Tracheal intubation after induction of anesthesia in children with propofol – remifentanil or propofol-rocuronium

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Purpose: To compare the intubating conditions after remifentanil-propofol with those after propofol-rocuronium combination with the aim of determining the optimal dose of remifentanil.

Methods: In a randomized, double-blind study 80 healthy children aged three to nine years were assigned to one of four groups (n=20): 2 or 4 $\mu g \cdot kg^{-1}$ remifentanil (Re2 or Re4); 2 $\mu g \cdot kg^{-1}$ remifentanil and 0.2 $mg \cdot kg^{-1}$ rocuronium (Re2-Ro0.2); 0.4 $mg \cdot kg^{-1}$ rocuronium (Ro0.4). After atropine, remifentanil was injected over 30 sec followed by 3.5 $mg \cdot kg^{-1}$ propofol and rocuronium. After 60 sec, laryngoscopy and intubation were attempted. Intubating conditions were assessed as excellent, good or poor based on ease of ventilation, jaw relaxation, position of the vocal cords, and coughing to intubation.

Results: In all children intubation was successful. Overall intubating conditions were better ($P < 0.01$), and the frequency of excellent conditions, 85%, was higher ($P < 0.01$) in the Re4 group than in the Ro0.4 group. No child manifested signs of muscular rigidity. In the remifentanil groups, arterial pressure decreased 11-13% and heart rate 6-9% after anesthetic induction, and remained at that level throughout the study.

Conclusion: The best intubating conditions were produced by the combination of 4 $\mu g \cdot kg^{-1}$ remifentanil and 3.5 $mg \cdot kg^{-1}$ propofol. It provided excellent or good intubating conditions in all children without causing undue cardiovascular depression.

Objectif : Comparer les conditions d'intubation après l'usage d'une combinaison de rémifentanil-propofol avec celles d'une combinaison de propofol-rocuronium dans le but de déterminer la dose optimale de rémifentanil.

Méthode : Lors d'une étude randomisée et à double insu, 80 enfants en bonne santé, de trois à neuf ans, ont été répartis en quatre groupes (n=20) et ont reçu : 2 ou 4 $\mu g \cdot kg^{-1}$ de rémifentanil (Ré2 ou Ré4); 2 $\mu g \cdot kg^{-1}$ de rémifentanil et 0,2 $mg \cdot kg^{-1}$ de rocuronium (Ré2-Ro0,2); 0,4 $mg \cdot kg^{-1}$ de rocuronium. Après l'administration d'atropine, le rémifentanil a été injecté pendant 30 s et a été suivi de 3,5 $mg \cdot kg^{-1}$ de propofol et de rocuronium. La laryngoscopie et l'intubation ont été tentées après 60 s. Les conditions d'intubation ont été évaluées comme excellentes, bonnes ou pauvres selon la facilité de la ventilation, la relaxation de la mâchoire, la position des cordes vocales et la toux pendant l'intubation.

Résultats : L'intubation a été réussie chez tous les enfants. Les conditions générales d'intubation ont été meilleures ($P < 0,01$), et la fréquence d'excellentes conditions, 85 %, plus élevée ($P < 0,01$) dans le groupe Ré4 que dans le groupe Ro0,4. Aucun enfant n'a manifesté de signe de rigidité musculaire. Dans les groupes rémifentanil, la tension artérielle a baissé de 11-13 % et la fréquence cardiaque de 6-9 % après l'induction de l'anesthésie et sont demeurées à ce niveau tout au long de l'étude.

Conclusion : Les meilleures conditions d'intubation ont été réalisées avec la combinaison de 4 $\mu g \cdot kg^{-1}$ de rémifentanil et de 3,5 $mg \cdot kg^{-1}$ de propofol. L'intubation a été bonne ou excellente chez tous les enfants sans causer de dépression cardiovasculaire indue.

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Accepted for publication May 14, 2000.

