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MAC of I-653 in Beagle Dogs and New Zealand White Rabbits

Brian M. Doorley, M.Sc., Stephen J. Waters, M.Sc.,† Ross C. Terrell, Ph.D.,‡ James L. Robinson, Ph.D.§*

The minimum alveolar concentration (MAC) of I-653 was determined in six beagle dogs and four New Zealand white rabbits. The MAC values (±SD) were 7.2 ± 1.0 atm % for dogs and 8.9 ± 0.3 atm % for rabbits. Comparison of these results with published MAC values for other anesthetics indicate that I-653 is one-third to one-eighth as potent as currently available volatile anesthetics (enflurane, isoflurane, and halothane). From these data and previous reports, human MAC was projected to be approximately 5.1 atm %. (Key words: Anesthetics, volatile: I-653. Potency: MAC.)

THE MINIMUM ALVEOLAR CONCENTRATION (MAC) is used as a standard by which the potency of inhaled anesthetics are compared. I-653 is a fluorinated methylethylether (CF_3 CHF-0-CHF_2) that has desirable physical characteristics, such as nonflammability at expected clinical concentrations, a low blood/gas partition coefficient of 0.424,[1] and stability in soda lime.[2] As expected from the low blood/gas partition coefficient, onset of anesthesia and recovery from anesthesia are both rapid.[3]

The object of this study was to determine the anesthetic potency of I-653 in dogs and rabbits using the method described by Eger *et al.*[4] These data, along with data from previous studies using dogs, rabbits, and rats, were used to project human MAC of I-653.

Materials and Methods

DOG PREPARATION

Male beagle dogs weighing 11–14 kg were used. Prior to induction, lead II of the ECG was recorded and heart rate determined from the R-R interval. A venous catheter was inserted in the right paw vein for administration of saline. Anesthesia was induced by face mask at a concentration of approximately 20 atm %. When deep anesthesia was apparent (relaxation of the vocal cords), the trachea was intubated and the anesthetic concentration reduced. The dogs were ventilated to maintain end-tidal carbon dioxide in a normal range. Body temperature was maintained at 38 ± 1.0° C.

RABBIT PREPARATION

Male New Zealand white rabbits weighing between 2.2 and 2.8 kg were used. Anesthesia was induced, using a small animal mask while the animal was secured in a rabbit restrainer, with approximately 20 atm % I-653. Using a method described previously,[5] the trachea was intubated, and the anesthetic concentration was reduced. The rabbits were ventilated to maintain end-tidal carbon dioxide in a normal range. Body temperature was maintained at 39 ± 1.0° C.

MAC DETERMINATION

Expired I-653 and carbon dioxide concentrations were monitored continuously using infrared analyzers. Analysis of I-653 was carried out using a Puritan Bennett anesthetic agent monitor. The gain of the methoxyflurane channel of the analyzer was adjusted to read 0.51 times the actual I-653 concentration delivered. A two point calibration was done using pre-mixed I-653 calibration cylinders. Gas chromatography was also used to assure accuracy.

MAC was determined in the same manner for both dogs and rabbits. Each animal was maintained initially for 20 min at an end-tidal concentration thought to approximate MAC. A large hemostat (rabbits) or vise grip clamp (dogs) with taped jaws, to prevent laceration of the tail, was clamped on a shaved portion of the animal's tail for 30 s and then removed. If gross purposeful movement (GPM) was not observed during the tail clamping, the concentration was lowered by 0.5 atm % and maintained for 15 min at the new end-tidal concentration before repeat application of the clamp. This procedure was followed until GPM was seen. At this point, the concentration was then increased to verify the no-response concentration. A final positive GPM concentration was determined to bracket the MAC concentration twice on each side. MAC was recorded as the concentration between the lowest concentration that prevented GPM and the highest concentration at which GPM occurred in response to tail clamp. MAC for each species was calculated as the mean of the individual MAC determinations.

* Associate Staff Pharmacologist, Department of Pharmacology.
† Staff Toxicologist, Department of Toxicology.
‡ Consultant, Department of Pharmacology.
§ Research Pharmacologist, Department of Pharmacology.

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Address reprint requests to Mr. Doorley: Anaquest, 100 Mountain Avenue, Murray Hill, New Jersey 07974.

