Laboratory Investigation

A comparison of sevoflurane with halothane, enflurane, and isoflurane on bronchoconstriction caused by histamine

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This study was conducted to assess the effect of sevoflurane on lung resistance and compliance, and its responsiveness to histamine. We studied eight dogs to compare the effect of sevoflurane, isoflurane, enflurane, and halothane on bronchoconstriction caused by histamine. Baseline values of pulmonary resistance (R_L) and dynamic pulmonary compliance (C_{dyn}) were measured prior to administration of histamine. Histamine (2, 4, and 8 $\mu g \cdot kg^{-1}$) were administered iv, and the values of R_L and C_{dyn} at the time of peak effect were recorded. Under 1 or 2 MAC anaesthesia, sevoflurane as well as the other three anaesthetics had no bronchoactive effects. The four anaesthetics, including sevoflurane, demonstrated inhibitory effect on increases in R_L and decreases in C_{dyn} caused by histamine. At 1 MAC anaesthesia, % changes in R_L caused by 2, 4, or 8 $\mu g \cdot kg^{-1}$ of histamine were 38 ± 11, 85 ± 21, or 132 ± 24% (mean ± SE) for halothane, and 65 ± 11, 132 ± 15, or 172 ± 19% for sevoflurane, respectively. Sevoflurane was less effective than halothane in preventing increases in R_L. In preventing decreases in C_{dyn}, sevoflurane was less effective than halothane only at 8 $\mu g \cdot kg^{-1}$ of histamine under 1 and 2 MAC anaesthesia. There was no difference in attenuating effect on changes in R_L and C_{dyn} between sevoflurane and isoflurane or enflurane. We concluded that sevoflurane was less potent than halothane in attenuating changes in R_L and C_{dyn} in response to iv histamine.

Cette étude a été réalisée dans le but d'évaluer les effets du sévoflurane sur la résistance et la compliance pulmonaires en réponse à l'histamine. Les effets du sévoflurane, de l'isoflurane, de l'enflurane et de l'halothane sur la bronchoconstriction induite par l'histamine sont comparés sur huit chiens. Avant l'administration d'histamine, on mesure les valeurs initiales de la résistance (R_L) et de la compliance dynamique (C_{dyn}) pulmonaires. L'histamine (2, 4, 8 $\mu g \cdot kg^{-1}$) est administrée par la voie veineuse et les valeurs maximales de la R_L et de la C_{dyn} sont enregistrées. Les quatre anesthésiques, dont le sévoflurane inhibent l'augmentation de la R_L et la diminution de la C_{dyn} provoquées par l'histamine. A MAC 1 d'anesthésie, les pourcentages de changement de R_L produits par 2, 4, ou 8 $\mu g \cdot kg^{-1}$ d'histamine sont respectivement de 38 ± 11, 85 ± 21, ou 132 ± 24% (moyenne + SD) pour l'halothane, et de 65 ± 11, 132 ± 15, ou 172 ± 19% pour le sévoflurane. Le sévoflurane est moins efficace que l'halothane pour prévenir les augmentations de R_L. Le sévoflurane est moins efficace pour prevenir la diminution de C_{dyn} mais seulement à 8 $\mu g \cdot kg^{-1}$ d'histamine sous anesthésie à MAC 1 et 2. Le sévoflurane, l'halothane et l'isoflurane ne sont pas de différents pour amortir les changements de R_L et C_{dyn}. Nous concluons que le sévoflurane est moins puissant que l'halothane pour diminuer la réponse à l'histamine de la R_L et de la C_{dyn}.

Key words
ANAESTHETICS, VOLATILE: enflurane, halothane, isoflurane, sevoflurane;
ALLERGY: histamine
CONSTRICTION: bronchospasm.

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Sevoflurane is widely used in clinical anaesthesia in Japan, and has several potential advantages in asthmatic patients including low arrythmogenecity in response to epinephrine,[1] rapid induction,[2] and low airway irritability.[3] Other volatile anaesthetics have been reported to have antagonistic effects to bronchoconstriction caused by chemical mediators or antigens.[4-6] The effect of sevoflurane on lung resistance and compliance, and its responsiveness to histamine, are not known. We compared the effect of sevoflurane, halothane, enflurane, and isoflurane in dogs on the bronchoconstriction caused by *iv* histamine – one of the primary mediators of immediate-type hypersensitivity.

