Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children

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Background. We studied 120 children aged 2–7 yr in a prospective, randomized, assessor-blinded fashion to define the optimal rocuronium dose which provides a 95% probability of acceptable intubation conditions (ED95TI) during inhalation induction with sevoflurane.

Methods. After inhalation induction with 8% sevoflurane in 60% nitrous oxide and 40% oxygen, and loss of the eyelash reflex, we administered rocuronium (0.1, 0.15, 0.22, 0.3, or 0.6 mg kg⁻¹) or placebo. We quantified neuromuscular function by stimulation of the ulnar nerve at 0.1 Hz to produce contraction of the adductor pollicis muscle using accelerometry. Intubation conditions were assessed 2 min after test drug injection. The optimal rocuronium dose was defined as the lowest dose, which allowed acceptable intubation conditions in 95% of children (ED95TI).

Results. Two minutes after injection of placebo or rocuronium, intubation conditions were acceptable in 35, 45, 80, 90, 95, and 100% of children, respectively. Rocuronium 0.07 [CI 0.02–0.11], 0.24 [0.19–0.31], and 0.29 [0.23–0.38] mg kg⁻¹ provided 50, 90, and 95% probability of acceptable intubating conditions. When thumb acceleration was depressed by 50% or more, intubating conditions were considered acceptable in 97% of children. Recovery of the train-of-four ratio to 0.8 averaged 12 (7), 16 (7), 24 (7), 24 (8), and 50 (22) min after the respective dose of rocuronium.

Conclusions. During inhalation induction with 8% sevoflurane in 60% nitrous oxide, rocuronium 0.29 mg kg⁻¹ (ED95) optimizes intubation conditions for surgery of short duration.

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anaesthesia with sevoflurane, the data cannot be applied to the clinical situation when intubation is performed soon after induction of anaesthesia. Accordingly, the purpose of this study was to define, during inhalation induction of anaesthesia with sevoflurane/nitrous oxide, the optimal rocuronium dose required to achieve acceptable intubation conditions in 95% of children (ED95TI) within 2 min. It was also planned to assess whether accelerometry of the adductor pollicis muscle provides useful information for predicting such intubation conditions.

Patients and methods

One hundred and twenty children, aged 2–7 yr (classified as ASA I or II), undergoing elective urological, ophthalmological, or otolaryngological surgical procedures, were enrolled after approval of the local ethics committee and written informed consent has been obtained from their parents. Children with neuromuscular disease or those receiving medication with potential effects on neuromuscular transmission were excluded.

We used a random allocation without stratification to allocate the 120 patients to six groups of 20 patients each. To determine which treatment a subject would receive, one of 120 sealed, opaque envelopes of equal weight was drawn from a hat immediately before the child was transported to the operating room. All patients received, from a blind assessor, 5 ml of test drug intravenously, that is either saline (placebo) or one of five doses (0.1, 0.15, 0.22, 0.3, or 0.6 mg kg⁻¹) of rocuronium flushed into the injection port of an i.v. cannula.

Anaesthetic technique

Patients received midazolam 0.5 mg kg⁻¹ orally and a local anaesthetic cream (EMLA®; Astra Chemicals, Wedel, Germany) applied to the intended venous cannulation site at least 30 min before being transported to the operating room. After insertion of an i.v. cannula, all children received inhalation induction with sevoflurane in 60% nitrous oxide/40% oxygen by mask using a re-breathing circuit (Cicero EM, Dräger Medizintechnik, Lübeck, Germany). Incremental sevoflurane dosing every five breaths (1, 2, 4, and 8% inspired) was applied with a fresh gas flow of 10 litre min⁻¹, and 8% sevoflurane inspired was maintained until the time of intubation. Ventilation was first assisted manually and then controlled throughout the study so as to maintain end-tidal carbon dioxide tensions of 4.7–5.6 kPa.

To assess cardiovascular stability during induction of anaesthesia, heart rate (ECG, Lead II) and arterial pressure (oscillometry, Dinamap) were recorded after loss of the eyelash reflex, 1 min after injection of rocuronium or placebo (to detect any relevant anticholinergic effect), and after tracheal intubation (to ensure adequate depth of anaesthesia).

Neuromuscular monitoring

Neuromuscular function was assessed using a (train-of-four) TOF-Watch® monitor (Organon Teknika, Eppelheim, Germany), measuring acceleration of a transducer taped to the thumb in response to supramaximal stimulation of the ulnar nerve.

We immobilized one hand and forearm in a splint, allowing free movement of the thumb, and placed stimulation electrodes (PNS Electrode, NDM, Dayton, OH) onto the cleaned and abraded skin over the ulnar nerve close to the wrist. The transducer of the TOF-Watch® acceleration monitor was then applied to the volar surface of the thumb, the temperature transducer was fixed to the skin close to the adductor pollicis muscle, and the extremities were wrapped with surgical cotton. The TOF-Watch® monitor was calibrated using its automatic start-up-procedure (6 s), and we then applied 0.1 Hz single twitch stimulation before giving rocuronium or placebo. After maximal neuromuscular block had been established, we switched to TOF stimulation (2 Hz, every 15 s) until the TOF ratio had recovered to at least 0.8.

