Remifentanil decreases sevoflurane requirements in children

[Le rémifentanil diminue les besoins de sévoflurane chez les enfants]

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Purpose: To establish the effect of increasing concentrations of remifentanil on sevoflurane requirements in children.

Methods: Fifty-eight healthy patients, ASA status I–II aged two to 12 yr, undergoing abdominal wall hernia or hydrocele repairs were serially assigned to one of four test groups to receive remifentanil 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ *iv*. Patients received a bolus of remifentanil 1 $\mu g \cdot kg^{-1}$ *iv* before the infusion began. End-tidal sevoflurane concentration was adjusted according to a Dixon up-and-down approach. Ten minutes after starting the remifentanil infusion, the surgical incision was made. The patient was observed for one minute from the time of incision by a solitary blinded rater for either flexion or withdrawal of one or more extremities in response to skin incision.

Results: The mean minimum alveolar concentration of sevoflurane was 2.39 ± 0.58 with 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil, 1.91 ± 0.36 with 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil, and 0.92 ± 0.11 with 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil. Remifentanil 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ lead to the sevoflurane being decreased to a level associated with spontaneous patient awakening.

The effective dose (ED_{50}) values of sevoflurane were 2.44 [95% confidence interval (CI) 2.16–2.72], 2.00 (95% CI 1.78–2.22), and 1.18 (95% CI 0.99–1.36) for remifentanil infusion rates of 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ respectively.

Conclusion: The administration of remifentanil produced a dose-dependent decrease in the minimum alveolar concentration of sevoflurane necessary for inhibition of movement reaction in response to surgical incision. The use of remifentanil may allow for flexible analgesic control and rapid recovery in children anesthetized with sevoflurane.

Objectif *: Établir l'effet de concentrations croissantes de rémifentanil sur les besoins de sévoflurane chez des enfants.*

Méthode *: Cinquante-huit patients sains, ASA I–II, de 2 à 12 ans, devant subir la réparation d'une hernie de la paroi abdominale ou d'une hydrocèle, ont été répartis en quatre groupes pour recevoir 0,03* $\mu g \cdot kg^{-1} \cdot min^{-1}$, *0,06* $\mu g \cdot kg^{-1} \cdot min^{-1}$, *0,12* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *ou 0,25* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *de rémifentanil iv. Un bolus iv de 1* $\mu g \cdot kg^{-1}$ *de rémifentanil a été donné avant que la perfusion commence. La concentration télé-expiratoire de sévoflurane a été ajustée selon la méthode ascendante et descendante de Dixon. L'incision chirurgicale a été pratiquée dix minutes après le début de la perfusion de rémifentanil. Un seul observateur impartial a noté, à partir de l'incision, la présence de flexion ou de retrait d'au moins une extrémité en réaction à cette incision.*

Résultats *: La concentration alvéolaire moyenne de sévoflurane a été de 2,39 ± 0,58 avec 0,03* $\mu g \cdot kg^{-1} \cdot min^{-1}$, *1,91 ± 0,36 avec 0,06* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *et 0,92 ± 0,11 avec 0,12* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *de rémifentanil. Une concentration de 0,25* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *de rémifentanil a produit une baisse du sévoflurane à un niveau associé au réveil spontané du patient.*

Les doses efficaces (ED50) de sévoflurane ont été respectivement de 2,44 [intervalle de confiance de 95 % (IC) 2,16–2,72], 2,00 (IC de 95 % 1,78–2,22) et 1,18 (IC de 95 % 0,99–1,36) pour 0,03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, *0,06* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *et 0,12* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *de rémifentanil.*

Conclusion *: L'administration de rémifentanil a produit une baisse, reliée à la dose, de la concentration alvéolaire moyenne de sévoflurane nécessaire pour inhiber le mouvement observé en réaction à l'incision chirurgicale. L'usage de rémifentanil peut rendre le contrôle anesthésique flexible et la récupération rapide chez des enfants anesthésiés avec du sévoflurane.*

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Accepted for publication August 24, 2005.
Revision accepted July 3, 2005.

