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The Minimum Alveolar Concentration (MAC) of Sevoflurane in Humans

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Forty surgical patients were divided into two groups and anesthetized with either sevoflurane and oxygen or sevoflurane, oxygen, and nitrous oxide. The minimum alveolar concentration (MAC) for sevoflurane required to prevent movement in response to surgical incision in healthy patients was 1.71 ± 0.07% (SE). The AD_{95} (anesthetic ED_{95}) that prevented 95% of patients from moving was 2.07%. The addition of 63.5% end-tidal nitrous oxide allowed a reduction in the alveolar sevoflurane concentration to 0.66 ± 0.06% (SE). The reduction in sevoflurane MAC was 61.4%. The AD_{95} for sevoflurane with 63.5% end-tidal nitrous oxide was 0.94%. (Key words: Anesthetics, volatile: sevoflurane. Potency, anesthetic: MAC.)

SEVOFLURANE (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether), a new, nonflammable inhalational anesthetic agent, has undergone phase 2 trials in surgical patients in Japan. Rapid induction and recovery consistent with a blood/gas partition coefficient of 0.59 have been reported in a preliminary clinical study[1] and in an animal study.[2] MAC, a measure of anesthetic potency, is the alveolar concentration of anesthetic at which 50% of patients do not move in response to a single stimulus (skin incision).[3] It is used for comparison of the pharmacologic properties of inhalation anesthetics. AD_{95} (anesthetic ED_{95}), the dose that prevents 95% of patients from moving in response to skin incision,[4] has greater clinical utility than MAC. The objectives of the present study are to determine the MAC and the AD_{95} of sevoflurane in ASA physical status I patients and the effectiveness of nitrous oxide in reducing sevoflurane requirement for surgical anesthesia.

Materials and Methods

Forty surgical patients of either sex, ASA physical status I, aged 30–59 yr, were studied. All patients had normal respiratory function. They were randomly divided into two groups (A and B). Each group of 20 patients was divided into four subgroups (A_1, A_2, A_3, and A_4 or B_1, B_2, B_3, and B_4) of five patients. The patients did not receive premedicant drugs. The anesthetic breathing system used was a semiclosed circuit. Anesthesia was induced with sevoflurane and oxygen in group A, or with 60–70% nitrous oxide, sevoflurane, and oxygen in group B. The fresh gas flow rate into the semiclosed circuit was 6 l per min (in group A, oxygen 6 l per min; in group B, 2 l per min oxygen and 4 l per min nitrous oxide). The trachea was intubated with a cuffed endotracheal tube without the use of muscle relaxants or other agents. After tracheal intubation, the end-tidal sevoflurane concentration was reduced to a predetermined level and held constant for at least 15 min prior to the skin incision. End-tidal carbon dioxide concentrations ranged from 30–40 mmHg during the study, and the rate and depth of mechanical ventilation were adjusted so that adequate sampling of end-tidal gas could be performed. Rectal temperature ranged from 35.8–37.0° C in all patients. Gas samples (200 ml/min) were collected with a teflon catheter placed at the tracheal end of the endotracheal tube at 200 ml per min. Sevoflurane, carbon dioxide, nitrous oxide, and oxygen concentrations were measured continuously by means of a mass spectrometer (Perkin-Elmer® MGA 1100; Perkin-Elmer, Pomano, CA). The mass spectrometer was calibrated against known concentrations of sevoflurane, which was verified by calibration with a gas chromatograph (Shimadzu® GC-9A; Shimadzu, Kyoto, Japan). The patients' response to skin incision was reported as movement or non-movement. We considered "movement" to be "gross purposeful muscular movement" usually of the head or extremities. Breath-holding, bucking, or grimacing was not "movement."[3]

The technique used to calculate MAC was adapted from Waud.[5] The doses selected and the sizes of the groups were predetermined to estimate standard error.[4,6] In group A_1, the end-tidal sevoflurane concentration held constant for more than 15 min ranged from 2.10–2.00% (2.05 ± 0.05%). In group A_2, this was 1.85 ± 0.05%; in A_3, 1.65 ± 0.05%; and in A_4, 1.45 ± 0.05%. In each subgroup of group B, the respective values were 1.0 ± 0.05, 0.8 ± 0.05, 0.6 ± 0.05, or 0.4 ± 0.05%, and the end-tidal nitrous oxide concentration ranged from 62.5–64.5%. Individual observations were fitted to a logistic curve by iterative technique, based on a Taylor series expansion. Analyses were performed with a PASCAL program that furnished median and slope values with their standard errors, as well as an expression for the best-fitting

