Postanesthetic Respiratory Depression in Humans: A Comparison of Sevoflurane, Isoflurane and Halothane

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The postanesthetic respiratory depression with sevoflurane, isoflurane and halothane was studied in twenty-one patients. They were divided into three groups of seven patients each. One group underwent sevoflurane anesthesia, another group isoflurane and the third group halothane. Following extubation, the decrease in blood concentration of the anesthetic agent was most rapid with sevoflurane and slowest with halothane. Twenty minutes following extubation, resting ventilation and ventilatory response to carbon dioxide returned to the preanesthetic state with sevoflurane and isoflurane anesthesia. With halothane anesthesia, however, the depressive respiratory effects of halothane remained; depressed ventilatory response to carbon dioxide, decreased tidal volume and increased respiratory frequency. Although halothane has been reported to have the least depressive respiratory effect of the three, its elimination was slowest. Thus the respiratory effects of halothane persisted up to and past the twenty minute mark, far longer than with sevoflurane or isoflurane. (Key words: postanesthetic respiratory depression, sevoflurane, isoflurane, halothane)

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It is well known that halogenated ether and halogenated hydrocarbon anesthetics are dose dependent respiratory depressants[1–3]. At the same anesthetic levels, sevoflurane and isoflurane depressed respiration more profoundly than halothane[2,3]. Postanesthetic respiratory depression is, however, presumed to be dependent on the pharmacokinetics of the anesthetic agents used. The objectives of this study are to compare the postanesthetic changes in blood concentrations of sevoflurane, isoflurane and halothane and also to compare the sustained respiratory depressive effects of these anesthetics.

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Methods

Twenty-one patients scheduled for a minor surgery on the extremities or head were studied. The study was approved by the institutional human research committee of Hamamatsu University Hospital. They were divided into three groups of seven patients each. One group was anesthetized with sevoflurane, another with isoflurane and the other with halothane. There were no significant differences in age, height, weight or the duration of anesthesia between the three groups (table 1). On the day before anesthesia, resting ventilation and ventilatory response to carbon dioxide were measured. The latter was measured using a modified Read's method[4]. Expiratory volume was measured through an electric Wright respirometer (BOC Co., Ltd.). Output from the Wright respirometer was linearized using the system developed by Sanjo et al.[5], so

Table 1. Patient demographics

	Sevoflurane	Isoflurane	Halothane
Number of subjects (M/F)	7(3/4)	7(4/3)	7(3/4)
Age (yr)	35.6±16.3	46.7±13.2	36.7±9.5
Height (cm)	159.6±8.1	158.6±7.3	156.9±11.9
Weight (kg)	50.7±6.6	57.7±4.6	54.0±7.0
Anesthesia time (min)	234±42	257±65	256±44

All values given as mean±SD.

Table 2. The intervals between the cut off of the anesthetic vaporizer, and bucking and extubation

	Sevoflurane	Isoflurane	Halothane
Bucking (min)	8.51±4.31	10.57±7.22	7.76±4.00
Extubation (min)	12.29±5.48	14.42±6.04	13.77±3.08

All values given as mean±SD.

that reliable measurements were attained even at low flow rates. The subjects fasted for at least 11 hr before anesthesia and received no premedicant drugs. Before anesthesia was induced, arterial blood samples were obtained and gas tentions were measured using an ABL-2 (Radiometer Co., Ltd.). Anesthesia was then induced by mask with nitrous oxide, oxygen and either sevoflurane, isoflurane or halothane. The trachea was intubated with 1mg/kg succinylcholine chloride. Immediately after tracheal intubation, nitrous oxide was cut off. Intraoperatively, anesthesia was maintained with 35–40% oxygen, 60–65% nitrogen and one of the three anesthetics. The anesthetic breathing system used was a semiclosed circuit. After the effects of succinylcholine chloride had worn off, respirations were spontaneous throughout the study. Respiratory gases were monitored through a mass spectrometer (Perkin Elmer MGA-1100). The end-tidal anesthetic concentration was maintained at 1.3 MAC for at least 30 min before the end of operation. There the MAC of sevoflurane[6], isoflurane[7] and halothane[8] were assumed to be 1.71, 1.15 and 0.77%, respectively. Both inspired and end-tidal nitrous oxide concentrations were maintained at zero levels until the operation was finished. After the completion of the operation, the intervals between the cut off of the anesthetic vaporizer, and bucking and extubation were measured. During recovery from the anesthesia, fresh gas was kept at 8l/min of pure oxygen and respirations were spontaneous. During this time, the patients were asked at frequent intervals to open their eyes. Criteria for extubation were, (1) completion of the stage of delirium and (2) spontaneous eye opening on request. The specfic criteria for extubation were determined and applied by the same anesthesiologist. Following extubation, the patients breathed spontaneously through oxygen masks. Three arterial blood samples for measurement of gas tensions and arterial anesthetic concentrations were obtained immediately following extubation, 10 min following extubation and 20 min following extubation. The method of measurement for arterial anesthetic concentration followed a modification of the technique described by Theye[9]. 2.55ml of arterial blood samples were injected into 5.10 ml vacuumed vials, and after 15 min had elapsed, the pressures in the vials were returned to atmospheric pressure. The vials tonometered for 120 min or more at 37°C. 0.25 ml of the gas phase was injected into a gas chromatograph and analyzed with a flame ionization detector. A GC-9A (Shimadzu Co., Ltd.) was used as the gas chromatograph. The arterial anesthetic concentration was calculated from the atmospheric pressure, water vapor pressure and the blood gas partition coefficients of the anesthtics. The blood gas partition coefficients of sevoflurane[10], isoflurane[11] and halothane[12] were assumed to be 0.60, 1.4 and 2.3, respectively. Twenty min following extubation, resting ventilation and ventilatory response to carbon dioxide were again measured.

