MAC of sevoflurane in humans and the New Zealand white rabbit

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The minimum alveolar concentration of sevoflurane necessary to prevent movement in 50 per cent of patients (MAC) was determined to be 2.05 per cent in 20 adult surgical patients. Because this value was higher than the only other experimentally determined human MAC value for sevoflurane (1.71 per cent), MAC was also determined in New Zealand white rabbits. Comparisons of the MAC ratios of sevoflurane to other volatile anaesthetics in both the human and the rabbit suggest that the human MAC value we obtained for sevoflurane is consistent with experimental determinations of MAC of other volatile anaesthetics in humans.

Sevoflurane is a new ether anaesthetic soon to be introduced into clinical practice in Japan. The minimum alveolar concentration (MAC) of sevoflurane required to prevent movement in 50 per cent of patients given a supramaximal stimulus has been recently reported by Katoh *et al.*[1] However, MAC of sevoflurane as determined by Katoh *et al.* differs substantially from that predicted on the basis of its oil/gas partition coefficient.[2] We independently began a human MAC study, unaware of the ongoing work of Katoh *et al.* Because our results in humans appeared more consistent with the predicted value but different than that reported by Katoh *et al.*, we also determined the MAC of sevoflurane in another species, the New Zealand white rabbit. Analysis of the MAC ratios of sevoflurane to other well characterized volatile anaesthetics in humans and the rabbit was undertaken to determine a possible explanation for the discrepancies between our results in humans and those of Katoh *et al.*

Key words
ANAESTHETIC, VOLATILE: sevoflurane; POTENCY, ANAESTHETIC: MAC, human, rabbit: sevoflurane.

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Methods

Human study

Following institutional Human Studies Committee approval and informed consent, the MAC of sevoflurane was determined in 20 adult surgical patients using the up and down method, in which the end-tidal (ET) sevoflurane concentration was chosen based on the response of the previous patient.[3] All patients were ASA physical status I or II and none suffered from significant cardiac, respiratory, hepatic or renal disease. No premedication was given prior to induction of anaesthesia. Following the establishment of basic monitoring, anaesthesia was induced by mask with sevoflurane in oxygen administered through a nonrebreathing modified Mapleson D system (Bain) using gas flows of at least 100 $ml \cdot kg^{-1}$. When anaesthetic depth appeared adequate, the trachea was intubated, without the aid of muscle relaxants. Following placement of the endotracheal tube, end tidal (ET) sevoflurane concentrations were measured continuously from the distal end of the endotracheal tube with a Puritan Bennett volatile anaesthetic analyzer calibrated before each MAC determination against tanks of known sevoflurane concentrations. Spontaneous ventilation was maintained at all times in every patient. Temperature was monitored by a temperature probe in the nasopharynx.

At least 15 minutes prior to skin incision, the end-tidal sevoflurane concentration was adjusted to a predetermined level and maintained through the preincision period. Upon incision, patients were observed for at least one minute for signs of gross, purposeful movement. Coughing, bucking or straining were not considered purposeful. Patients who moved were immediately given an intravenous bolus dose of sodium thiamylal. The first six patients received concentrations of sevoflurane between 1.55 and 2.42 per cent. Thereafter, we increased or decreased the ET concentration by 0.25 per cent depending on the response of the previous patient.

The quantal responses, i.e., purposeful movement or

no movement, were analyzed according to the methods of Waud in order to determine MAC.[4]

Rabbit study

Six New Zealand white rabbits were anaesthetized by mask with sevoflurane in oxygen. When anaesthetic depth was judged adequate, the trachea was intubated following direct laryngoscopy. Animals were ventilated at a rate sufficient to maintain end tidal (ET) PCO_2 in the normal range. The base of the tail was shaved and the ET sevoflurane concentration was adjusted to a preselected level. Both ET CO_2 and ET sevoflurane were measured continuously through a catheter with its tip lying near the distal end of the endotracheal tube. A Puritan-Bennett volatile anaesthetic analyzer calibrated before each use was used to measure sevoflurane concentrations. After 15 minutes, a clamp was applied to the base of the tail and the animal observed for signs of gross or purposeful movement. If the animal moved, the ET sevoflurane concentration was increased by ten per cent and the determination repeated in this manner until no movement was observed following application of the clamp. Likewise, if no movement was observed with initial tail clamping, the ET sevoflurane concentration was decreased by ten per cent. The MAC for each individual animal was taken as the midpoint between the ET concentrations preventing and allowing movement. These values were averaged to generate a mean and standard deviation for the group as a whole.