TABLE 1. MAC Values (atm %) for Dog (Beagle), Rabbit (New Zealand White), and Rat (Sprague-Dawley)

	I-653	Isoflurane	Enflurane	Halothane
Human	5.09*	1.15†	1.68†	0.77†
Dog	7.20	1.41†	2.20†	0.87†
Rabbit	8.90	2.05‡	2.86‡	1.39‡
Rat	5.72§	1.38†	2.21†	1.11†

* Projected MAC.
† Ref[7]
‡ Ref[6]
§ Ref[8]

I-653 has a vapor pressure of approximately 700 mmHg at 22° C and has a boiling point of 23.5° C. These properties make I-653 difficult to deliver in conventional vaporizers. For the dog experiments, I-653 was delivered from a cooled isoflurane vaporizer. The vaporizer containing I-653 was cooled to approximately 14° C using a Lauda cooling unit. Cooling I-653 to 14° C reduced the vapor pressure to approximately twice the vapor pressure of isoflurane. This enabled the delivery of anesthetic concentrations of I-653 from an isoflurane vaporizer, since preliminary reports indicated that I-653 was one-fourth to one-fifth as potent as isoflurane and an isoflurane vaporizer allows delivery of concentrations approximately three and one-half times MAC.

A modified Ohio Medical Products DM 5000 was used for the delivery of I-653 to rabbits. The machine was designed to operate with the vaporizer at about two atmospheres absolute pressure, so that the vehicle oxygen, which passes through the vaporizer, will be saturated with an equal volume of I-653 vapor as it emerges from the vaporizer. The vaporizers were electrically heated with thermostatic control to maintain the temperature of I-653 at 23–25° C. This provided constant concentrations of anesthetic delivery, regardless of flow through the units.

PROJECTION OF HUMAN MAC

A method, which was validated with isoflurane, enflurane, and halothane, was used to project I-653 human MAC.[6] This method involved calculation of a potency ratio for each species (rat, rabbit, and dog) with I-653 and each volatile anesthetic. For each ratio, I-653 MAC was used as the numerator and, for each anesthetic, the corresponding species MAC was used as the denominator. The mean ratio for the three species was then multiplied by the human MAC for that anesthetic to estimate human MAC for I-653. This calculation was performed using isoflurane, enflurane, and halothane. The mean of these three calculations constitutes our estimate of human MAC for I-653.

TABLE 2. Projected Human MAC (From Ratio Comparisons) and Published Values for Human MAC of Isoflurane, Enflurane, and Halothane

	Actual MAC (atm %)	Projected MAC (atm %)	% Deviation From Actual MAC
Isoflurane	1.15*	1.11	−3.6
Enflurane	1.68*	1.75	+4.2
Halothane	0.77*	0.79	+2.6

* Ref[7]

Results

The mean MAC value (±SD) for I-653 in six beagle dogs was 7.2 ± 1.0 atm %. The range of MAC determinations for I-653 in dogs was 6.2–8.3 atm %. The mean MAC value (±SD) for I-653 in four New Zealand white rabbits was 8.9 ± 0.3 atm %. The range of MAC determinations for I-653 in rabbits was 8.4–9.2 atm %.

The projected human MACs of I-653 from isoflurane, enflurane, and halothane were 5.16, 5.04, and 5.08 atm %, respectively. The mean projected human MAC for I-653 was 5.09 atm %.

Discussion

The dog and rabbit MAC values from the present study, along with MAC values for humans and laboratory animals in which determinations for isoflurane, enflurane, and halothane are available, are shown in table 1. The results from our study indicate that I-653 is one-third to one-eighth as potent as currently available inhalational anesthetics in dogs and rabbits. From these data, we project MAC of I-653 in humans to be approximately 5.1 atm %. This projection is based on the potency comparisons between anesthetics.

Our method of using existing MAC values from different species to determine an anesthetic potency ratio was validated by substituting isoflurane, enflurane, and halothane for I-653. Table 2 illustrates the results of this validation test. These results indicate that we may expect a deviation of approximately plus or minus 4% from our projection of I-653 human MAC.

In conclusion, I-653 is a fluorinated volatile anesthetic with a potency of one-third to one-eighth that of presently used inhalational anesthetics. On the basis of present *in vivo* data, the MAC of I-653 in humans should approximate 5.1 atm %. Our estimate lies between previously reported MAC estimates of 5.6 atm %[1] and 4.0 atm %,[8] based upon oil/gas partition coefficient data and rat MAC, respectively. We have shown that our method is accurate to within 4% of actual human MAC values when used to estimate human MAC for isoflurane, enflurane, and halothane. Our method

of prediction is consistent with results described by Katoh and Ikeda in their determination of human MAC for sevoflurane.[9] Their results indicate that human MAC predictions based on determinations in other species or systems are more accurate than predictions based on oil/gas partition coefficients.

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