

## MAC for Halothane, Enflurane, and Isoflurane in the New Zealand White Rabbit: And a Test for the Validity of MAC Determinations

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MAC determinations for halothane, enflurane, and isoflurane were performed in New Zealand white rabbits ( $n = 8$ , approximate age 6 months). The MAC values ( $\pm$ SD) were as follows: halothane  $1.39 \pm 0.23\%$ , enflurane  $2.86 \pm 0.18\%$ , and isoflurane  $2.05 \pm 0.18\%$ . Comparison of these results with published MAC values for other species suggests that the ratio of the potencies for any pairing of these three agents is constant from species to species. This observation provides a means for assessing the validity of preexisting or newly determined MAC values. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Potency, anesthetic: MAC.)

COST CONSIDERATIONS have caused us to reduce the use of dogs in our laboratory and to employ, where feasible, smaller animals, including the rabbit. We discovered, however, that MAC values (as summarized in a review by Quasha *et al.*<sup>1</sup>) for that species were either unavailable (enflurane and isoflurane) or suspect (halothane MAC: 0.82% an apparent underestimate).

We therefore determined MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit. We present these data in the hope that they will be of value to other investigators comparing the physiologic effects of volatile agents. In addition, an examination of these results, in conjunction with previously published MAC determinations for several other species, suggested a general means for assessing the validity of MAC determinations.

### Methods and Results

MAC determinations for halothane and isoflurane were performed in eight rabbits (three female, five male; approximate age 6 months; weight  $3.04 \pm 0.25$  kg). Each rabbit was studied twice at an interval of not less than seven days. The initial anesthetic exposure was to halothane or isoflurane on an alternating basis. MAC

for enflurane was determined in a separate group of eight rabbits (two female, six male; approximate age 6 months, weight  $3.09 \pm 0.24$  kg). All studies were performed between 8:00 and 12:00 and all animals were allowed *ad libitum* access to food and water until the time of study.

Induction of anesthesia was accomplished in a plexi-glass box, using the agent under study in balance oxygen, and the trachea was intubated with a cuffed endotracheal tube. The animals were ventilated mechanically (tidal volume, 15 ml/kg; rate, 20 breaths/min), and CO<sub>2</sub> was added to the inspired gas mixture to maintain a normal end-tidal CO<sub>2</sub> concentration (5.0–5.5%). Esophageal temperature was servo-controlled to 37.5° C using a warming pad and heat lamps. Expired volatile agent and carbon dioxide concentrations were monitored continuously using infrared analyzers (Beckman LB-II®). The sample for volatile agent analysis was drawn from the tip of the endotracheal tube via a polyethylene catheter.

The technique for the ensuing MAC determination was similar to that described by Eger *et al.*<sup>2</sup> Each animal was maintained initially for 20 min at an end-tidal concentration thought, on the basis of pilot study, to approximate MAC. A 10-inch rubber-shod hemostat then was applied (first ratchet) to the proximal one-third of the rabbit's shaved tail. The hemostat was moved continuously during a 60-s application and then removed. Any purposeful movement constituted a positive response. Stiffening, shivering, swallowing, or changes in respiratory pattern were disregarded. The end-tidal concentration was then adjusted by 20% (upward after a positive response, downward after a negative) and maintained for 15 min at the new end-tidal concentration before repeat application of the hemostat. When the no-response concentration had been bracketed in this fashion, an intermediate end-tidal level (*i.e.*, a 10% adjustment) was achieved and a final clamping performed. MAC for each animal was defined as the average of the lowest end-tidal concentration at which a negative response occurred and the highest concentration at which a positive response was observed. The MAC value thus obtained allowed a maximum error of

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TABLE 1. MAC Values ( $\pm$ SD) for Humans, Rabbit (New Zealand white), Cat, Rat (Sprague-Dawley), Mouse (Swiss Webster and Charles River CD-1), Dog, and the Java Monkey

	Halothane	Enflurane	Isoflurane	$\frac{\text{Halothane}}{\text{Enflurane}}$	$\frac{\text{Halothane}}{\text{Isoflurane}}$	$\frac{\text{Isoflurane}}{\text{Enflurane}}$
Human	0.77	1.68	1.15	0.46	0.67	0.68
Rabbit	1.39 $\pm$ 0.23	2.86 $\pm$ 0.18	2.05 $\pm$ 0.18	0.49	0.68	0.72
Cat	1.19 $\pm$ 0.15	2.37 $\pm$ 0.16	1.61 $\pm$ 0.10	0.50	0.74	0.68
Rat (Sprague-Dawley)	1.05 $\pm$ 0.04	2.21 $\pm$ 0.08	1.46 $\pm$ 0.06	0.48	0.72	0.66
Mouse (Swiss Webster)	0.95 $\pm$ 0.07	1.95 $\pm$ 0.16	1.34 $\pm$ 0.10	0.49	0.71	0.69
Mouse (Charles River)	1.00 $\pm$ 0.13	2.19 $\pm$ 0.28	1.41 $\pm$ 0.12	0.46	0.71	0.64
Dog*	0.87 $\pm$ 0.04	2.06 $\pm$ 0.13	1.28 $\pm$ 0.25	0.42	0.68	0.62
Java Monkey*	1.15 $\pm$ 0.20	1.84 $\pm$ 0.16	1.28 $\pm$ 0.18	0.63	0.90	0.70