THERE is a trend towards performing more surgery on children on a day-stay basis. Most of the procedures are short and, from a surgical point of view, there is seldom need for muscle relaxation. In these circumstances, techniques that allow tracheal intubation without muscle relaxants might be useful. They obviate the need both for succinylcholine with its potential side effects,[1] and for non-depolarizing neuromuscular blocking agents with a duration of action that may be too long in relation to the length of the procedure. The trachea can be successfully intubated after alfentanil-propofol induction sequence in most adult[2-4] and pediatric patients[5,6] with normal airway anatomy. However, the dose of alfentanil required to achieve good intubating conditions might have a duration of action that would be too prolonged for short ambulatory surgery procedures.

Remifentanil is a recently introduced μ-receptor agonist with a unique pharmacokinetic profile. Owing to metabolism by non-specific esterases in blood and tissues, remifentanil is characterised by an extremely rapid clearance and offset of effect.[7] Therefore, in contrast to other opioids, the time of recovery is not greatly influenced by the dose.[8] Moreover, the onset of effect is rapid, and similar to that of alfentanil.[9] Providing an option for intense opioid effect without compromising recovery after short operations, remifentanil might offer benefits over alfentanil especially in ambulatory surgery. In adult patients, intubating conditions after 2 $\mu g \cdot kg^{-1}$ remifentanil were inferior to those achieved after 50 $\mu g \cdot kg^{-1}$ alfentanil when combined with propofol.[4] In order to ensure good intubating conditions a dose of 3-4 $\mu g \cdot kg^{-1}$ remifentanil was required.[10,11] In children, intubating conditions were similar after 1 $\mu g \cdot kg^{-1}$ remifentanil or 15 $\mu g \cdot kg^{-1}$ alfentanil followed by propofol.[12] However, neither dose appeared optimal regarding intubating conditions.

To determine the optimal dose of remifentanil to facilitate tracheal intubation with propofol in children, we conducted a randomized, controlled study to compare intubating conditions and cardiovascular responses following induction of anesthesia with 3.5 $mg \cdot kg^{-1}$ propofol, supplemented with either 2 or 4 $\mu g \cdot kg^{-1}$ remifentanil, or 0.4 $mg \cdot kg^{-1}$ rocuronium . In addition, we tested the hypothesis that a small dose of rocuronium, 0.2 $mg \cdot kg^{-1}$ in this setting might improve intubating conditions.[13] This small dose was given in conjunction with remifentanil 2 $\mu g \cdot kg^{-1}$.

Methods

After obtaining approval from the Ethics Committee of the Otolaryngological Clinic and informed written consent from the parents, we studied 80 healthy children (ASA I-II), aged three to nine years presenting for elective ENT-surgery. Patients with a history of difficult intubation, or whose preoperative examination suggested that there might be difficulties with intubation, were not included.

All children had EMLA® cream applied over the dorsum of the hand 60 min before venous cannulation. Midazolam, 0.5 $mg \cdot kg^{-1}$ *po*, was given as premedication about 20-30 min before anesthesia. Using a sealed envelope method, children were randomized to one of four study groups of 20 children to receive the following in a double-blind manner: 2 $\mu g \cdot kg^{-1}$ remifentanil (Re2); 4 $\mu g \cdot kg^{-1}$ remifentanil (Re4); 2 $\mu g \cdot kg^{-1}$ remifentanil and 0.2 $mg \cdot kg^{-1}$ rocuronium (Re2-Ro0.2); 0.4 $mg \cdot kg^{-1}$ rocuronium (Ro0.4). The doses of remifentanil were chosen on the basis of preliminary pilot studies. For every child, an independent assistant nurse prepared four syringes containing the study drugs or saline. Depending on the child´s weight, she drew the study drug I, remifentanil, either into a syringe of 5 or 10 ml, and the study drug II, rocuronium, into a syringe of 1 or 2 ml, while filling the other syringe with saline. After drawing the appropriate doses of remifentanil or rocuronium into syringes, she filled the syringes with saline to make up a total volume of 15 ml or 3 ml, respectively. In the operating room, intravenous access was established by inserting a 24-gauge cannula into a vein in the dorsum of the hand. Atropine, 0.015 $mg \cdot kg^{-1}$ *iv*, was given to all children. Two minutes after atropine, study drug I was injected over 30 sec. It was followed by 3.5 $mg \cdot kg^{-1}$ propofol over 20 sec and then study drug II was injected as a rapid bolus.

