

Remifentanil Requirements during Sevoflurane Administration to Block Somatic and Cardiovascular Responses to Skin Incision in Children and Adults

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Background: **The authors found no studies comparing intraoperative requirements of opioids between children and adults, so they determined the infusion rate of remifentanil to block somatic (IR_{50}) and autonomic response ($IRBAR_{50}$) to skin incision in children and adults.**

Methods: **Forty-one adults (aged 20–60 yr) and 24 children (aged 2–10 yr) undergoing lower abdominal surgery were studied. In adults, anesthesia induction was with sevoflurane during remifentanil infusion, whereas in children remifentanil administration was started after induction with sevoflurane. After intubation, sevoflurane was administered in 100% O_2 and was adjusted to an ET% of 1 MAC-awake corrected for age at least 15 min before surgery. Patients were randomized to receive remifentanil at a rate ranging from 0.05 to 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for at least 20 min before surgery. At the beginning of surgery, only the skin incision was performed, and the somatic and autonomic responses were observed. The somatic response was defined as positive with any gross movement of extremity, and the autonomic response was deemed positive with any increase in heart rate *or* mean arterial pressure equal to or more than 10% of preincision values. Using logistic regression, the IR_{50} and $IRBAR_{50}$ were determined in both groups of patients and compared with unpaired Student *t* test. A *P* value less than 0.05 was considered significant.**

Results: **The IR_{50} ± SD was 0.10 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in adults and 0.22 ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in children ($P < 0.001$). The $IRBAR_{50}$ ± SD was 0.11 ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in adults and 0.27 ± 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in children ($P < 0.001$).**

Conclusions: **To block somatic and autonomic responses to surgery, children require a remifentanil infusion rate at least twofold higher than adults.**

HIGHER doses of inhalational agents are needed in infants and children compared with adults.[1–4] Opioids are also one of the most used drugs in anesthesia, and there are no studies comparing intraoperative requirements between children and adults. However, as age decreased, significantly lower plasma fentanyl concentrations were found in infants and children than in adults after the administration of a bolus dose of this opioid,[5] without evidence of pharmacodynamic changes.[6] In the case of alfentanil and sufentanil, higher clearance of these drugs has been found in children compared with adults.[7,8] These findings suggest that children may require higher maintenance doses of these drugs.

Remifentanil is increasingly used in pediatric anesthesia, but there is no information on the effective dose in this age group. Although the pharmacokinetics of remifentanil determined in children and adults has shown contradictory results,[9,10] a clear age-related increase in sensitivity to remifentanil has been demonstrated at least in adults.[11] This last finding in a way agrees with our clinical impression that children require higher intraoperative infusion rates of remifentanil than adults. Thus, the aim of this study was to determine the effective infusion rate of remifentanil to block the somatic (IR_{50}) and autonomic responses ($IRBAR_{50}$) to skin incision in 50% of children and to compare these values with those of adults.

Materials and Methods

After institutional ethics committee approval and obtaining informed consent from patients or parents, adult patients, aged 20–60 yr, and pediatric patients, aged 2–10 yr, scheduled for first time lower abdominal surgery with general anesthesia were studied. All were American Society of Anesthesiologists (ASA) physical status I, did not receive premedication, and were within ± 20% of the ideal body weight for height. Exclusion criteria included pregnancy, chronic or acute (within the past 48 h) intake of any drug known to affect minimum alveolar concentration (MAC), and any known adverse effect to the study drugs. In the operating room, routine noninvasive monitoring of arterial pressure, electrocardiogram, and pulse oximetry was initiated. In all patients, induction of anesthesia was with increasing concentrations of sevoflurane in oxygen 100% and spontaneous ventilation. In adults, inhalational induction was during remifentanil administration; in children, remifentanil infusion was started after induction and placement of the intravenous line. Tracheal intubation was facilitated with 0.1–0.15 mg/kg mivacurium in adults, and no neuromuscular blocking drugs were used in children. Patients were connected to mechanical ventilation adjusted to maintain the end-tidal CO_2 at 30–35 mmHg. After intubation, anesthesia was maintained with the remifentanil infusion and sevoflurane in oxygen 100%. Sevoflurane was adjusted to an ET% of 1 MAC-awake corrected for age (0.62–0.67% in adults[12,13] and 0.78% in children[14]) at least 15 min before surgery. An initial randomization with random numbers generated by a

