Apnea during induction of anesthesia with sevoflurane is related to its mode of administration

[L'apnée pendant l'induction de l'anesthésie avec du sévoflurane est reliée au mode d'administration]

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Purpose: The incidence and duration of apnea during sevoflurane anesthesia have not been fully characterized. We hypothesized that sevoflurane at slowly increasing concentrations reduces incidence and shortens the duration of apnea compared to administration of a highly concentrated anesthetic mixture.

Methods: 131 women were randomly assigned to receive 35% oxygen in air and sevoflurane at: incremental concentrations of 1%, from 1% to 8% (group 1–8%, $n = 42$); decremental-incremental concentrations of 2%, from 8% to 4% and then from 4% to 8% (group 8–4–8%, $n = 36$); or fixed concentrations of 8% for induction of anesthesia (group 8%, $n = 53$). A blinded investigator observed whether and for how long patients stopped breathing.

Results: All groups reached 2.5 minimum alveolar concentration of end-tidal sevoflurane. Although apnea was observed in all groups, it was more frequent in the 8% group than in 1 to 8% (68% *vs* 21%, $P < 0.05$) or 8 to 4 to 8% groups (68% *vs* 20%, $P < 0.05$). Duration of apnea was also more pronounced in the 8% group than in 1 to 8% and 8 to 4 to 8% groups (58 ± 25 s *vs* 32 ± 18 sec, $P < 0.05$ and *vs* 35 ± 16 sec, $P < 0.05$, respectively).

Conclusions: Sevoflurane induces apnea more frequently and for longer duration at a fixed high concentration compared to incremental or decremental-incremental concentrations. Decremental-incremental concentrations offer the additional advantage of a speed of induction similar to that elicited by the 8% concentration.

Objectif : *L'incidence et la durée de l'apnée pendant l'anesthésie au sévoflurane n'ont pas été entièrement définies. Nous avons cru que le sévoflurane administré en concentrations lentement progressives réduisait l'incidence et la durée de l'apnée comparativement à un mélange anesthésique très concentré.*

Méthode : *Nous avons réparti au hasard 131 femmes qui ont reçu un mélange de 35 % d'oxygène dans de l'air et du sévoflurane : en concentrations incrémentielles de 1 %, de 1 % à 8 % (groupe 1–8 %, n = 42) ; en concentrations décrémentielles-incrémentielles de 2 %, de 8 % à 4 %, puis de 4 % à 8 % (groupe 8–4–8 %, n = 36) ou en concentrations fixes de 8 %, pour l'induction de l'anesthésie (groupe 8 %, n = 53). Un chercheur impartial a vérifié la présence et le temps d'apnée.*

Résultats : *Une concentration alvéolaire minimale de 2,5 de sévoflurane télé-expiratoire a été atteinte chez toutes les patients. L'apnée a été observée dans tous les groupes, mais était plus fréquente dans le groupe de 8 % que dans celui de 1 à 8 % (68 % vs 21 %, P < 0,05) ou de 8-4-8 % (68 % vs 20 %, P < 0,05). La durée de l'apnée a été aussi plus prononcée dans le groupe de 8 % que dans ceux de 1 à 8 % et de 8-4-8 % (58 ± 25 s vs 32 ± 18 s, P < 0,05 et vs 35 ± 16 s, P < 0,05, respectivement).*

Conclusion : *L'apnée est plus fréquente et dure plus longtemps avec de fortes concentrations fixes de sévoflurane qu'avec des concentrations incrémentielles ou décrémentielles-incrémentielles. Ces dernières concentrations ont un avantage supplémentaire, celui de permettre une induction aussi rapide qu'une concentration à 8 %.*

SEVOFLURANE is a potent inhaled anesthetic that provides rapid induction of anesthesia and rapid recovery. It is increasingly used for induction of anesthesia because it does not have an unpleasant odour and is less irritating to the upper airways than other inhalational agents, permitting administration of anesthesia via face mask.[1] Similar to isoflurane, sevoflurane causes

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This study has been supported by departmental funds from the University of Perugia.