Once the child became unconscious, ease of ventilation via a facemask was scored as easy (=1), satisfactory (=2) or impossible (=3). Sixty seconds after study drug II, laryngoscopy and intubation were attempted by an experienced anesthesiologist (U-MK or AH) using a Macintosh laryngoscope blade of appropriate size, and an uncuffed orotracheal tube the internal diameter of which was calculated using the formula, 4.0 + age/ 4 mm. The intubating conditions were assessed and scored for four variables: jaw relaxation (jaw mobile= 1, partly mobile=2, or immobile=3), position of the vocal cords (open=1, midposition=2, or tightly closed=3), and patient response to intubation (no coughing=1, one or two coughs=2, or persistent coughing=3). Using the above criteria intubating conditions were assessed as excellent (all criteria scored as 1), good (criteria scored as 1 or 2) or poor (any of the criteria scored as 3). Tracheal intubation was not attempted if the vocal cords were judged to be tightly closed in order to avoid injury to them.

TABLE I Demographic data; mean ± standard deviation. Re2 = 2 μg·kg^{-1} remifentanil; Re4 = 4 μg·kg^{-1} remifentanil; Re2-Ro0.2 = 2 μg·kg^{-1} remifentanil and 0.2 mg·kg^{-1} rocuronium; Ro0.4 = 0.4 mg·kg^{-1} rocuronium. 20 patients in each group.

	Re2	*Re4*	*Re2-Ro0.2*	*Ro0.4*
Age (yr)	5.7 ± 1.9	4.8 ± 1.4	5.3 ± 1.8	5.4 ± 1.9
Weight (kg)	21.1 ± 4.6	20.8 ± 5.4	21.6 ± 4.6	21.9 ± 5.3
Sex (M/F)	12/8	11/9	8/12	13/7

TABLE II Mean arterial pressure (MAP) and heart rate (HR); mean ± standard deviation. Re2 = 2 μg·kg^{-1} remifentanil; Re4 = 4 μg·kg^{-1} remifentanil; Re2-Ro0.2 = 2 μg·kg^{-1} remifentanil and 0.2 mg·kg^{-1} rocuronium; Ro0.4 = 0.4 mg·kg^{-1} rocuronium.

	Re2	*Re4*	*Re2-Ro0.2*	*Ro0.4*
MAP (mmHg)				
Control	78 ± 14	69 ± 10	81 ± 9	73 ± 15
Postinduction	69 ± 10	60 ± 12	72 ± 8	87 ± 15
Postintubation	68 ± 10‡†	58 ± 10‡	70 ± 6‡§	96 ± 14
Heart rate (bpm)				
Control	104 ± 19	100 ± 13	112 ± 20	101 ± 25
Postinduction	95 ± 16	96 ± 10	104 ± 20	106 ± 22
Postintubation	101 ± 15‡	96 ± 10‡	108 ± 18*	126 ± 18

* = $P < 0.05$; ‡ = $P < 0.001$ Re2, Re4 and Re2-Ro0.2 *vs* Ro0.4
† = $P < 0.05$; § = $P < 0.001$ Re2, Re2-Ro0.2 *vs* Re4