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computer assigned eight adults and six children to one of four remifentanil infusion rates: 0.05, 0.15, 0.25, or 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$. It was *a priori* decision to perform a preliminary analysis of the data when half the study had been completed to confirm that the four infusion rates were realistic in terms of defining the ED_{50}. This analysis showed that the only adult included in the subgroup 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and all eight already included in the subgroup 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ presented no response to surgical incision. Accordingly, the remaining seven adult cases that would receive 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were canceled, and two additional remifentanil infusion rates (0.10 and 0.20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were included in the randomization to more precisely define the dose–response curve in adults. In the children, no evidence of an infusion rate too far away from the ED_{50} was found, and rates for this group were not modified. The assigned infusion rate of remifentanil was kept constant for at least 20 min before surgery. Double burst stimulation (DBS) was used to assess the recovery of neuromuscular function after mivacurium. In all cases, DBS was applied at least 5 min before skin incision on the cubital nerve at the level of the wrist with a maximum stimulation of 40 mA, and the response was evaluated at the adductor pollicis. At the beginning of surgery, only the skin incision with scalpel was performed in all patients, and the somatic and autonomic responses were observed during the following 90 s. The somatic response was evaluated by two surgeons blinded to the remifentanil infusion rate and was defined as positive with any gross movement of extremity. Heart rate (HR) and mean arterial pressure (MAP) were recorded from automated noninvasive arterial pressure devices, and any increase in HR *or* MAP equal to or more than 10% of preincision values was considered a positive autonomic response. Using logistic regression, the IR_{50} and $IRBAR_{50}$ in both groups of patients were determined and were compared with unpaired Student *t* test. One-way analysis of variance and chi-square test were used to compare demographic and anesthetic data among the different subgroups of adults and children. A *P* value less than 0.05 was considered significant. Results are shown as mean ± SD. Data analysis was performed with S-Plus 2000 (MathSoft, Cambridge, MA).

Results

Forty-one adults and 24 children were included in the study. There were no significant differences regarding general and anesthetic data among the different dose subgroups of adults and children. Global demographic and anesthetic data of both groups are shown in table 1.

All adults had recovered from evidence of neuromuscular blockade from mivacurium before skin incision. There were no somatic or autonomic responses to DBS.

Table 1. Demographic and Anesthetic Data

	Adults (n = 41)	Children (n = 24)
Age (yr)*	38.5 ± 10.5	5.2 ± 2.5
Weight (kg)*	72.2 ± 13.9	21.3 ± 8.7
Height (cm)*	166.2 ± 10.9	110.2 ± 17.6
Sex (male/female)	20/21	20/4
ET sevoflurane (%) at skin incision*	0.63 ± 0.02	0.79 ± 0.02
Duration of 1 MAC awake administration (min)*	20.6 ± 6.1	19.5 ± 9.7
Duration of remifentanil administration (min)*	30.4 ± 8.5	27.4 ± 12.6

*Values are mean ± SD.

MAC = minimum alveolar concentration; ET = end-tidal.

No patient required treatment for hemodynamic alterations during the study period.

To block somatic response, the IR_{50} (IR_{95}) was 0.10 (0.20) ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in adults and 0.22 (0.46) ± 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in children ($P < 0.001$; fig. 1). The $IRBAR_{50}$ ($IRBAR_{95}$) was 0.11 (0.20) ± 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in adults and 0.27 (0.62) ± 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in children ($P < 0.001$; fig. 2). Of 14 adults who presented a positive cardiovascular response, 11 had an increase in HR and MAP, 2 had an increase only in HR (0.05 and 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and 1 had an increase only of MAP (0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$). In the children, of 15 with a positive response, 1 had an increase only in HR (0.15 and 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 1 had an increase only of MAP (0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and the remaining 13 had an increase in both variables. Figure 3 shows the number of patients with positive and negative somatic and cardiovascular responses to skin incision at each remifentanil infusion rate.

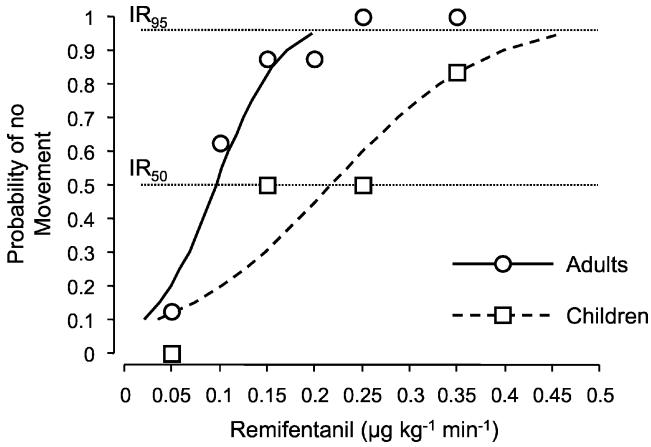

Fig. 1. The percentage of patients not presenting somatic response to skin incision as function of the infusion rate (IR) of remifentanil. The individual data points show the real percentage not responding at each dose. The solid and dashed lines indicate the dose–response relationships predicted by logistic regression in both groups. The two dotted lines show the IR needed to prevent response in 50% and 95% of patients.