Methods

With approval from the local ethics committee, we performed experiments on eight beagle dogs weighing 9.0 to 12.5 kg. Each dog served as its own control. The studies were conducted in random order. At least one week elapsed between successive studies in any one dog. The anaesthetic breathing system used was a non-rebreathing circuit. Anaesthesia was induced with pentobarbital 30 $mg \cdot kg^{-1}$ *iv*. Following tracheal intubation with an 8.0 mm cuffed oral endotracheal tube of which flow resistance was 0.23 cm $H_2O \cdot s^{-1} \cdot L^{-1}$, the lungs were ventilated at a tidal volume of 20 $ml \cdot kg^{-1}$ and a frequency of about 10 min^{-1} to maintain end-tidal carbon dioxide partial pressure at about 35 mmHg by a piston type ventilator (Harvard Apparatus, Millis, MA). End-tidal gas samples were collected with a catheter, the tip of which was placed at the tracheal end of an endotracheal tube. Concentrations of oxygen, carbon dioxide, nitrogen, and inhalational anaesthetics were continuously measured via with a mass spectrometer (Perkin Elmer 1100, Pomona, CA). Mas spectrometer was calibrated with calibration gas in prior to every experiment.

The effects of halothane, enflurane, isoflurane, and sevoflurane on pulmonary resistance (R_L) and dynamic pulmonary compliance (C_{dyn}) were compared at a constant and equivalent depth of anaesthesia. The MAC values of halothane, enflurane, isoflurane, and sevoflurane were taken to be 0.87%, 2.2%, 1.48%, and 2.36%, respectively.[7-10] A constant end-tidal anaesthetic concentration was established and held for a minimum of 15 min before each measurement. After a steady-state end-tidal anaesthetic concentration at the desired MAC (0, 1 or 2 MAC) was established, the lungs were inflated a few times until the airway pressure increased to 40 cm H_2O. Five minutes later, baseline values of R_L and C_{dyn} were recorded prior to administration of histamine.

The R_L and C_{dyn} were calculated from simultaneous pressure and airflow curves during fixed volume-controlled ventilation. The tip of an oesophageal balloon was placed at the level of the nipple line and adjusted to minimum cardiac and oesophageal artifacts. The balloon contained 0.8 ml air. A separate catheter connected to suction was placed in the oesophagus to keep it empty of air and liquid. Transpulmonary pressure was measured by a differential pressure transducer (RMP-6008, Nihon Koden Co., Tokyo, Japan) placed between the oesophagus and the proximal end of the endotracheal tube. Airflow was measured with a Fleisch pneumotachograph (21-070B, Yokogawa Hewlett Packard Co, Tokyo, Japan). The pressure and airflow signals were recorded with a digital signal recorder and simultaneously projected in an X-Y display on a microcomputer terminal. After analogue to digital conversion of these electrical signals, we integrated airflow to obtain tidal volume and calculated C_{dyn} by dividing the tidal volume by the pressure change measured between points at which the airflow was zero and subtracted a numeric value proportional to lung volume from transpulmonary pressure to eliminate the portion of pressure due to elastic recoil. The slope of the resulting line is R_L. The R_L and C_{dyn} were calculated repeatedly every two to three breaths. Running averages of two consecutive values were recorded with a microcomputer throughout the experiment. Flow signal was calibrated with a soap bubble flow meter (F-1, Igarashi Ika Co, Tokyo, Japan) and pressure signal was calibrated with a pressure calibrator (VERI-CAL, Utah Medical Inc., Midvadle, UT). We did not calibrate volume directly, because it was calculated by integrating flow signal. We confirmed that the volume measurement was correct by using a 500 ml calibration syringe. Freshly prepared solutions of histamine (2, 4, and 8 $\mu g \cdot kg^{-1}$) were administered *iv*. The solutions were injected into a catheter in the saphenous vein, and the catheter was rapidly flushed with 5 ml saline. Values of R_L and C_{dyn} prior to histamine administration and values at the time of peak effect on R_L and C_{dyn} were used for statistical analysis. Time to peak effect on resistance and compliance was within 90 sec. The R_L and C_{dyn} were expressed as absolute values and as a percentage of change from pre-administration values. All data are reported as mean ± SEM and were analyzed by paired Student's t tests with Bonferroni's correction. The level of statistical significance used was $P < 0.05$.

