Scott Medical Products, Plumstead, PA). Gas samples were obtained intermittently from a side port at the proximal end of the endotracheal tube. Because the rate of controlled ventilation was less than 25 per minute at the time of sampling, the results displayed by the mass spectrometer were considered to accurately reflect the true end-tidal concentration of each anesthetic agent. End-tidal anesthetic concentrations detected with the mass spectrometer were identical over a range of respiratory frequencies of 10-25/minute. Rectal and esophageal temperatures were continuously monitored and maintained between 36.5 and 37.5° C by means of a heating blanket and/or cooling devices. When the MAC for each agent was determined, 2 ml of blood were collected from the arterial catheter to measure: pH, PaO<sub>2</sub>, PaCO<sub>2</sub> (ILS 1303), hemoglobin concentration, arterial oxygen saturation (CO-oximeter ILS 282), and the concentration of halothane, enflurane, or isoflurane in arterial blood by gas chromatography (Hewlett Packard 5880A).<sup>5</sup> The blood gas apparatus and the CO-oximeter were calibrated for use with ferret blood. Reported arterial gas tensions and pH were not corrected for temperature when samples had been obtained at 30° C. The gas chromatograph was cali-

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TABLE 1. Mean ( $\pm$ SD) Values of Temperatures and MAC

|                                   | n | Temperature    | MAC             |
|-----------------------------------|---|----------------|-----------------|
| Isoflurane                        | 8 | 37.0 $\pm$ 0.3 | 1.52 $\pm$ 0.10 |
| Enflurane                         | 8 | 37.1 $\pm$ 0.4 | 1.99 $\pm$ 0.18 |
| Halothane                         | 8 | 37.2 $\pm$ 0.3 | 1.01 $\pm$ 0.10 |
| Halothane in 70% N <sub>2</sub> O | 8 | 36.9 $\pm$ 0.4 | 0.75 $\pm$ 0.11 |
| Halothane                         | 8 | 29.9 $\pm$ 0.2 | 0.85 $\pm$ 0.11 |

brated daily against known standards of isoflurane, enflurane, and halothane (10 ppm in hexane).

MAC was determined in a manner similar to that described by Eger *et al.*<sup>6</sup> We determined MAC of isoflurane, enflurane, and halothane in each of the eight ferrets in order of increasing blood solubility to allow for fast elimination of isoflurane and enflurane, respectively. The final protocol which was identical for the eight ferrets was, therefore: MAC of isoflurane, enflurane, halothane, and N<sub>2</sub>O (all at 37° C), and of halothane at 30° C, in that order.

After determination of isoflurane MAC, isoflurane was discontinued, and enflurane was administered. Isoflurane was barely (0.043  $\pm$  0.007%) and not (<0.03%) detectable in end-tidal gas, respectively, 55.0  $\pm$  29.2 min and 83.9  $\pm$  32.2 min after it was discontinued (all values mean  $\pm$  SD). The interval between the determination of isoflurane and enflurane MAC was 97.0  $\pm$  24.4 min. Following determination of enflurane MAC, enflurane was discontinued, and halothane was administered. Enflurane was barely (0.063  $\pm$  0.014%) and not (<0.05%) detectable in end-tidal gas, respectively, 63.3  $\pm$  28.1 min and 79.9  $\pm$  29.8 min after it was discontinued. The interval between the determination of enflurane and halothane MAC was 89.0  $\pm$  24.1 min. At the time of determination of enflurane MAC, no isoflurane was detected in blood; at the time of halothane MAC determination, neither enflurane nor isoflurane were detected in blood by gas chromatography. For the determination of MAC itself, the response to a standard supramaximal stimulus, the tail clamp,<sup>7</sup> was examined in a steady-state anesthetic concentration. For that purpose, a full-length 6-inch hemostat was applied close to the base of the tail and clamped to the first ratchet position for 20 s. The site of the clamp was changed to avoid producing local damage and potentially changing sensitivity of the tail. Gross purposeful muscular movements of the body or extremities were considered a positive response to the stimulus. If the animal moved, the anesthetic concentration was increased by 5–10%. If the animal did not move, the anesthetic concentration was decreased a similar amount.