SEVOFLURANE is currently one of the volatile agents of choice in pediatric anesthesia because of its acceptance for inhalation induction.[1] Sevoflurane is suitable because it has a pleasant smell, does not irritate the airways, and its blood-gas partition coefficient is slightly greater than that of desflurane or nitrous oxide.[2]

Remifentanil is an analogue of fentanyl (4-piperidyl anilide) with a methyl-ester group that allows the molecule to be hydrolyzed by esterases in plasma and tissues. Its context-sensitive half time of approximately three to five minutes and rapid onset make it an easy drug to control for achieving the desired depth of anesthesia.[3]

Anesthesiologists routinely combine different drugs to minimize their side effects and maximize their benefits. The ability of fentanyl to decrease anesthetic requirements in children has been studied previously.[2,4] In children, remifentanil and fentanyl have been shown to be interchangeable clinically.[5,6] Remifentanil has been shown to have superior recovery characteristics and is effective at dosages much lower than those required for other commonly-used opioids such as fentanyl.[7] The effect of remifentanil in reducing the minimum alveolar concentration MAC-BAR of sevoflurane has been demonstrated in adults.[8] The effect of remifentanil on sevoflurane MAC in children remains to be determined.

In this study, we evaluated the effect of remifentanil on the sevoflurane end-tidal volume required to eliminate movement reaction upon surgical incision in children undergoing painful procedures.

Methods

This randomized, double-blind study took place between January 2001 and July 2001 after having obtained Hospital Ethics Committee and parental approval. Healthy patients, ASA status I–II aged two to 12 yr, undergoing abdominal wall hernia or hydrocele repairs were recruited. Exclusion criteria included patients requiring premedication, patients for which inhalation induction was contraindicated, and patients taking medication known to affect anesthetic requirements such as antiepileptic agents. Patients with symptomatic cardiovascular, respiratory, and neurological disease were also excluded. Subjects did not receive premedication or additional analgesic/anesthetic agents until the study measurements were recorded.

Standard monitoring included electrocardiography, pulse oximetry, and non-invasive arterial pressure. Anesthesia was induced with sevoflurane 8% in oxygen 6 $L \cdot min^{-1}$ via facemask. A remifentanil bolus (1 $\mu g \cdot kg^{-1}$ *iv*) was infused over one minute and then the appropriate group-dependent infusion rate was started. After endotracheal intubation, ventilation was assisted to maintain an end-tidal carbon dioxide concentration of 35 to 45 mmHg, and the inspired sevoflurane concentration was adjusted to maintain the target end-tidal concentration. Precisely ten minutes after the commencement of the remifentanil infusion, the surgical incision was made.

Subjects were serially assigned to one of four test groups. The corresponding remifentanil infusion rates were as follows: Group A (0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$), Group B (0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$), Group C (0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and Group D (0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

The sevoflurane MAC for each remifentanil infusion rate was determined using the standard Dixon up-and-down approach.[9] This rule tends to concentrate testing in the range of sevoflurane concentrations which gives a 50% probability of blocking response to incision.[9] From the time of incision, the patient was observed for one minute by a solitary rater blinded to group assignment for any movement of the arms or legs. A positive response was defined as either flexion or withdrawal of one or more extremities in response to skin incision. Breath holding, grimacing, and movement of the head were not accepted as movement. The response to movement was a yes or no response.

For the initial test subjects in each test group, the inhaled sevoflurane concentration was adjusted to end-tidal concentrations guided by literature and the mean MAC value obtained using the previous remifentanil infusion rate.[2,7,8] These were taken to be : Group A (2.4 vol%), Group B (2.0 vol%), Group C (1.8 vol%), and Group D (1.0 vol%). For each succeeding patient in that test group, the end-tidal sevoflurane concentration was adjusted depending on the previous patient's response to incision. If a movement response to incision was previously observed, the succeeding subject was administered a 20% higher concentration of sevoflurane. If a movement response to incision was not previously observed, the subsequent sevoflurane concentration being administered was decreased by 20%. Our sample size was determined by the number of patients required in order to observe a minimum of four crossovers for each dose of remifentanil.[10] Once the response was recorded, further administration of anesthetic and analgesic agents was at the attending anesthesiologist's discretion.