Results

Baseline R_L and C_{dyn} were not different during anaesthesia with each dose of each inhalational anaesthetic agent (Table). Intravenous histamine produced increases in R_L and decreases in C_{dyn} in a dose-related manner. The average percentage change in pulmonary resistance and dynamic compliance after histamine challenge are shown in Figures 1 and 2. Sevoflurane, isoflurane, en-

TABLE Baseline values for resistance (R_L) and compliance (C_{dyn})

	R_L (cm $H_2O \cdot L^{-1} \cdot s^{-1}$)			C_{dyn} (ml · cm H_2O^{-1})		
Pentobarbital	4.6 ± 0.23			52 ± 5		
	0 MAC	*1 MAC*	*2 MAC*	*0 MAC*	*1 MAC*	*2 MAC*
Halothane	4.4 ± 0.22	4.8 ± 0.21	4.4 ± 0.23	58 ± 6	68 ± 10	65 ± 8
Isoflurane	4.8 ± 0.22	4.4 ± 0.24	4.8 ± 0.21	52 ± 6	58 ± 10	59 ± 9
Enflurane	4.3 ± 0.22	4.6 ± 0.23	4.5 ±0.22	54 ± 5	59 ± 12	57 ± 6
Sevoflurane	4.5 ± 0.22	4.8 ± 0.22	4.6 ± 0.21	49 ± 4	58 ± 8	62 ± 8

Mean ± SE of eight dogs.

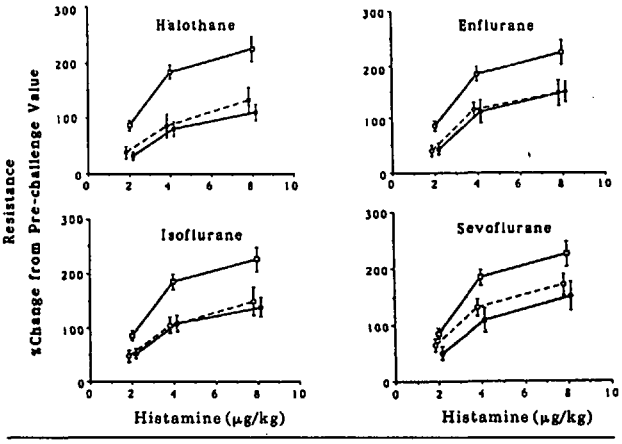

FIGURE 1 Mean percent change (±SE) in pulmonary resistance after increasing doses of histamine in the same eight dogs during pentobarbital anaesthesia = control (— □ —), 1 MAC (— ○ —), and 2 MAC (— ● —) anaesthesia with halothane, isoflurane, enflurane, and sevoflurane.

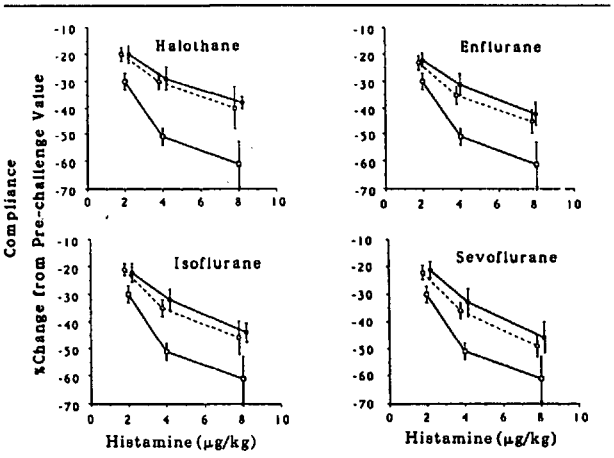

FIGURE 2 Mean percent change (±SE) in dynamic compliance after increasing doses of histamine in the same eight dogs during pentobarbital anaesthesia = control (— □ —), 1 MAC (— ○ —), and 2 MAC (— ● —) anaesthesia with halothane, isoflurane, enflurane, and sevoflurane.

flurane, and halothane reduced the increases in pulmonary resistance and decreases in dynamic compliance caused by histamine; 2 MAC sevoflurane was not detectably more effective than 1 MAC sevoflurane.

There was no difference in the effects on changes in R_L and C_{dyn} between sevoflurane and isoflurane or enflurane (Figure 3). Percent change in R_L caused by 2, 4, or 8 $\mu g \cdot kg^{-1}$ histamine was 38 ± 11, 85 ± 21, or 132 ± 24% (mean ± SE) at 1 MAC halothane, and 65 ± 11, 132 ± 15, or 172 ± 19% at 1 MAC sevoflurane, respectively. Percent change in R_L caused by 8 $\mu g \cdot kg^{-1}$ histamine was 110 ± 15% at 2 MAC halothane, and 152 ± 26% at 2 MAC sevoflurane. Sevoflurane was less effective than halothane in preventing increases in R_L at each dose of histamine under 1 MAC anaesthesia and at 8 $\mu g \cdot kg^{-1}$ of histamine under 2 MAC anaesthesia. In preventing a decrease in C_{dyn}, sevoflurane was less effective than halothane only at 8 $\mu g \cdot kg^{-1}$ of histamine under 1 MAC and 2 MAC anaesthesia.