The rabbit values are from the present study. The cat MAC determinations were performed by Drummond *et al.*<sup>5</sup> Values for the rat and the Swiss Webster mouse were provided by R. I. Mazze, M.D., (personal communication, unpublished data). MAC for the Charles River mouse was determined by Deady *et al.*<sup>6</sup> The remaining determinations are taken from the review by Quasha *et al.*,<sup>1</sup> which provides references. MAC ratios for halothane and enflurane, halothane and isoflurane, and isoflurane and enflurane are in the right-hand columns.

\* Standard deviation calculated as the reported standard error times the square root of n.

$\pm$ 5%. MAC for the species was calculated as the mean of the eight individual values thus obtained.

MAC values ( $\pm$ SD) were as follows: halothane 1.39  $\pm$  0.32%, enflurane 2.86  $\pm$  0.18%, and isoflurane 2.05  $\pm$  0.18%.

### Discussion

The rabbit MAC values from the present study along with MAC values for humans and for the laboratory animals in which determinations for halothane, enflurane, and isoflurane are available are shown in table 1. It is apparent for humans, rabbit, cat, rat, and two mouse strains that the within-species ratios of MAC values for any given pairing of halothane, enflurane, and isoflurane are very similar (see table 1). For example, the halothane/isoflurane MAC ratio is approximately 0.7 in these five species (and also the dog), indicating that in each isoflurane is 70% as potent as halothane. This apparent constancy of potency ratios from species to species appears consistent with the demonstration by Miller *et al.*<sup>3</sup> and Eger *et al.*<sup>4</sup> that anesthetic potency is related to lipid solubility. That latter observation suggests that the anesthetic effects of inhaled agents are dependent upon their entry (by diffusion) into lipids, and, as it might be anticipated that the relative solubilities of these agents in the lipids of various species would be constant, their relative potencies likewise should be similar.

However, in spite of the apparent logic of this occurrence, the author is not aware that this specific observation has been made or predicted previously. In fact, the relationship is much less than consistent among the previously available MAC data tabulated by Quasha *et al.*

*et al.*<sup>1</sup> The MAC values from that review for the dog and for the Java monkey represent cases in point and are presented in table 1. For the Java monkey, the halothane/isoflurane MAC ratio of 0.9 contrasts with the 0.7 apparent for all of the other species, while its isoflurane/enflurane ratio conforms. The halothane value therefore might be suspect and, assuming the applicability in the Java monkey of the ratios that prevail in the other species, one would predict a halothane MAC of 0.90%.<sup>†</sup> This value, perhaps not coincidentally, is a close approximation of an MAC value of 0.89% reported for another monkey subspecies (stump tail<sup>1</sup>). A similar examination of MAC values for the dog would suggest an enflurane MAC value of approximately 1.8% rather than the reported values of 2.06 and 2.2%.<sup>1</sup>

It is possible that deviations from the recurring ratios apparent in table 1 (halothane/enflurane approximately 0.48, halothane/isoflurane approximately 0.70, and isoflurane/enflurane approximately 0.68) will represent the existence of some species specific effect of a particular agent, which results in an alteration of consciousness or produces analgesia in a manner not dependent on lipid solubility. Nonetheless, a deviation from these potency ratios should prompt a rigorous review of the methods employed in the MAC determinations. In addition to technical matters, relevant methodologic variables will include factors known to influence MAC including age, temperature, and pregnancy.<sup>1</sup> If MAC values are determined in separate populations that differ with respect to these variables, the derived ratios may not conform

<sup>†</sup> If halothane MAC/isoflurane MAC = 0.7, then the predicted halothane MAC for the Java monkey should equal 0.7  $\times$  1.28 = 0.90%.

with those provided above. Such determinations probably should not be viewed as representing equipotency when applied to truly comparable populations.

New Zealand white rabbits were employed in the MAC determinations in this study. It is possible that other inbred rabbit strains would present different MAC values. However, the observations regarding the MAC ratios would suggest that the MAC values reported herein will represent equipotent concentrations and will provide the basis for valid comparisons of the physiologic effects of halothane, enflurane, and isoflurane.

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