Statistical analysis

Minimum alveolar concentration values were calculated as the mean of independent crossovers during which a subject's response changed from movement to no movement.[2] Data were analyzed using a logistic

TABLE Demographic and experimental data

	Group A (0.03 μg·kg^{-1}min^{-1})	*Group B (0.06 μg·kg^{-1}·min^{-1})*	*Group C (0.12 μg·kg^{-1}min^{-1})*	*Group D (0.25 μg·kg^{-1}·min^{-1})*	*P*†
n	22	14	16	6	
Sex (M:F)	18 : 4	7 : 7	11 : 5	6 : 0	0.13
Age (yr)	5.7 ± 2.9	6.9 ± 2.8	5.2 ± 2.7	7.3 ± 2.7	0.23
Weight (kg)	22.8 ± 9.0	21.2 ± 5.6	22.9 ± 8.1	27.1 ± 5.0	0.84
Sevoflurane MAC (vol%)	2.39 ± 0.58	1.91 ± 0.36	0.92 ± 0.11	not completed	0.00
Response (+:-)*	11 : 11	7 : 7	7 : 9	1 : 5	0.92

Data are presented as mean ± SD. *Positive response : flexion or withdrawal of one or more extremities in response to skin incision.
†Group A *vs* Group B *vs* Group C.

regression in order to determine the effective end-tidal sevoflurane concentration needed to inhibit movement response to incision in 50% and 95% of patients (ED_{50} and ED_{95} respectively). The ED_{50} and ED_{95} values were calculated using the best fit curve.

Unless otherwise specified, results are reported as mean ± standard deviation (SD). Data analysis was performed using Student's t test, analysis of variance, and analysis of covariance (Minitab Release 12; Minitab Inc., PA, USA). A 20% decrease in sevoflurane requirements with the addition of remifentanil and a SD of 10% in the calculated mean MAC value was predicted. A probability value of 0.05 or less was considered statistically significant and ß was set to 0.80.

Results

Fifty-eight patients were enrolled in the study. Group demographics were similar except for a smaller number of females in Groups A and C. There were no females in Group D (Table). Gender did not significantly impact the end-tidal sevoflurane concentrations in Group A (P = 0.157) or Group C (P = 0.829). A type II error was possible due to the inadequate power of the study to detect gender differences. The administration of remifentanil produced a dose-dependent decrease in the MAC of sevoflurane necessary for inhibition of movement reaction in response to surgical incision. Individual responses are shown in Figure 1. The ratio of positive movement responses to negative movement responses were 11:11 in Group A, 7:7 in Group B, and 7:9 in Group C indicating that the range of sevoflurane concentrations studied were in the range of concentrations that give a 50% probability of blocking movement response to surgical incision.

The mean MAC of sevoflurane was 2.39 ± 0.58 with 0.03 μg·kg^{-1}·min^{-1} remifentanil (Group A, n = 22), 1.91 ± 0.36 with 0.06 μg·kg^{-1}·min^{-1} remifentanil (Group B, n = 14), and 0.92 ± 0.11 with 0.12 μg·kg^{-1}·min^{-1} remifentanil (Group C, n = 16). The administration of 0.25 μg·kg^{-1}·min^{-1} of remifentanil (Group D, n = 6) permitted the MAC of sevoflurane to decrease to 0.29. This concentration of sevoflurane has been associated with spontaneous patient awakening and thus, no further experimentation with remifentanil at this dosage was performed.[11] In increasing the remifentanil dose from 0.03 μg·kg^{-1}·min^{-1} to 0.06 μg·kg^{-1}·min^{-1} the MAC of sevoflurane was unchanged (P = 0.197). The increase of remifentanil from 0.06 μg·kg^{-1}·min^{-1} to 0.12 μg·kg^{-1}·min^{-1} resulted in a significant reduction in the MAC of sevoflurane (P = 0.001). The power of the study was adequate to detect the reduction of mean MAC sevoflurane values from group to group. The corresponding decrease in the MAC of sevoflurane in response to remifentanil administration can be seen in Figure 2.

Using logistic regression, values for sevoflurane ED_{50} and ED_{95} were obtained for each corresponding

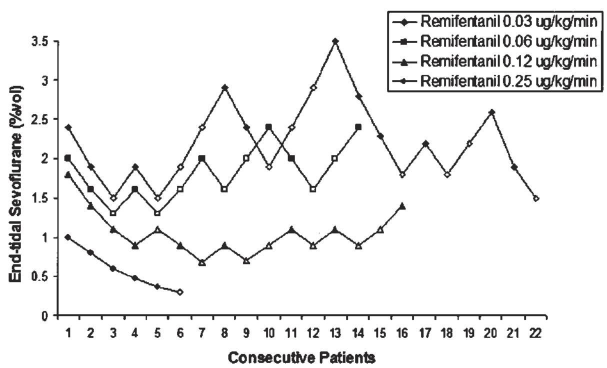

FIGURE 1 Individual end-tidal sevoflurane concentration, remifentanil infusion rate, and response to surgical skin incision for test subjects. Data were gathered using the Dixon up-and-down approach. A solid box indicates a negative movement response to surgical incision.