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TABLE 1. Data Obtained in Group A, Sevoflurane Alone

Group	Age	F_E (%)	F_I (%)	$\frac{(F_I-F_E)}{F_E}\times 100$	Movement	Duration (Min)
A_1	43	2.03	2.21	8.94	No	21
2.10–2.00%	43	2.04	2.25	10.1	No	20
	49	2.07	2.19	5.58	No	29
	58	2.10	2.26	7.48	No	16
	52	2.03	2.27	11.8	No	21
A_2	50	1.85	2.12	14.3	Yes	30
1.90–1.80%	59	1.86	2.02	8.89	No	15
	42	1.85	1.98	6.70	No	21
	53	1.85	2.01	8.48	Yes	16
	52	1.82	1.99	9.55	No	17
A_3	51	1.69	1.85	9.80	Yes	19
1.70–1.60%	30	1.64	1.89	15.7	No	20
	32	1.64	1.80	10.1	No	16
	55	1.66	1.81	8.96	Yes	42
	54	1.69	1.93	13.7	No	23
A_4	40	1.49	1.60	7.22	Yes	34
1.50–1.40%	41	1.48	1.53	3.35	Yes	18
	53	1.41	1.55	10.6	Yes	26
	41	1.41	1.50	5.85	Yes	18
	53	1.45	1.67	15.4	Yes	16

F_E = End-tidal sevoflurane concentration; F_I = Inspired sevoflurane concentration; Duration = Total duration of end-tidal sevoflurane at time of incision.

logistic curve.[5] AD_{95} was calculated directly from the expression for the best-fitting logistic curve.[4]

Results

The data are listed in tables 1 and 2. Age, body temperature, and total duration of the end-tidal sevoflurane concentration at time of incision in group A were not significantly different from those in group B. MAC for sevoflurane alone was 1.71 ± 0.07% (SE), AD_{95} was 2.07%, and the slope of the logistic function was 15.32 ± 0.24 (SE) (fig. 1). Addition of 63.5 ± 0.4% (SE) end-tidal nitrous oxide reduced sevoflurane MAC to 0.66 ± 0.06% (SE) and the AD_{95} to 0.94%.

Discussion

We assume that end-tidal sevoflurane concentration (partial pressure) adequately reflects arterial (brain) sevoflurane partial pressure. The end-tidal concentration was kept constant for a minimum of 15 min, thus assuring that the sevoflurane partial pressure in the brain was equilibrated with that in the arterial blood. Eger *et al.* suggested that the end-tidal anesthetic partial pressure reflected arterial anesthetic partial pressure when the difference between inspired and end-tidal concentration was small.[7] Sevoflurane, with a blood/gas partition coefficient of 0.60,[8] is similar to that of nitrous oxide, and is less soluble than the other, more potent agents currently used in clinical practice. Thus, the inspired-end-tidal difference decreases rapidly. The inspired-arterial (end-tidal) difference averaged less than 10% (mean 9.6%) of the alveolar concentration in group A. With as much as 10% contamination of alveolar gas with inspired gas, the measured end-tidal partial pressure would be less than 2.5% higher than true alveolar (arterial) partial pressure.[7]

Many studies have suggested that MAC is correlated with the oil/gas partition coefficient.[9,10] The product of