This report was presented at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 16, 2001.

Accepted for publication October 19, 2004.

Revision accepted February 23, 2005.

depression of the central nervous,[2,3] cardiovascular,[4] and respiratory [5] systems in a dose-dependent fashion.

Sevoflurane is an acceptable induction agent in adult patients [6,7] and is useful for allowing intubation without muscle relaxants.[1] Like other inhaled anesthetics, sevoflurane causes respiratory depression at clinically relevant doses,[8] including a reduction in tidal volume and increased breathing frequency insufficient to compensate for the reduction in tidal volume.[5] When maintenance of spontaneous breathing is desired, apnea during the administration of anesthetics is potentially dangerous. Anesthetics or anesthetic techniques with subtler respiratory depressant effects might be of great value.

We hypothesized that duration and incidence of apnea are related to the speed of the administration of sevoflurane during induction of anesthesia.

Methods

After obtaining patient written informed consent and approval of the local Ethics Committee, 131 healthy females, ASA physical status I undergoing gynecological procedures under general anesthesia as day patients were randomly allocated to three groups with carefully prepared opaque sealed envelopes: 1) Induction with sevoflurane at incremental concentrations of 1%, from 1% to 8% each three breaths (group 1–8%, $n = 42$); 2) Induction at decremental-incremental concentrations of 2%, from 8% to 4% each three breaths; when patients lost consciousness, the vaporizer was reset at 8% (group 8–-4–8%, $n = 36$); or 3) Induction at a fixed concentration of 8% (group 8%, $n = 53$).

After loss of consciousness, administration of 8% sevoflurane was continued until every patient in each group reached an end-tidal value of 5% [2.5 minimum alveolar concentration (MAC)]. At that point we considered the induction of anesthesia complete, surgery began, and the vaporizer was set at a concentration that varied depending upon the need of the patient. Patients with any clinically significant history of alcohol or drug abuse were excluded. No patients were premedicated. Standard monitors were applied. All patients were breathing room air before induction of anesthesia. Patients were instructed to breathe regularly, maintaining their resting tidal volume and respiratory rate. Then a transparent mask was applied gently to the face, and the patients slowly began to breathe one of the anesthetic mixtures identified above.

We used sevoflurane with a mixture of 35% oxygen in air at a fresh gas flow of 8 $L \cdot min^{-1}$, without prefilling the anesthetic circuit. The inspiratory and expiratory limbs of the circle were connected by a Y-connector. Respiratory gases were sampled from the mask elbow connector at a rate of 200 $mL \cdot min^{-1}$ into the anesthesia machine gas monitor in order to monitor end-tidal concentrations of gases.

TABLE Demographic data

Variable	*1 to 8% group (n = 42)*	*8 to 4 to 8% group (n = 36)*	*8% group (n = 53)*
Age (yr)	27.4 ± 5.1	29 ± 4.6	29.3 ± 4.4
Weight (kg)	60.8 ± 10.6	61 ± 11.5	62.2 ± 8.5
Height (cm)	161.9 ± 6	163.4 ± 4.9	162.3 ± 6.8

Values are mean ± SD.

Loss of consciousness was defined as the failure to respond to verbal commands. Verbal commands were repeated at ten-second intervals until patients failed to respond. An intern blinded to the anesthetic technique observed whether and for how long the patients stopped breathing; in addition, any adverse events during induction of anesthesia were recorded. If a patient stopped breathing, the head was repositioned and a gentle jaw thrust was applied for five seconds to ensure that apnea was not caused by upper airway obstruction. Recording of adverse events started at the first tidal breath inspiration and ended when sevoflurane reached the end-tidal value of 5%. Before discharge (four hours after surgery), patients were asked whether the induction technique used was pleasant/unpleasant.