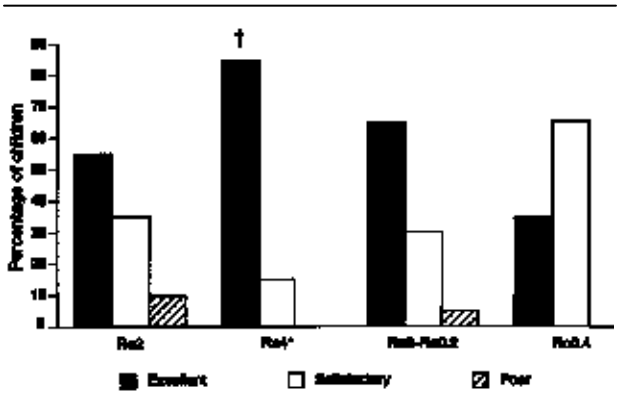

FIGURE Overall intubating conditions. Re2 = 2 μg·kg^{-1} remifentanil; Re4 = 4 μg·kg^{-1} remifentanil; Re2-Ro0.2 = 2 μg·kg^{-1} remifentanil and 0.2 mg·kg^{-1} rocuronium; Ro0.4 = 0.4 mg·kg^{-1} rocuronium.
* $P < 0.01$ better overall intubating conditions than in the Ro0.4 group
† $P < 0.01$ higher frequency of excellent conditions than in the Ro0.4 group.

Children whose tracheas could not be intubated after receiving the assigned induction drugs were so noted, and were given 0.5 mg·kg^{-1} rocuronium.

Monitors included an automated arterial pressure cuff, ECG, peripheral pulse oximeter ($Sp0_2$), and capnometer. Control values of arterial pressure (MAP), heart rate, and $Sp0_2$ were obtained after atropine. Thereafter, the measurements were performed after anesthetic induction, and immediately after intubation.

Parametric data were analysed by one-way analysis of variance. Differences among groups were evaluated using Student´s unpaired t test. Student´s paired t test was used for changes within each patient. Chi-square test or Fisher´s exact test, when appropriate, was used for nonparametric data. Bonferroni correction was performed for multiple comparisons. Significance was defined as $P < 0.05$.

Results

There were no demographic differences among the groups (Table I). The ease of mask ventilation was scored as easy in all children except in one in the Re2 group when it was satisfactory. No child appeared to manifest signs of opioid-induced rigidity at any time. In all children, intubation was successful at the first attempt. Overall intubating conditions were ($P < 0.01$) better, and the number of patients showing excellent conditions (mask ventilation easy, jaw relaxed, vocal cords open, and no coughing) was higher in the Re4 group ($P < 0.01$) than in the Ro0.4 group (Figure). The jaw was judged to be mobile in all children. The vocal cords were open in 70%, 95%, 95% or 100% in the Re2, Re4, Re2-Ro0.2 or Ro0.4 groups, respectively. In the groups receiving rocuronium, vocal cords were judged more frequently ($P < 0.05$) to be open than in the Re2 or Re4 groups. The patient response after intubation was judged to be excellent with no coughing in 70%, 90%, 70% or 30% in the Re2, Re4, Re2-Ro0.2 or Ro0.4 groups, respectively. There was a difference between the Re4 and the Ro0.4 group ($P < 0.01$).

Cardiovascular responses to induction and intubation are shown in Table II. After anesthetic induction, MAP decreased 11-13% in the groups receiving 2 ($P < 0.05$) or 4 μg·kg^{-1} remifentanil ($P < 0.01$), and increased 18% in the Ro0.4 group ($P < 0.05$). However, the differences among the groups were not statistically significant. After intubation, MAP remained at the same level in the remifentanil groups but increased in the Ro0.4 group ($P < 0.05$) which differed from the Re4 group ($P < 0.001$). After induction, heart rate decreased 6-9% in the remifentanil

groups ($P < 0.05$) but was similar to preinduction values after intubation. In the Ro0.4 group, heart rate increased after intubation ($P < 0.01$), and the difference from the other groups was significant ($P < 0.001$ to the Re2 or Re4 group; $P < 0.05$ to the Re2-Ro0.2 group). Peripheral oxygen saturation remained over 95% in all children throughout the investigation.