TABLE 2. Data Obtained in Group B, Sevoflurane With N_2O

Group	Age	F_E (%)	F_I (%)	$\frac{(F_I-F_E)}{F_E}\times 100$	N_2O (%)	Movement	Duration (Min)
B_1	56	0.99	1.02	3.81	63.3	No	24
1.05–0.95%	35	0.98	1.02	4.81	63.6	No	18
	42	1.02	1.10	7.34	64.3	No	37
	32	0.98	1.03	5.77	63.2	No	23
	47	1.03	1.10	6.36	63.8	No	21
B_2	44	0.84	0.92	8.82	63.3	No	36
0.85–0.75%	52	0.81	0.86	6.12	64.5	No	21
	58	0.79	0.85	7.29	62.3	No	23
	36	0.81	0.85	5.10	63.7	Yes	19
	43	0.81	0.86	6.17	63.7	No	19
B_3	54	0.64	0.67	5.19	64.3	Yes	27
0.65–0.55%	59	0.62	0.63	1.33	62.6	No	22
	41	0.60	0.64	5.48	64.1	Yes	32
	40	0.64	0.65	2.60	63.3	Yes	27
	42	0.60	0.63	4.11	63.2	No	16
B_4	40	0.41	0.43	4.00	62.7	Yes	31
0.45–0.35%	39	0.41	0.45	8.00	63.0	Yes	18
	49	0.43	0.45	3.85	63.0	Yes	19
	41	0.40	0.41	2.04	64.3	Yes	20
	39	0.42	0.45	5.88	63.5	Yes	16

F_E = End-tidal sevoflurane concentration; F_I = Inspired sevoflurane concentration; N_2O = End-tidal nitrous oxide concentration; Duration = Total duration of end-tidal sevoflurane at time of incision.

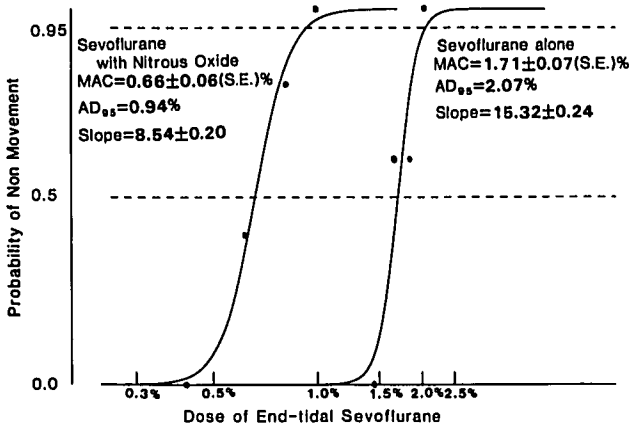

FIG. 1. The percentage of patients within each subgroup that moved was plotted against the subgroup's mean end-tidal sevoflurane concentration. Dose-response curves derived from data in tables 1 and 2. These two curves are the best-fitting logistic curves to individual observations. Probability of non-movement (not responding to skin incision) is represented by the vertical axis. The logarithm of the end-tidal sevoflurane concentration is represented by the horizontal axis. The curve on the right is for sevoflurane alone. MAC, the concentration at which probability of movement equals 0.5, is 1.71 ± 0.07% (SE). AD_{95}, the concentration at which 95% of patients do not move in response to skin incision, is 2.07%. The slope of the logistic curve is 15.32 ± 0.24 (SE). The curve on the left is for sevoflurane with 63.5 ± 0.4 (SD) end-tidal nitrous oxide. MAC is 0.66 ± 0.06% (SE). AD_{95} is 0.94%. The slope is 8.53 ± 0.20 (SE).

oil/gas partition coefficient times MAC for all anesthetics is a constant. The predicted sevoflurane MAC based on its oil/gas partition coefficient of 55[11] is 2.6%—or 52% greater than what was actually found. However, sevoflurane MAC predicted by Halsey is 1.7%, based on determinations in other species or systems.[12] The AD_{95} of 2.07% was about 20% greater than MAC, a similar relationship to that which exists with halothane.[4]

Nitrous oxide was very effective in decreasing sevoflurane MAC. The decrease was almost identical to the reduction in halothane MAC caused by a similar concentration of nitrous oxide.[10] If nitrous oxide has an additive effect, we can calculate the MAC for nitrous oxide alone as 104% (63.5 divided by 0.614). This is identical to that found by Hornbein *et al.* when nitrous oxide in oxygen was used under hyperbaric conditions.[13]

The addition of 63.5% end-tidal nitrous oxide reduced sevoflurane MAC by 1.05% (1.71 minus 0.66). If 63.5% nitrous oxide is equipotent to 1.05% sevoflurane, the predicted AD_{95} for sevoflurane with 63.5% end-tidal nitrous oxide is 1.02% (2.07 minus 1.05)—close to what was actually found, 0.94%.

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