Discussion

Histamine, one of the primary mediators of immediate-type hypersensitivity, is a potent bronchoconstrictor. Our study was designed to minimize the physical stimulation by administrating histamine intravenously. We measured R_L, not airway resistance, and R_L is the sum of airway resistance and tissue resistance. The increase of R_L in response to histamine can be caused not only by an increase of airway resistance but also by an increase of tissue resistance. Therefore increases in the response of R_L to intravenous histamine may reflect increases in airway resistance, increases in tissue resistance, or both.

Neither halothane, enflurane, isoflurane, nor sevoflurane altered R_L and C_{dyn} in an unmedicated airway; nor did R_L or C_{dyn} change as anaesthetic depth increased. These findings agree with previous studies by Hickey *et al.*,[5] and Colgan[11] in dogs anaesthetized with halothane. On the other hand, Klide and Aviado showed that halothane in oxygen caused a decrease in R_L and an increase

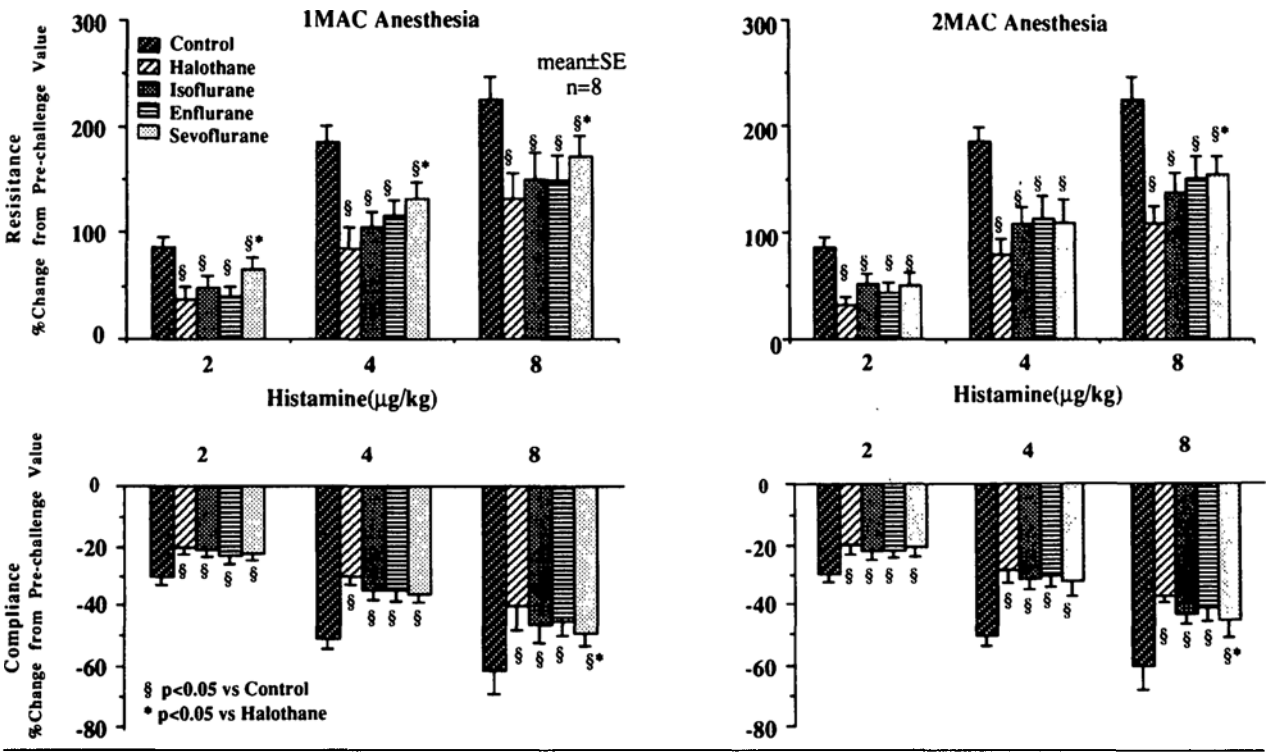

FIGURE 3 Histogram showing the mean percent increase (±SE) in pulmonary resistance and the mean percent decrease in dynamic compliance after increasing doses of histamine in the same eight dogs during pentobarbital anaesthesia (control), 1 MAC, and 2 MAC anaesthesia of halothane, isoflurane, enflurane, and sevoflurane.

in C_{dyn} and the mechanism was stimulation of beta receptors in the airway.[12] However, the control values of R_L measured in their studies were higher than in other studies including our study. This suggests that the airways of their dogs were constricted initially. The baseline values of both R_L and C_{dyn} seemed to differ substantially from those observed in dogs by other investigators.[4] Both R_L and C_{dyn} were not independent of the size of subjects. A small dog has a high pulmonary resistance and a low pulmonary compliance. The dogs in their study[4] were about twice as heavy as our dogs and this explains why the baseline values of both R_L and C_{dyn} in the present study differ from those of other studies.