The ratio of the MAC of sevoflurane to the MACs of other volatile anaesthetics were determined for both the human and the rabbit as a test of the validity of the MAC determinations by the method of Drummond.[5]

The predicted human MAC for sevoflurane was calculated from the oil/gas solubility coefficient by the method of Halsey.[2]

Results

Twenty-one MAC determinations were performed in 20 patients. In one patient (#16 and #17), MAC was determined twice during the same anaesthetic. This patient underwent bilateral femoral rod removal. Sixteen patients were between the ages of 30 and 48 (Group I) and four patients were between the ages of 19 and 30 (Group II). Two patients (#3 and #9) were dropped from the study because of technical errors and were not given sevoflurane.

The two age groups will be considered separately in the analysis because most human MAC studies including the study of Katoh *et al.* have examined patients between the ages of 30 and 55.[6–8] Table I lists the ages, gender, ET sevoflurane concentration at skin incision and response to skin incision of the patients in the two groups. All patients receiving less than 2.0 per cent ET sevoflurane in Group I moved with skin incision. All patients in Group I receiving more than 2.25 per cent ET sevoflurane failed to move with skin incision. The MAC of sevoflurane in Group I patients was 2.05 ± 0.08 per cent (mean ± SEM). The small number of patients in Group II precluded determining MAC for this group. In all patients, nasopharyngeal temperature was above 36° at the time of MAC determination.

TABLE I Human MAC determination

	No.	*Age*	*Sex*	*%*	*Moved*
Group I: (MAC = 2.05 ± 0.08%)					
	1	39	M	2.42	No
	2	44	F	2.0	No
	5	48	F	1.55	Yes
	6	34	M	1.8	Yes
	7	31	M	2.1	Yes
	10	45	M	2.5	No
	11	30	M	2.25	No
	12	34	F	2.0	No
	13	38	F	1.75	Yes
	14	40	F	2.00	Yes
	15	40	F	2.25	Yes
	19	38	M	2.50	No
	20	43	F	2.25	No
	21	38	F	2.00	No
	22	32	M	1.75	Yes
	23	34	F	2.00	Yes
Group II: MAC not determined					
	4	23	M	1.97	No
	8	27	M	2.25	Yes
	16	26	M	2.50	Yes
	17	26	M	2.75	No
	18	19	M	2.50	Yes

Ages, gender and responses of individual patients to surgical stimulation at various end-tidal (ET) sevoflurane concentrations. Note that patients #3 and 9 were dropped from the study and not given sevoflurane. Patient #16 and 17 is the same patient. Group I MAC determined by the method of Waud.[3] Group I MAC expressed as mean ± SEM.

MAC of sevoflurane in the rabbit was 3.70 ± 0.16 per cent.

Using these data and other previously determined MAC values for enflurane, halothane and isoflurane in humans and the rabbit, the ratios of MAC of sevoflurane to MAC of enflurane, halothane and isoflurane in humans are 1.22, 2.69 and 1.78 respectively. In rabbits these ratios are 1.29, 2.66 and 1.80 respectively.[5–8]

Using the human MAC data of Katoh *et al.*, these same MAC ratios are 1.02, 2.25, and 1.48 respectively in the human (Table II).

Discussion

The MAC for sevoflurane determined in humans in the present study differs substantially from that determined

TABLE II MAC ratios

MAC ratio	*Sevoflurane Isoflurane*	*Sevoflurane Halothane*	*Sevoflurane Enflurane*
Human (this study)	1.78	2.69	1.22
Rabbit (this study)	1.80	2.66	1.29
Human (Katoh *et al.*[1])	1.48	2.25	1.02

MAC ratios of various volatile anaesthetic pairs in the human and the New Zealand white rabbit using previously published data,[4,6–8] the data from the present study and the data of Katoh *et al.*[1]

by Katoh *et al.*[1] There are a number of methodological differences in the two studies which must be addressed however. Firstly, Katoh *et al.* used mass spectrometry to measure sevoflurane concentrations whereas we used an infra-red gas analyzer. Both systems sampled gas at a rate of 200 $ml \cdot min^{-1}$ and assuming both devices were accurately calibrated, this should not have introduced any variability. Secondly, Katoh *et al.* employed a semi-closed system presumably with a carbon dioxide absorber, whereas we used a non-rebreathing circuit. It is known that sevoflurane is slightly unstable in the presence of soda lime or baralyme and there are at least six breakdown products (personal communication, Dr. E.I. Eger II, San Francisco). If any of these products had anaesthetic properties, but was not detected as sevoflurane by mass spectrometry, this could serve to artificially lower the apparent sevoflurane MAC in the study by Katoh *et al.* This seems very unlikely because the concentrations of the various breakdown products are extremely small compared to sevoflurane MAC.