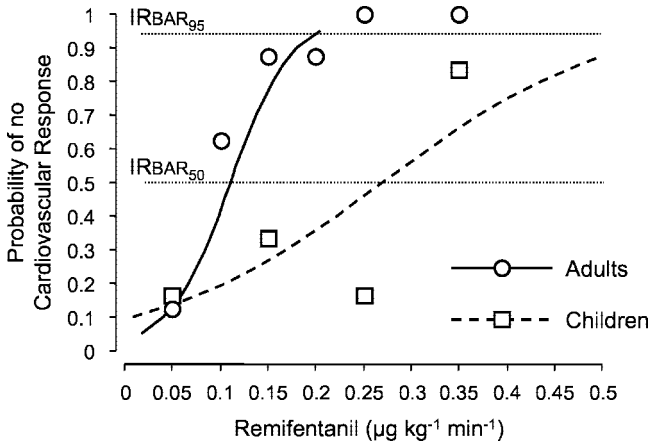

Fig. 2. The percentage of patients not presenting cardiovascular response to incision as function of the infusion rate (IR) of remifentanil. The individual data points show the real percentage not responding at each dose. The solid and dashed lines indicate the dose–response relationships predicted by logistic regression in both groups. The two dotted lines show the IR needed to prevent response in 50% and 95% of patients.

Discussion

The main finding of this study is that the infusion rate of remifentanil needed to block the somatic and cardiovascular responses to skin incision is twice as high in children compared with adults at MAC-awake sevoflurane in oxygen.

Clinically relevant differences between children and adults have been shown previously in the requirements of inhalational agents. However, despite the widespread use of opioids, we are not aware of any study comparing surgical requirements of these drugs in children and adults. The clinically significant higher requirements of remifentanil in children should be taken into account when using a remifentanil-based anesthetic technique in this group of patients.

The findings of this study could be explained on the basis of pharmacokinetic or pharmacodynamic differences between these two age groups. Singleton *et al.*[5] found that after a single bolus dose of fentanyl, infants had significantly lower plasma fentanyl concentrations compared with adults, whereas children aged 1–9 yr presented intermediate plasma levels. This study did not determine whether these differences were the result of age-related changes in distribution or elimination.[5] In addition, this group found no differences among infants, children, and adults in postoperative ventilatory depression at similar plasma concentrations of fentanyl.[6] These studies suggest that potentially higher fentanyl requirements in younger patients may be the result of pharmacokinetic rather than pharmacodynamic factors. With sufentanil, Guay *et al.*[8] found that the apparent volume of distribution in children was similar to adults, but the clearance in children was one and a half times greater than in adults; the authors suggested that children would require relatively greater maintenance doses than adults.

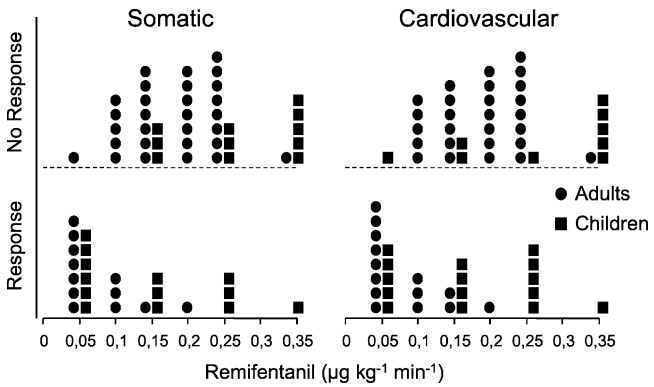

Fig. 3. Number of patients with positive and negative somatic and cardiovascular responses to skin incision at each remifentanil infusion rate. Circles represent adults (n = 41), and squares represent children (n = 24).

In the case of alfentanil, however, conflicting results have been found regarding its pharmacokinetics. Goresky *et al.*[15] found no differences in volume of distribution at a steady state and clearance of alfentanil in infants and children compared with values in adults. On the other hand, whereas Roure *et al.*[7] found similar apparent volume of distribution of alfentanil in children and adults and a clearance rate twice higher in children, Meistelman *et al.*[16] found a similar clearance and an apparent volume of distribution in children corresponding to one third of that in adults. Thus, from these results it is difficult to predict with certainty intraoperative requirements of alfentanil in children and to make a relative comparison with those of adults.