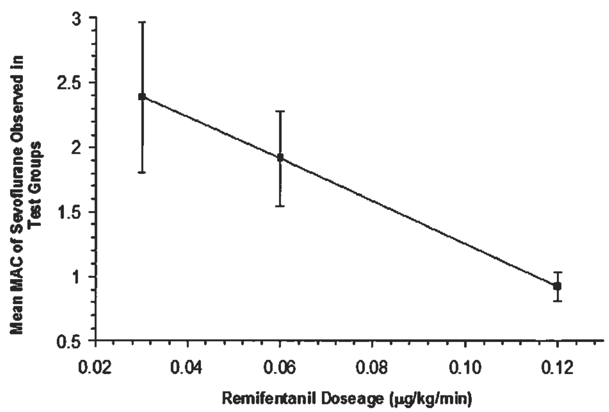

FIGURE 2 The mean sevoflurane concentration required to prevent movement response to surgical incision in test subjects at varying infusion rates of remifentanil. Data were collected using the Dixon up-and-down approach and are presented as mean ± standard deviation.

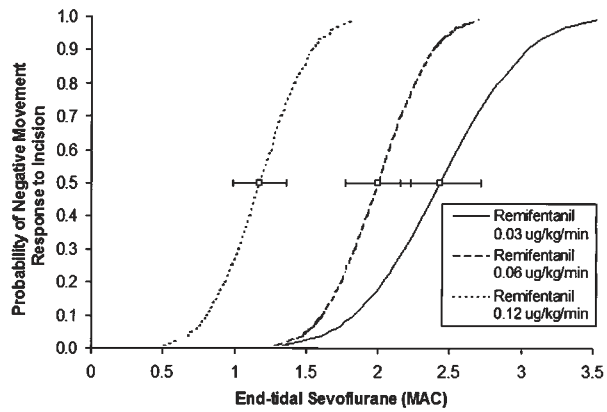

FIGURE 3 Probability of negative movement response to surgical skin incision ten minutes after administration of remifentanil. Anesthesia comprised sevoflurane, a remifentanil bolus of 1 μg·kg^{-1} and a continuous infusion rate of 0.03 μg·kg^{-1}·min^{-1}, 0.06 μg·kg^{-1}·min^{-1}, or 0.12 μg·kg^{-1}·min^{-1}. ED_{50} is represented by an open box. Error bars represent 95% confidence limits around minimum alveolar concentration.

remifentanil infusion rate. The ED_{50} and ED_{95} values were 2.44 (95% CI 2.16–2.72) and 3.21 respectively for a remifentanil infusion rate of 0.03 μg·kg^{-1}·min^{-1}. Likewise, for a remifentanil infusion rate of 0.06 μg·kg^{-1}·min^{-1}, ED_{50} and ED_{95} values were 2.00 (95% CI 1.78–2.22) and 2.50 respectively. A remifentanil infusion rate of 0.12 μg·kg^{-1}·min^{-1}, resulted in an ED_{50} and ED_{95} of 1.18 (95% CI 0.99–1.36) and 1.65 respectively (Figure 3). The inverse linear relationship between MAC of sevoflurane and remifentanil infusion rates is shown in Figure 4.

Discussion

The MAC of volatile anesthetics is highest in pediatric patients and decreases with age.[12,13] The MAC of sevoflurane has been documented to range between 2.03 to 2.5% in children aged one to 12 yr.[13,14] The reduction in MAC by remifentanil is in agreement with previous studies of sevoflurane.[7,8,15] In adults, Albertin *et al.* have observed that a target-controlled plasma concentration of 1 ng·mL^{-1} remifentanil results in a 60% decrease in the MAC-BAR of sevoflurane combined with 60% nitrous oxide. Increasing the target concentration of remifentanil to 3 ng·mL^{-1} produced a further 30% decrease in the MAC-BAR of sevoflurane.[8]

To date, there is little literature available regarding the effect of remifentanil on the MAC of sevoflurane in pediatric patients. The effect of fentanyl on sevoflurane, which has been shown to be interchangeable with remifentanil in children, has been documented.[5,6] There exists a 1:1.5 potency ratio between fentanyl and remifentanil.[7] Zhang *et al.* have shown that in children aged five to ten, an increase in fentanyl serum levels from 0.62 ± 0.13 μg·L^{-1} to 1.51 ± 0.18 μg·L^{-1} produces a decrease in sevoflurane MAC from 1.03 ± 0.07% to 0.64 ± 0.01%.[4] Likewise, Katoh *et al.* have observed that in pediatric patients aged two to six, increasing fentanyl from 2 μg·kg^{-1} to 4 μg·kg^{-1} decreases MAC-BAR of sevoflurane from 0.63 MAC to 0.38 MAC.[2]