The determination of the effect of anaesthetics on the chemical mediator-challenged airway as well as the unmedicated airway is essential. This study demonstrated that *iv* histamine causes bronchoconstriction in dogs in a dose-related manner. Halothane, enflurane, isoflurane, and sevoflurane attenuated the bronchoconstriction, but did not abolish it. A difference between 1 MAC and 2 MAC in this effect was not detected. This finding agrees with other studies[5,13] in halothane-anaesthetized dogs. Vettermann *et al.* showed that isoflurane and enflurane inhibited bronchoconstriction caused by vagus nerve stimulation in a dose-related manner during <1 MAC anaesthesia.[14] During >1 MAC anaesthesia, however, the dose–effect relationship was not clear. At <1 MAC anaesthesia, these agents were not so effective in inhibiting the bronchoconstriction.

Histamine has both a direct action on H1-receptors on the airway smooth muscle and an indirect action by a vagovagal reflex evoked by stimulation of subepithelial irritant receptors within the airway. However, the precise contribution of each of those components to the bronchoconstriction provided by histamine has varied in numerous studies. Some studies showed that most of the bronchoconstriction that occurred with histamine was mediated by vagovagal reflex,[13] whereas other studies demonstrated primarily a direct effect.[15,16] One of the methodological problems which may account for the differences in findings is the route of administration of histamine. Histamine infused *iv* or injected into the pulmonary circulation, which supplies the respiratory bronchioles and alveoli, had only a direct effect on smooth muscle, whereas inhalation of histamine aerosols resulted in a pronounced vagally mediated response.[17] The dose of histamine also appears to be important. Drazen and Austen demonstrated that the effects of low-dose histamine (3.0 $\mu g \cdot kg^{-1}$) on the airway, which were abolished by atropine, were mediated by cholinergic reflex

mechanism, and at higher dose (9.0 $\mu g \cdot kg^{-1}$) there was both a direct and a neurally mediated cholinergic action, when histamine was administered intravenously.[18]

In the present study, at low doses (2.0 and 4.0 $\mu g \cdot kg^{-1}$) of histamine, the difference in the attenuating effect between halothane and sevoflurane was detected in resistance changes, not in compliance changes. The fact that vagal efferent nerve endings are distributed predominantly in central and upper airways may explain the finding.

A large dose of histamine acts not only by increasing cholinergic tone, but also by direct constriction of peripheral airway smooth muscle.[13] Therefore by using a large dose of histamine, the difference of a direct effect between anaesthetics could be more detectable than by using a low dose. Sevoflurane was less effective than halothane in preventing a decrease in C_{dyn} at the high dose of histamine. Changes in R_L or C_{dyn} could result from changes in central or peripheral airway resistance or compliance or from both. Although our measurement technique could not allow one to distinguish such regional differences, these findings suggest that halothane has a direct inhibitory effect on constriction of airway smooth muscle and sevoflurane has also a direct effect but that is weaker than halothane. Yamakage *et al.* reported that halothane directly inhibited tracheal smooth muscle contraction more effectively than sevoflurane, using muscle strips.[19]

The modest differences in the effects of halothane and sevoflurane observed may have some importance in clinical practice. Sevoflurane, however, still has several potential advantages in asthmatic patients including low arrythmogenecity in response to epinephrine,[1] rapid induction,[2] and low airway irritability.[3] Sevoflurane is superior to halothane in respect of low arrythmogenecity and rapid induction. We did not think the findings of the study showed halothane was more useful in anaesthesia for asthmatic patients than sevoflurane.

In summary, neither halothane, enflurane, isoflurane, nor sevoflurane altered R_L and C_{dyn} in the unmedicated airway nor did R_L or C_{dyn} change as anaesthetic depth increased. These four anaesthetics, including sevoflurane, attenuated the bronchoconstricter response to intravenous histamine. There was no difference in attenuating effect on changes in R_L and C_{dyn} between sevoflurane and isoflurane or enflurane. Sevoflurane was less effective than halothane in preventing increases in R_L and decreases in C_{dyn} provoked by histamine at equivalent multiples of MAC.

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