Each end-tidal concentration was maintained for at least 15 min prior to clamping the tail. In five additional ferrets, we determined MAC of halothane as the first anesthetic, and compared these MAC values with those obtained in the main protocol where exposure to halothane was preceded by exposure to, and elimination of, isoflurane and enflurane.

After obtaining the MAC of the halogenated anesthetics in each of the eight ferrets, the reduction in halothane MAC caused by 70.4  $\pm$  0.4% nitrous oxide was determined.<sup>8</sup> Subsequently, the gas mixture was reverted to 100% O<sub>2</sub>, and halothane MAC at 30° C (n = 8) was determined. Ferrets were cooled externally by means of ice packs surrounding the whole body and head. An esophageal temperature of 29.9  $\pm$  0.2° C was reached in 29.1  $\pm$  4.3 min (mean  $\pm$  SD), and halothane MAC was determined after 54.1  $\pm$  11.3 min, times at which arterial blood gases and blood concentrations of halothane were again determined.

All values are expressed as mean  $\pm$  standard deviations. The protocol was approved by the Institutional Animal Care and Use Committee.

## Results

The values of MAC for halothane (n = 8), isoflurane (n = 8), and enflurane (n = 8), and of halothane in the presence of 70% N<sub>2</sub>O at a rectal temperature of 37° C and at an esophageal temperature of 29.9  $\pm$  0.2° C (n = 8), are displayed in table 1. There were no differences between the temperatures at which MACs were measured among groups at 37° C ( $P = 0.59$ ; one-way analysis of variance). Figure 1 illustrates pooled data of all experiments, in which only the highest alveolar concentration of anesthetic that permitted movement and the lowest concentration that prevented movement, are shown. Mean values of arterial hemoglobin concentration at the beginning and end of the study were, respectively, 11.6  $\pm$  1.9 g/l and 10.7  $\pm$  1.8 g/l, and were not statistically significantly different ( $P = 0.25$ ; two-sided paired Student's *t* test). Mean arterial PaO<sub>2</sub> at the time of determination of MAC of halothane, isoflurane, and enflurane at normothermia on 100% inspired oxygen was 458  $\pm$  32 mmHg; during N<sub>2</sub>O exposure, mean arterial PaO<sub>2</sub> was 153  $\pm$  10 mmHg. Mean arterial PaCO<sub>2</sub> during normothermia was 29  $\pm$  5 mmHg, and mean pH of arterial blood was 7.47  $\pm$  0.06. During hypothermia, the following values were measured in arterial blood: PaO<sub>2</sub> 549  $\pm$  15 mmHg, PaCO<sub>2</sub> 32  $\pm$  4 mmHg, and pH 7.40  $\pm$  0.03.

In the second group of five ferrets, MAC of halothane was 0.984  $\pm$  0.074% at 37.3  $\pm$  0.2° C. This value does not differ significantly from halothane MAC de-

terminated in the first group of ferrets that had been exposed to isoflurane and enflurane ( $P = 0.59$ , Student's non-paired  $t$  test).

### Discussion

The purpose of this study was to provide information on the relative anesthetic potencies of halothane, enflurane, isoflurane, and nitrous oxide in ferrets, which have become more widely used as laboratory animals.<sup>1-4</sup>

Our experimental protocol in which MAC was determined for three volatile anesthetics in order of increasing solubility raises the question of whether prior exposure to one anesthetic has an influence on MAC of a subsequently administered anesthetic, a possibility which could introduce small errors in our enflurane and halothane MAC values. This is unlikely for the following reasons. Previous reports indicate that the residual anesthetic in brain during washout is insignificant after 90 min.<sup>9,10</sup> Isoflurane elimination from rabbit brain, as revealed by <sup>19</sup>F nuclear magnetic resonance spectroscopy, was rapid, and, after 90 min, the isoflurane signal could not be distinguished from noise.<sup>10</sup> The time interval between the determinations of isoflurane and enflurane MAC, and of enflurane and halothane MAC, respectively, was of that order of magnitude, and both end-tidal gas and blood did not contain any anesthetic other than the one of which the MAC was being determined.