Our starting sevoflurane end-tidal volume was 2.4% for the initial test subject in Group A. This value was chosen since it lies within the upper limits of the recommended sevoflurane MAC for the studied age group.[13,14] According to Paul *et al.*, this method of determining the initial sevoflurane concentration may have introduced a bias toward the calculated mean MAC sevoflurane value.[10] They have shown that using starting concentrations larger than population MAC yields average results for mean MAC slightly greater than population MAC. Similarly, using starting concentrations less than the population MAC yields values for mean MAC less than population MAC.[10] This source of error was unavoidable given that the effect of remifentanil on sevoflurane MAC in pediatric patients has not been studied previously and other than our own data, there was little information to guide us in determining starting sevoflurane concentrations. In using starting end-tidal sevoflurane concentrations

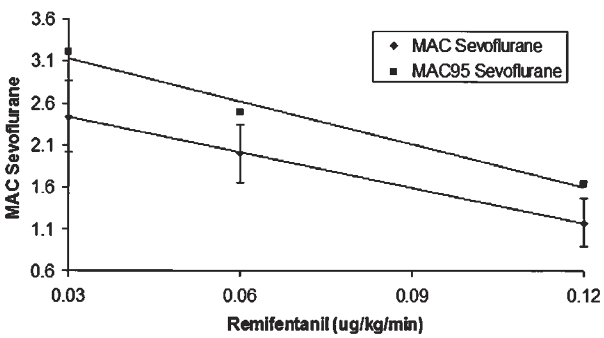

FIGURE 4 Inverse linear relationship between minimum alveolar concentration (MAC), MAC_{95} of sevoflurane and various remifentanil infusion rates as determined by logistic regression. Error bars represent 95% confidence limits around MAC.

that were greater than the predicted mean MAC value, we complied with ethical considerations and minimized the number of patients that experienced a positive movement response to incision.

The concentration of sevoflurane chosen for the initial test subject has been shown to impact the sample size required to complete the study. Paul *et al.* noted that if the initial sevoflurane value deviated greatly from the population MAC, a larger sample size was required in order to obtain the desired number of crossovers.[10] The opposite was observed in our study. For example, the initial sevoflurane value used for Group A was 2.4% and the mean MAC sevoflurane was calculated to be 2.39 ± 0.58% (Table). Twenty subjects were required in order to observe five crossovers (Figure 1). For Group C, the starting sevoflurane concentration was 1.8% and mean MAC sevoflurane was calculated to be 0.92 ± 0.11% (Table). Here, 16 subjects were required in order to observe five crossovers and the difference between starting sevoflurane concentration and mean MAC sevoflurane was greater than in Group A (Figure 1).

Munoz *et al.* have determined the remifentanil infusion rate required to block somatic response (IR_{50}) to be 0.22 ± 0.03 $\mu g \cdot kg^{-1}$ at an end-tidal sevoflurane concentration of 0.78% in children aged two to ten years.[16] In our study however, the administration of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil allowed for the MAC of sevoflurane to be decreased to 0.29% before our defined movement reaction to incision was observed. MAC-AWAKE of sevoflurane in children is accepted to be 0.78%.[17] More specifically, the MAC-AWAKE gradually decreases to 0.60% in 12-yr-old subjects.[11,12] Due to the possibility of spontaneous awakening at the low sevoflurane MAC obtained with 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil, further experimentation at this infusion rate was discontinued.

There was no ceiling effect observed at the remifentanil dosages investigated, suggesting that sevoflurane end-tidal concentrations could be greatly reduced or even eliminated with administration of high doses of remifentanil. Remifentanil however, is not recommended for use as the sole agent in general anesthesia because loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity, and tachycardia.[3] There was no muscle rigidity or tachycardia observed within our test population. Patients were intubated and ventilated so apnea could not be detected.

Common clinical endpoints for assessing the depth of anesthesia are hemodynamic variables including mean arterial pressure and heart rate.[18] In contrast to somatic reflexes however, hemodynamic responses to noxious stimuli do not correlate well with end-tidal drug concentration.[19] It is for the above reasons that the effects of remifentanil on MAC of sevoflurane and not MAC-BAR of sevoflurane were studied.