For intragroup comparisons, the values were analyzed by Student's paired t-test and for intergroup comparisons the values

Table 3. Postanesthetic changes of arterial carbon dioxide tension and arterial anesthetic concentration

	$Paco_2$ (torr)			Arterial anesthetic concentration (MAC)		
	Sevoflurane	Isoflurane	Halothane	Sevoflurane	Isoflurane	Halothane
Preanesth.	41.2±1.1	39.6±3.0	39.1±3.8			
Postanesth.						
0 min	47.8±6.8*	44.0±7.6	43.2±5.5	0.22±0.07	0.27±0.07	0.32±0.09
10 min	43.8±2.7*	41.1±1.6	42.6±2.9*	0.13±0.03#§	0.18±0.05	0.24±0.06
20 min	41.6±2.3	41.1±2.3	41.7±2.5	0.10±0.02#§	0.15±0.04§	0.21±0.04

All values given as mean±SD. Differences considered statistically significant when $P<0.05$.
The arterial anesthetic concentrations are converted to the alveolar anesthetic concentrations and are expressed in multiples of minimum alveolar concentration (MAC).
Preanesth: Before induction of anesthesia. Postanesth.: 0 min, immediately following extubation; 10 min, ten minutes following extubation; 20 min, twenty minutes following extubation.
*Differs from preanesthetic value. # Differs from isoflurane at the same time.
§ Differs from halothane at the same time.

Table 4. Comparison of resting ventilation and ventilatory response to CO_2 between preanesthesia and 20 min following extubation

	Preanesthesia			Postanesthesia		
	Sevoflurane	Isoflurane	Halothane	Sevoflurane	Isoflurane	Halothane
V_T (ml)	379±50	429±122	356±64	330±53	366±106	299±76*
f (breaths/min)	15.4±2.2	15.9±2.9	16.3±3.5	16.0±3.0	17.4±3.0	19.8±2.6*
$\dot{V}_E$ (l/min)	5.81±1.01	6.57±1.39	5.60±0.80	5.17±0.95	6.07±1.00	5.79±1.26
S (l/min/torr)	1.16±0.38	1.14±0.38	1.15±0.41	1.17±0.43	0.96±0.35	0.73±0.20*§

All values given as mean±SD. Differences considered statistically significant when $P<0.05$.
Preanesthesia: The day before anesthesia. Postanesthesia: 20 min following extubation.
V_T: tidal volume. f: respiratory frequency. $\dot{V}_E$: expired minute volume. S: slope of CO_2 response curve. * Differs from preanesthetic value. § Differs from sevoflurane.

were analyzed by Student's t-test. Statistical significance was assumed when $P < 0.05$.

Results

Among the three groups, there were no significant differences in the intervals between the cut off of the anesthetic vaporizer, and bucking and extubation (table 2). Assuming that the arterial anesthetic partial pressure is equal to the alveolar anesthetic partial pressure, the arterial anesthetic concentration is converted to the alveolar anesthetic concentration and is expressed in multiples of minimum alveolar concentration (MAC) (table 3). Immediately following extubation, although there were no significant differences in the anesthetic levels (multiples of MAC) between the three groups, the anesthetic level was highest in the halothane group and lowest in the sevoflurane group, with the isoflurane group between. Ten min following extubation, the anesthetic level in the sevoflurane group was significantly lower than in the isoflurane or halothane groups. Twenty min following extubation, the anesthetic level in the sevoflurane group was significantly lower than in the isoflurane or halothane groups, and the anesthetic level in the isoflurane group was significantly lower than in the halothane group.

Postanesthetic changes in arterial carbon dioxide tension are shown in table 3. In the sevoflurane group, immediately following

extubation and 10 min following extubation, arterial carbon dioxide tensions were significantly higher than the preanesthetic values. Twenty min following extubation, they had returned to the preanesthetic levels. In the halothane group, 10 min following extubation, arterial carbon dioxide tension was significantly higher than the preanesthetic value. Immediately following extubation and 20 min following extubation, they were not significantly different from the preanesthetic value. In the isoflurane group, there were no significant differences in arterial carbon dioxide tensions between preanesthesia and all three postanesthetic points. For all three groups, every arterial blood sample had an oxygen tension of 90 torr or more.