A recent study on pharmacokinetics of remifentanil in a pediatric population aged from neonate to 18 yr found an inverse relationship of age with volume of distribution and clearance that led to a fairly constant elimination half life over this age range.[10] However, these age-related changes were particularly marked in infants aged less than 2 months. In children aged 2–10 yr, as in our study, the volume of distribution was 234.8 ± 110.0 ml/kg, clearance was 69.4 ± 21.8 ml · kg^{-1} · min^{-1}, and elimination half life was 4.1 ± 1.7 min.[10] In adults, a volume of distribution of 300–400 ml/kg, a clearance of 40–60 ml · kg^{-1} · min^{-1}, and an elimination half life of 8 min have been reported.[9] These pharmacokinetic parameters do not rule out pharmacokinetic differences as an explanation for the higher requirements of remifentanil in children compared with adults. In addition, pharmacodynamic differences regarding remifentanil between children and adults are also possible. Indeed, although Scott and Stanski[17] found no age-related differences in pharmacokinetics in adults aged 20–89 yr, they found a marked linear increase in sensitivity (*i.e.*, a pharmacodynamic effect) to fentanyl and alfentanil with age. Moreover, more recently Minto *et al.*[11] found in adults aged 20–85 yr that age was inversely correlated with remifentanil central volume of distribution and clearance and directly correlated with its potency. Thus, the final

explanation for the findings of our study remains to be established.

Regarding the effective remifentanil infusion rate in adults, Dershwitz *et al.*[18] performed a study in two hospitals to determine the ED_{50} infusion rate of remifentanil for ablation of somatic and autonomic responses to skin incision in adults. They found conflicting results, not clearly explained, regarding the ED_{50} that was 0.020 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in one hospital and 0.087 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the other. This last infusion rate is very close to the IR_{50} in our patients (0.10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) despite very different anesthetic techniques (including the use of nitrous oxide and repeated bolus doses of propofol as maintenance, and the administration of vecuronium with no confirmation of normal neuromuscular function at the moment of stimulation in the study conducted by Dershwitz *et al.*[18]). However, given the large intersite variability and the fact that the ED_{50} included blockade of somatic and autonomic responses in the last study, it is difficult to make a direct comparison with our results.

With respect to the protocol design, the constant rate infusion period of remifentanil of at least 20 min before surgery was chosen because in adults it should allow that more than 90% of the final steady state plasma concentration for that rate be reached.[19] In children, however, we are not aware of studies determining all the pharmacokinetic parameters of remifentanil to ensure that 20 min are enough to reach a steady state plasma concentration during a constant infusion rate. However, because pharmacokinetic factors of remifentanil in children and adults seem not to be extremely different,[9,10] this period of time probably allowed a high percentage of the final steady state plasma concentration to also be reached in the younger group. Regarding the use of mivacurium only in the adult group, a competition for plasma esterases between mivacurium and remifentanil could have led to a reduced clearance of both drugs and to an increased plasma level of remifentanil at a given infusion rate. This could account in part for the reduced requirements of remifentanil in adults compared with children in our study. However, although theoretically possible, we think that this possibility is clinically implausible.

A potential flaw of the protocol is the use of DBS only in the adults, which could have led to a certain degree of arousal or modification of the pain threshold in this age group. However, DBS was applied before the surgical washing up, and no patient showed any somatic or cardiovascular response, suggesting that the intensity of DBS is most probably significantly lower compared with the skin incision. The similarity between our results and those from Dershwitz *et al.*[18] also suggests that the effect of DBS on remifentanil requirements, if any, was minimal. In addition, if a degree of arousal persisted at the moment of skin incision, conceivably higher remifentanil infusion rates would have been needed to block responses, and our results would have overestimated adult requirements, therefore reducing differences between adults and children. We believe that the findings of this study are still valid because, despite this last possibility, there were statistical and clinical differences in remifentanil requirements between these two age groups.

Finally, because the extrapolated value for $IRBAR_{95}$ in children was much higher than the highest infusion rate of remifentanil actually used, an important degree of uncertainty in the estimation of this value cannot be ruled out.

In conclusion, children aged 2–10 yr require remifentanil at an infusion rate twice higher than adults to block somatic and cardiovascular responses to skin incision. These differences should be taken into account when using a remifentanil-based anesthesia in children. Our study, however, does not define whether these differences are the result of pharmacokinetic or pharmacodynamic factors.

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