Patient temperature and equilibration times were similar in the two studies and therefore cannot explain the differences in the results of the two studies.

In the study of Katoh *et al.* the mean patient age was 48. In our Group I patients, the mean age was 38. Furthermore, 11 of 20 patients in the study of Katoh *et al.* were older than 50. None of our patients were older than 48. Studies examining the effects of age on MAC have demonstrated an inverse realtionship between MAC and age. For example, Gregory *et al.* determined that halothane MAC should be approximately 0.05 per cent lower in 48-year-old patients compared to 38-year old patients.[9] This difference may account for some, but not all of the observed differences in the values determined in the two studies. This is supported by examination of the data from our Group II patients all of whom were less than 30 years of age. Of the four patients (#16 and 17 are the same patient) in Group II, two moved at an ET sevoflurane concentration of 2.5 per cent, whereas neither of the two Group I patients equilibrated at 2.5 per cent moved in response to a surgical incision. This suggests that age differences may have been an important factor in the interpretation of these results.

It has been suggested that the product of MAC and the olive oil/gas solubility ratio of volatile anaesthetics will be a constant for a given species. However, MAC of sevoflurane as predicted by its oil/gas solubility coefficient of 55 depends upon the agents to which it is compared. For example, the products of the oil/gas solubilities and MACs for halothane and enflurane agree very well, being 1.62 and 1.64 respectively. Using this value, the predicted MAC for sevoflurane would be 2.96 per cent (=1.63/55). However, if we use the product of the MAC of isoflurane (1.15 per cent) and isoflurane's oil/gas solubility ratio (94) in the equation, the predicted value for the MAC of sevoflurane is 1.97 per cent (=1.08/55). Although experimental evidence suggests that the product of the oil/gas solubility coefficient and MAC for all volatile anaesthetics should be relatively constant within a species, there are exceptions such as those noted above with regards to the isomers enflurane and isoflurane which have discrepant MACs but similar solubility coefficients. Halsey has proposed that these differences may be due to differential effects of these agents on the central nervous system with, for example, enflurane being neuroexcitatory compared to isoflurane and hence having a higher MAC.[2] However, the ratios of any given pair of volatile anaesthetic MAC values within a species should be relatively constant across species if both anaesthetics affect the nervous systems similarly in the species under consideration. This idea was originally proposed by Drummond as a way to test the validity of the MAC data. Empirically, these relationships appear remarkably constant in all species in which they have been examined so far.[5]

We undertook the determination of MAC of sevoflurane in the rabbit in order to check the validity of the results we obtained in humans. It is clear from the data in Table II that the ratios of sevoflurane MAC to other well characterized volatile anaesthetic MACs agree very well between the human and the rabbit using our human data. When the human MAC data from Katoh are used, these ratios are more discrepant.

One possible explanation for the discrepancy between our data and that of Katoh *et al.* is that MAC is actually different in the two populations we studied (Japan vs United States). If this were true, then it might also follow that MAC for isoflurane, halothane and enflurane in Japanese could be lower than values determined in North America. Because only North American human MAC values were used in our analysis, the ratios in Table II may be an improper or incomplete representation of the data of Katoh *et al.* The hypothesis that MAC may be influenced by genetic or environmental factors of which we are

unaware has not been investigated in the human. This may prove to be fertile ground for future research. For example, a recent report indicates that a fat free diet may significantly lower MAC in rats.[10]

In conclusion, the MAC of sevoflurane was determined to be 2.05 per cent in adults and 3.70 per cent in rabbits. The ratios of these values to other experimentally determined MAC values of volatile anaesthetics in humans and rabbits suggest they are consistent with one another, but higher than would be predicted based on earlier human work. However, methodological differences, primarily in the ages of the patients studied in the present study and the earlier human study may account for some of this apparent discrepancy.

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Résumé

La concentration alvéolaire minimale du sévoflurane nécessaire afin de prévenir les mouvements dans 50 per cent des patients (MAC) a été déterminée à 2.05 per cent chez 20 patients adultes subissant une chirurgie. Etant donné que cette valeur était plus élevée que celle obtenue expérimentalement chez les humains avec le sévoflurane (1.71 per cent), le MAC a aussi a été déterminé chez les lapins blanc de la Nouvelle-Zélande. Des comparaisons des rapports de MAC entre le sévoflurane et d'autres agents anesthésiques volatiles tant chez l'humain que chez le lapin suggèrent que les valeurs du MAC qu'on a obtenues chez l'humain avec le sévoflurane sont comparables avec celles déterminées expérimentalement pour d'autres agents anesthésiques volatiles chez l'homme.