Discussion

The results of this study show that 4 $\mu g \cdot kg^{-1}$ remifentanil administered with 3.5 $mg \cdot kg^{-1}$ propofol provided excellent or good intubating conditions in all children aged three to nine years without the use of muscle relaxants. The intubating conditions after 4 $\mu g \cdot kg^{-1}$ remifentanil were better than those offered by propofol supplemented with 0.4 $mg \cdot kg^{-1}$ rocuronium. In addition, 2 or 4 $\mu g \cdot kg^{-1}$ remifentanil prevented the cardiovascular intubation response without causing undue decreases in arterial pressure or heart rate.

Excellent intubating conditions were found in 85% of the patients after 4 $\mu g \cdot kg^{-1}$ remifentanil whereas , in the control group where propofol was supplemented with 0.4 $mg \cdot kg^{-1}$ rocuronium, the corresponding number was 30%. The difference among the groups was due to slight coughing occurring in 70% of the patients in the control group. The vocal cords were more frequently judged to be open in the groups receiving rocuronium than without it. Thus, our results were similar to those showing a rapid onset of action for rocuronium at the laryngeal muscles.[13,14] Barclay *et al.* demonstrated that the vocal cords were open in 90% of patients after propofol combined with 0.1 or 0.3 $mg \cdot kg^{-1}$ rocuronium.[13] After 0.25 $mg \cdot kg^{-1}$ rocuronium, the onset time to maximum neuromuscular block of the laryngeal adductor muscles was 1.6 min.[14] However, for doses producing complete neuromuscular block the onset time decreased as the dose of rocuronium increased but remained similar with lower doses insufficient to produce complete block.[15]

In clinical practice, we considered it reasonable to take advantage of the observations that intubating conditions were acceptable after relatively low doses of rocuronium.[13,16] Pollard *et al.* showed that the trachea could be intubated in all patients at 60 sec after 0.45 $mg \cdot kg^{-1}$ rocuronium with satisfactory intubating conditions. The authors recommended this dose as appropriate for day case patients undergoing very short procedures. In children aged two to ten years, 0.4 $mg \cdot kg^{-1}$ rocuronium was shown to be the ED_{95} value[17] but, for a mean onset time of 46-48 sec at the adductor pollicis, a dose of 0.6-0.8 $mg \cdot kg^{-1}$ was required.[17,18] In consideration of the wide interindividual variability, the duration of action of this dose is too long for most of the procedures characteristic of our clinical practice. In the present study, 0.4 $mg \cdot kg^{-1}$ rocuronium after propofol resulted in good jaw relaxation and open vocal cords in all children. Hence, rather than inadequate muscle relaxation, the slight coughing observed in the group might be a question of the depth of anesthesia. As a practical conclusion, we emphasise the advantages associated with combinations of an hypnotic and an opioid instead of an hypnotic alone when treating noxious stimulation.[19] Succinylcholine with its very rapid onset and offset of action has been popular in both pediatric and adult anesthesia for nearly five decades. However, because of its many problems, we have followed those clinicians and investigators who have encouraged it be avoided in pediatric anesthetic practice except in emergency situations.[1]

Concerning the optimal dose of remifentanil combined with propofol to facilitate tracheal intubation without the use of muscle relaxants, our results are in agreement with those obtained in adult patients. Alexander *et al.* demonstrated that 4 or 5 $\mu g \cdot kg^{-1}$ remifentanil improved intubating conditions compared with 3 $\mu g \cdot kg^{-1}$.[11] Further, Stevens *et al.* reported that 3-4 $\mu g \cdot kg^{-1}$ remifentanil provided satisfactory intubating conditions more reliably than 1-2 $\mu g \cdot kg^{-1}$ remifentanil.[10] In both studies, remifentanil was combined with 2 $mg \cdot kg^{-1}$ propofol. In the present study, a dose of 3.5 $mg \cdot kg^{-1}$ propofol was chosen because children require a larger induction dose than adults. Moreover, children less than five years of age seem to need a higher dose than older children.[20] In the younger children, the increased propofol requirement seems to be due to pharmacokinetic differences whereas the volume of the central compartment and the systemic clearance were both greater than those reported in older children and adults.[21]