A Chi-square test was used to compare the incidence of apnea, and analysis of variance, followed by a Tukey *post hoc* test, was used to compare the duration of apnea and the time for loss of consciousness among groups. A Chi-square *post hoc* analysis was performed to analyze the power of the study. Statistical analysis was performed with SigmaStat 2.0 (Jandel Scientific Software, San Rafael, CA, USA). Results are presented as mean ± SD or 95% conficence interval (CI). $P < 0.05$ was considered significant.

Results

The three study groups were comparable (Table). The patients were 19 to 34 yr of age, with a weight range of 42 to 100 kg and a height range of 150 to 180 cm. Anesthesia was induced successfully in all patients. In all groups, oxygen saturation was higher than 95% on room air and increased slightly following application of the face mask.

Apnea was observed in all groups, but more frequently in the 8% group [68% (95% CI 54–79%)] than in 1 to 8% [21% (CI 12–36%)] and 8 to 4 to 8% groups

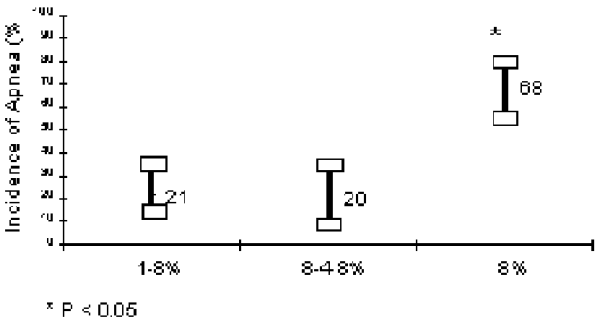

FIGURE 1 Apnea was more frequent during induction of anesthesia at 8% doses (8% group) than with incremental (1–8% group) and decremental (8–4–8% group) administrations of sevoflurane. Results are presented as 95% confidence intervals. *$P < 0.05$ compared to incremental and decremental groups.

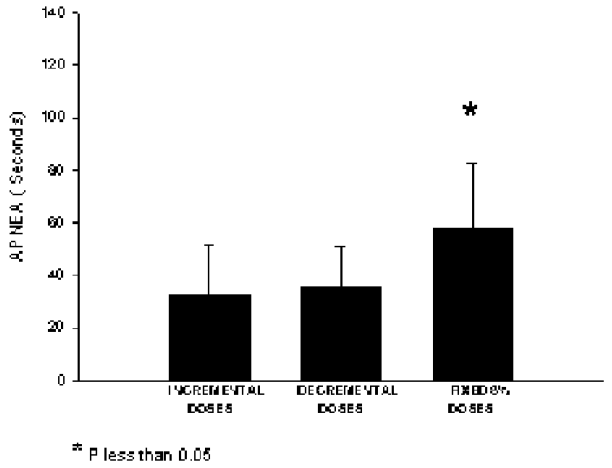

FIGURE 2 Apnea lasts longer after 8% administration (8% group) than after incremental (1–8%) or decremental (8–4–8%) doses. Each bar represents the mean ± SD. $P < 0.05$ compared to incremental and decremental groups.

[20% (CI 10–36 %), $P < 0.05$]; (Figure 1). A Chi-square *post hoc* analysis showed a power of 0.8 with alpha of 0.05. Additionally, the duration of apnea was more prolonged by the 8% concentration (58 ± 25 sec) than at incremental or decremental-incremental doses (32 ± 18 and 35 ± 16 sec, respectively); (Figure 2). The mean time required for loss of consciousness was significantly delayed in the 1 to 8% group (75 ± 9 sec) compared to the 8 to 4 to 8% (54 ± 8 sec) and 8% groups (47 ± 11 sec); ($P < 0.05$).

In all groups apnea was observed only once; when patients re-established spontaneous ventilation, they had no further episode of apnea even at an end-tidal concentration of 2.5 MAC. All patients re-established spontaneous breathing, making assisted ventilation unnecessary and no abdominal or chest wall movements were observed before or after applying the jaw thrust once apnea was observed.