Preceding anesthesia, there were no significant differences in the slopes of ventilatory response curves to carbon dioxide between the sevoflurane, isoflurane and halothane groups (table 4). In the halothane group, 20 min following extubation, the slopes of ventilatory response curves to carbon dioxide were flatter than preanesthetic values. In the sevoflurane and isoflurane groups, however, the slopes of the curves had returned to preanesthetic levels at this point. Furthermore, 20 min following extubation, the slopes in the halothane group were flatter than in the sevoflurane group. But there were no significant differences between the sevoflurane and isoflurane groups or between the isoflurane and halothane groups.

In the halothane group, 20 min following extubation, tidal volume decreased and respiratory frequency increased when compared with preanesthetic values. In the sevoflurane and isoflurane groups, tidal volume, minute volume and respiratory frequency were not significantly different between preanesthesia and 20 min following extubation. In both preanesthesia and 20 min following extubation, tidal volume, minute volume and respiratory frequency were not significantly different between the sevoflurane, isoflurane and halothane groups.

Discussion

It had been expected that the intervals between the cut off of the anesthetic vaporizer, and bucking and extubation in the sevoflurane and isoflurane groups would be shorter than in the halothane group because of their low blood gas partition coefficients. Contrary to the expectations, however, the intervals were not significantly different between the three groups. A possible cause for this might be due to the greater respiratory depressive effects of sevoflurane and isoflurane at the same anesthetic depth[2,3]. During recovery from anesthesia, sevoflurane and isoflurane possibly decreased the alveolar ventilation more than halothane, so that the elimination of these anesthetics was retarded. And the slow elimination might antagonize the rapid decrease of anesthetic blood concentrations due to the low blood gas partition coefficients in the sevoflurane group and the isoflurane group.

After extubation, it is difficult to accurately sample end-tidal gas which can be assumed to be alveolar gas. Therefore, we adopted arterial anesthetic partial pressures to evaluate the cerebral anesthetic partial pressure. It is doubtful, however, whether the arterial anesthetic partial pressure could be equal to the cerebral anesthetic partial pressure when the steady state has not been established, as in the state of recovery from anesthesia in this study. Stoelting et al.[13] reported that the MAC awake to MAC ratio of halothane was 0.52 and that the ratios were fairly close for four agents; halothane, methoxyflurane, ether and fluroxene, when the alveolar concentrations were held constant. And when the alveolar concentrations were allowed to fall spontaneously, the MAC awake to MAC ratio wtih halothane was 0.33, which was much lower than at constant alveolar concentrations, while the ratio with methoxyflurane was similar to the value at constant alveolar concentration. Therefore, they suggested that poorly soluble anesthetics would have large partial pressure differences between the cerebrum and alveolar gas. In this study, the alveolar anesthetic concentration to MAC ratios immediately following extubation in the sevoflurane, isoflurane and halothane groups

were 0.22, 0.27 and 0.32, respectively. These data indicate that anesthetics with low blood gas partition coefficients have a large alveolar cerebral anesthetic partial pressure difference. Therefore, intergroup comparisons of arterial anesthetic concentration changes following extubation are not meaningful. Thus, the ratios of arterial anesthetics concentrations between 20 min following extubation and immediately following extubation were calculated. In the sevoflurane, isoflurane and halothane groups, the ratios were 0.45, 0.56 and 0.66, respectively. These data suggest that sevoflurane and isoflurane are eliminated more rapidly than halothane.

Twenty min following extubation in the halothane group, the ventilatory response to carbon dioxide was depressed and the characteristic effects of halothane on resting ventilation remained, i.e., decreased tidal volume and increased respiratory frequency. Both indicate that the respiratory depression with halothane continued for at least 20 min following extubation. In the sevoflurane and isoflurane groups, however, the ventilatory responses to carbon dioxide and resting ventilations had completely recovered by 20 min following extubation. Although sevoflurane and isoflurane have more profound respiratory depressive effects than halothane, their low solubility may allow more rapid recovery from respiratory depression than halothane.

In all three groups, the arterial carbon dioxide tensions had almost returned to normal range 10 min following extubation. Therefore, when patients not suffering from pulmonary disease undergo non-thoracic or non-abdominal surgery (that can not disturb respiration), postanesthetic respiratory depression will not be great and will not persist too long when any of the three anesthetic agents are used. However, in patients where some respiratory depression factors are present, e.g. respiratory disease, surgical damage to respiration, heavy premedication or persistence of muscle relaxants, the persistent respiratory depression to halothane may interact with these factors and act as a profound respiratory depressant even 20 min following extubation.

In conclusion,

1) The postanesthetic decrease of blood anesthetic concentration was most rapid with sevoflurane and slowest with halothane following extubation.

2) Respiratory depression with sevoflurane and isoflurane diminished more rapidly than with halothane because of their low solubility.

3) Respiratory effects of halothane remained for at least 20 min following extubation

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