Although pharmacokinetic studies of remifentanil on children are limited, available data suggest that pharmacokinetic variables are similar to adults. The plasma-effect site (brain) equilibration time ($T_{1/2}k_{e0}$) for remifentanil has been determined by Glass *et al.* to be 1.31 $\pm$ 1.5 min.[20] The time required to reach steady state could then be estimated to be 3.93 $\pm$ 4.5 min (3 $T_{1/2}k_{e0}$). Thus, our ten-minute equilibration period would have allowed for near steady state to be attained. In addition, pharmacokinetic modelling was used to quantify the likely effect of the bolus and infusion rates used in our study. We used the program STANPUMP (SL Shafer, Palo Alto, CA, USA) and parameters calculated by Minto and Schnider to model the selected infusion rates.[21] A single bolus of 1 $ug \cdot kg^{-1}$ for all groups provided a simple protocol and concentrations at ten minutes that were predicted to be within 20% of final equilibrium concentrations.

In most MAC studies, 15 min is used as the equilibrium time for sevoflurane. Originally, the 15 min time period was chosen in regards to the pharmacokinetics of halothane however, the equilibration of sevoflurane is more rapid, especially in children. A computer simulation with Gas Man® (Med Man Simulations Inc, Chestnut Hill, MA, USA) was undertaken to provide confirmation of the likely equilibration of brain and alveolar sevoflurane levels after ten minutes of constant end-tidal concentration. Multiple simulations of the protocol using different size patients confirmed that equilibrium is reached in less than ten minutes when sevoflurane is used for intubation.

The Dixon up-and-down approach is most commonly used when reporting the potency of inhaled anesthetics in humans.[10] When this study design is used, inter-individual variability of MAC is set to 20%, and four to six crossovers are used for calculation, the SD of mean MAC is typically 11%.[10] In our study, the mean MAC sevoflurane SD was 24% (five crossovers), 19% (four crossovers), and 12% (five crossovers) respectively for the 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ groups. Paul *et al.* have shown that the SD of mean MAC values is minimized with the use of six crossovers yet, the mean MAC value obtained using four crossovers is the same as that obtained when a greater number than four crossovers are used.[10] For our purposes, there was no further statistical benefit derived from, and it was against ethical considerations, to use more than four crossovers in our experimental design. In order to balance ethical considerations and to minimize the SD of mean MAC values obtained, most clinical trials terminate after four crossovers.[10]

One criticism of the Dixon up-and-down approach is that it underestimates true inter-individual variability of MAC.[10,22] The logistic regression provided a SD larger than that provided using the Dixon up-and-down method for Groups B and C (Group B: ± 0.44 *vs* ± 0.36, Group C: ± 0.37 *vs* ± 0.11). For Group A the SD was similar whether logistic regression (SD = ± 0.56) or the Dixon up-and-down approach (SD = ± 0.58) was used. The ED_{50} value obtained using logistic regression may be a better approximation of population MAC sevoflurane and inter-individual variability.

A retrospective power analysis, in regards to the mean MAC calculated, was performed and is as follows: 99.05% (Group A *vs* B), > 100% (Group B *vs* C), > 100% (Group A *vs* C). The power of the study was adequate to detect the reduction of mean MAC sevoflurane values from group to group. The initial sevoflurane concentrations for Groups A and B were greater yet, very close to the calculated mean MAC value for the group. The choice of initial sevoflurane concentration for each group was guided by literature however, given the novel nature of this study, it was largely unknown until after the research was completed whether the choice of starting concentration was appropriate. The variability between each crossover value used in calculating the mean MAC value was also greater than expected in Groups A and B, and could not be predicted. In a dose-finding study, we would require a greater number of crossovers in order to ensure a smaller SD from the mean MAC calculated.

In conclusion, the administration of remifentanil produced a dose-dependent decrease in the MAC of sevoflurane necessary for inhibition of movement reaction in response to surgical incision. The use of remifentanil allows for flexible analgesic control and rapid recovery after surgery. In anticipation of postoperative pain, it is imperative that alternative analgesics be administered prior to discontinuation of remifentanil. In children, the effect of remifentanil on the MAC-BAR of sevoflurane has yet to be determined and requires further study.

Acknowledgements

The authors acknowledge the support of their colleagues in anesthesia and general surgery. Also, we thank research assistants Kim Villeneuve and Sherry Bourbonnais for their crucial assistance.

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