There were no episodes of cough, laryngospasm, or excessive salivation. Involuntary movements did not interfere with induction of anesthesia. The incidence was 30% in the 8 to 4 to 8% group compared to the 8% and 1 to 8% groups (23% and 17% respectively), P = NS. All but one of the patients anesthetized with the slow technique (and all patients in the other two groups) rated the anesthetic technique as pleasant.

Discussion

The current study shows that the duration and incidence of apnea is associated with the mode of administration of sevoflurane: the higher the initial concentration delivered, the higher the incidence and the longer the duration of apnea.

Since all patients reached the same end-tidal concentrations (2.5 MAC), if the mechanism of apnea were dose-dependent, at a given concentration, all groups should have shown almost the same incidence and duration of apnea. However, groups differed with respect to both the incidence and duration of apnea, and these differences were more pronounced between the 1 to 8% and 8% groups. Our study shows that gradually increasing the inspired concentration of sevoflurane during induction of anesthesia limits the incidence and duration of apnea. Using decremental-incremental concentrations offers the additional advantage of accelerating loss of consciousness compared to gradually increasing concentrations.

As with the majority of *iv* anesthetics,[9] the faster sevoflurane is administered the higher is the chance the patient will become apneic. A possible explanation is that the speed of administration of the inhaled agent could lower the carbon dioxide threshold for establishing apnea. However, the end-tidal CO_2 values showed no differences between groups, either before or during sevoflurane administration. The other possibility is that respiratory brain stem neurons are affected differently in relation to the speed at which the anesthetic is delivered. *In vivo* animal studies showed that sevoflurane reduced the activity of expiratory neurons in the brainstem by depressing glutamatergic excitation and by enhancement of overall GABAergic inhibition.[10] It could be that the activity of the expira-

tory brainstem neurons can be temporarily "switched off", depending on how quickly the inhaled anesthetic is administered. It would be interesting to test such a hypothesis in an animal model.

It is noteworthy that only one patient in the entire study experienced an episode of apnea throughout induction, and no patient became apneic after the 2.5 MAC concentration was attained. No upper airway obstruction was observed in any patient during apnea, since neither head repositioning nor jaw-thrust allowed patients to resume breathing. In addition, no movement of the patient's chest or abdominal wall was observed during apnea, and capnographic monitoring showed no abnormality indicative of upper airway obstruction.

A limitation of the present study is that we did not administer sevoflurane to patients in whom respiratory or cardiac function was compromised. Although oxygen desaturation or other major respiratory side effects were not observed, no conclusions about safety can be drawn regarding other groups of patients who may not be able to tolerate long periods of apnea during induction of anesthesia. Another potential limitation is that sevoflurane concentrations were sampled through a face mask, a technique that may not be as accurate as with a laryngeal mask airway or an endotracheal tube for end-tidal gas sampling.

Although several studies have examined the incidence of apnea during sevoflurane induction of anesthesia,[1,11–13] few have relevance to our study. An important distinguishing feature is that these studies used nitrous oxide, which is known to elicit an increase in tidal volume if added to sevoflurane.[5] During sevoflurane 8%-nitrous oxide administration, Thwaites *et al.* found a 16% incidence of apnea,[11] which is slightly lower than the rate found in our slow induction group. Other investigators reported no apnea after sevoflurane and nitrous oxide induction, but apnea was evaluated after laryngeal mask airway insertion[6,12] or at the end of surgery,[8] two potent respiratory stimuli. Although other investigators showed that rebreathing reduces the incidence of apnea during sevoflurane anesthesia,[13] end-tidal sevoflurane values reached were lower than those found in the current study.

In summary, we have shown that the incidence and the severity of apnea are related to the mode of administration of sevoflurane. Gradual induction using decremental-incremental concentrations of sevoflurane preserves spontaneous ventilation up to an end-tidal concentration of 2.5 MAC, and does not delay induction of anesthesia. This technique could be considered a viable option when preservation of spontaneous ventilation while achieving a deep level of anesthesia are desired, as in the management of the difficult airway.[14]

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