Consequently, we find it difficult to agree with the conclusion made by Robinson *et al.* that remifentanil does not appear to offer any advantage when compared with alfentanil for routine use in children aged two to 12 yr.[12] By taking remifentanil as being 15 times more potent than alfentantanil, they found intubating conditions after 1 $\mu g \cdot kg^{-1}$ remifentanil comparable with those provided by 15 $\mu g \cdot kg^{-1}$ alfentanil when both were followed by 4 $mg \cdot kg^{-1}$ propofol. By scrutinizing their results, however, it seems that neither dose was optimal. In adults, intubating conditions after propofol combined with 2 $\mu g \cdot kg^{-1}$ remifentanil were inferior to those after 50 $\mu g \cdot kg^{-1}$ alfentanil.[4] Thus, it seems that the study design and the conclusion made by Robinson *et al.* was based on an incorrect estimate of potency of the drugs.

Depending on the chosen endpoint, remifentanil has been found to be 20 to 40 times more potent than alfentanil.[22,23] However, in this context, a more useful approach for defining the optimal dose of remifentanil might start from the recognition of its unique pharmacokinetic properties. In contrast to alfentanil, remifentanil, with its very rapid elimination, allows a greater margin to dosing, since the time to recovery is not influenced by dose.[9]

Generally, muscular rigidity may be associated with rapid infusions of large doses of potent opioids.[24] After remifentanil, muscular rigidity was demonstrated in 11-32% of patients with target concentrations escalating from 2.0 to 16.0 ng·ml^{-1}.[25] However, none of our benzodiazepine premedicated patients exhibited signs of opioid-induced muscular rigidity such as a stiff chest. The lungs of all children could be ventilated without difficulty, and there was no jaw rigidity. Our results are in agreement with those obtained previously, in which drug combination and dosage were similar to ours.[10,11] The absence of signs of rigidity in our patients might have been due to the moderate injection rate of remifentanil. It has been suggested that the incidence and severity are dependent not only on the dose but the rate of administration.[24] Further, pretreatment with a benzodiazepine is effective in preventing opioid-induced muscle rigidity.[26]

With regard to cardiovascular variables, there was a marked similarity between the changes caused by the different doses of remifentanil both after induction and intubation. Indeed, it has been shown that after remifentanil the decreases in arterial pressure and heart rate of about 20% were independent of the dose from 2 to 30 μg·kg^{-1}.[27] In the present study, the mean reduction in MAP after anesthetic induction, 11-13%, was of a similar magnitude as that reported by Robinson *et al.* after 1 μg·kg^{-1} remifentanil,[12] but considerably less than that after 2 or 4 μg·kg^{-1} remifentanil shown by Alexander *et al.*[4,11] In the present study, pretreatment with atropine might have constituted a link for the absence of cardiovascular depression. Without a concurrent anticholinergic agent remifentanil was associated with bradycardia or hypotension, or both, in 30-50% of healthy patients during anesthetic induction and intubation.[10,11,28] On this basis, we considered the administration of an anticholinergic agent necessary, which might have contributed also to the observed stability of heart rate in our study in contrast to the results obtained without using an anticholinergic agent. In the present study, the cardiovascular intubation response was totally prevented in the groups receiving 2 or 4 μg·kg^{-1} remifentanil. This result is consistent with those obtained by others.[4,10,11]

It is concluded that the administration of 4 μg·kg^{-1} remifentanil in combination with 3.5 mg·kg^{-1} propofol provided excellent to good conditions for tracheal intubation thereby allowing successful tracheal intubation in all premedicated children aged three to nine years with favourable airway anatomy. Moreover, the combination of 2 or 4 μg·kg^{-1} remifentanil with propofol prevented the cardiovascular response to intubation. The technique may be appropriate when rapid return of spontaneous ventilation is aimed at, or if neuromuscular blockade is undesirable or not required for the planned surgical procedure.

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