In addition, there were no differences in halothane MAC values between the group of eight ferrets in which halothane MAC was determined after prior exposure to, and elimination of, isoflurane and enflurane, and the group of five ferrets wherein halothane MAC was determined first.

MAC has been determined in humans and in various animals, including monkey, dog, horse, swine,<sup>8</sup> calves, rabbits, rats, toad, and goldfish.<sup>11</sup> The anesthetic potency of various anesthetics differs among animal species over a twofold range, and the relative potency among individual halogenated anesthetic agents also differs. The ratio of 1 MAC of isoflurane to 1 MAC of halothane is about 1.5 in humans, dog, horse, and cat, and 1.1 in monkey. The ratio of enflurane MAC to halothane MAC is 2.2 in humans, dog, and horse, but only 1.6 in monkey and 1.2 in cat. Our MAC values for halothane ( $1.01\% \pm 0.10$ ), enflurane ( $1.99\% \pm 0.18$ ), and isoflurane ( $1.52\% \pm 0.10$ ) fall within the range of values reported for other mammals (except cat and monkey). In the ferret, the relative potencies of isoflurane and enflurane expressed as ratios of 1 MAC to 1 MAC of halothane are 1.5 and 2, respectively; close to those found in humans, dog, and horse.

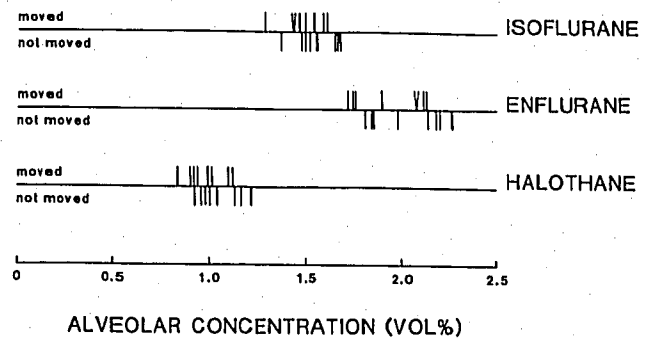


FIG. 1. Graphical illustration of responses to tail clamp as a function of alveolar anesthetic concentration for isoflurane ( $n = 8$ ), enflurane ( $n = 8$ ), and halothane ( $n = 8$ ) at  $37^\circ\text{C}$  in ferrets. For each ferret, a line extending up from the horizontal line represents the highest concentration of the anesthetic that permitted movement, while the lowest concentration that prevented movement is shown as a downward line.

Halothane MAC was reduced by 26% in the presence of 70% nitrous oxide. On the basis of additivity of anesthetic potencies of volatile anesthetics,<sup>12</sup> one could calculate a MAC value for nitrous oxide of  $267 \pm 54\%$ , which is in the range of nitrous oxide MAC values reported for other small mammals.<sup>11</sup> Yet, since MAC of nitrous oxide can only be truly determined in hyperbaric conditions, one should interpret this value with caution. The mean MAC value of halothane decreased by 16% when body temperature was lowered from  $37^\circ\text{C}$  to  $30^\circ\text{C}$ . Our value for the reduction in halothane MAC (2.3% per degree C) is less than that found previously in dogs (50% reduction of halothane MAC for a  $10^\circ\text{C}$  decrease from  $38^\circ\text{C}$ )<sup>13</sup> and in rats (4.82% per degree C).<sup>14</sup> Reasons for this difference are not clear.

In summary, the MAC values for isoflurane, enflurane, and halothane in ferrets at normothermia are similar to those reported for humans.

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