Intubating conditions

Intubation conditions were assessed 2 min after test drug injection by one of six experienced anaesthetists, blinded to both the test drug injected and the measurements of neuromuscular function. To assess intubation conditions, we used the scoring system described by Magorian and colleagues, who defined intubation conditions using the ‘worst quality’ observed within the classifications: ‘excellent’ (=1), jaw relaxed, vocal cords abducted and immobile, and no diaphragmatic movement; ‘good’ (=2), jaw relaxed, vocal cords abducted and immobile, and some diaphragmatic movement; ‘poor’ (=3), jaw relaxed, vocal cords moving, and coughing or bucking; and ‘inadequate’ (=4), jaw not relaxed and vocal cords closed.

According to the consensus conference criteria, ‘excellent’ and ‘good’ intubating conditions were considered as clinically ‘acceptable’, whereas ‘poor’, and ‘inadequate’ conditions were considered as ‘not acceptable’. In addition, we assessed the individual variables, jaw relaxation, relaxation of the vocal cords, and reaction to intubation, each on a four point numerical rating scale (1=best quality, 4=worst quality).

If jaw relaxation and vocal cord position were found inadequate for tracheal intubation after administration of the test drug, the anaesthetist was allowed to inject rocuronium 0.3 mg kg⁻¹ and the trachea was intubated 2 min later. These children were regarded as having been intubated under clinically ‘not acceptable’ conditions.
Statistics

We performed a power analysis based on a previous study,8 which assessed intubating conditions during steady-state anaesthesia after low-dose rocuronium. In that study, the intubation score was 1.7 (1.15) and 1.2 (0.42) after rocuronium 0.15 and 0.3 mg kg\(^{-1}\), respectively. From the data, we calculated that 20 patients in each group would be sufficient to find a significant difference in intubating conditions between groups (\(\alpha\)-error=0.05, power=0.8). Data are expressed as mean (SD). Measurements of neuromuscular function were compared by analysis of variance. Intubating conditions were analysed using the Kruskal–Wallis test and the Mann–Whitney \(U\) test, as appropriate. Using SAS software (version 6.12, AIX operating system), a bootstrap technique with re-sampling (\(n=500\)) was performed.13 The rocuronium dose was fitted into the equation for logistic regression against the dichotomous variable, the acceptable intubation condition, to calculate a 50, 90, and 95% [95% confidence interval] probability of clinically ‘acceptable’ intubation conditions. The optimal rocuronium dose (ED\(_{95TI}\)) was defined as the lowest dose, which allowed tracheal intubation under ‘acceptable’ conditions in 95% of the children.

The null hypotheses were that:

1. intubation conditions under anaesthesia with sevoflurane are not improved by rocuronium and
2. intubation conditions are not correlated with the results of accelerometry of the adductor pollicis muscle.

Hypotheses were rejected and statistical significance assumed with a \(P\)-value of <0.05. For multiple comparisons, the \(\alpha\)-level was adjusted according to the Bonferroni–Holm correction, if appropriate.

Results

There were no differences between groups with regard to age (mean (SD) 60 (21) months), height (110 (14) cm), or weight (19 (6) kg). No complications attributable to the study or to anaesthesia were observed. Time from application of the facemask to loss of the eyelash reflex averaged 58 (11) s and sevoflurane was given for 64 (11) s before test drug injection.

Intubating conditions

Two minutes after drug injection, jaw relaxation, and vocal cord position were considered adequate to proceed with tracheal intubation in 107 of 120 patients. In the remaining 13 children (7, 4, 1, and 1 after placebo, rocuronium 0.1, 0.15, and 0.3 mg kg\(^{-1}\), respectively), the anaesthetist chose to give an additional dose of rocuronium as the vocal cords were moving (\(n=6\)) or closed (\(n=7\)), and/or the jaw was not relaxed (\(n=8\)), resulting in the classification of unacceptable intubating conditions.

With injection of placebo, intubating conditions were considered acceptable in only 35% of children (Fig. 1). Rocuronium 0.15 mg kg\(^{-1}\) or more, improved intubating conditions significantly, and 16, 18, 19, and 20 out of 20 children could be intubated with good or excellent conditions 2 min after rocuronium 0.15, 0.22, 0.3, and 0.6 mg kg\(^{-1}\), respectively (\(P<0.01\) vs placebo; Fig. 1). From the data we calculated that rocuronium 0.07 [CI 0.02–0.11], 0.24 [0.19–0.31], and 0.29 [0.23–0.38] mg kg\(^{-1}\) provides a 50, 90, and 95% probability of acceptable intubating conditions, 2 min after injection.

When rating the three main criteria of intubation, jaw relaxation was improved with rocuronium 0.1 mg kg\(^{-1}\).
while position of the vocal cords and reaction to intubation were significantly improved only with the higher rocuronium doses.

**Contraction of adductor pollicis and intubating conditions**

None of the rocuronium doses was sufficient to fully abolish contraction of the adductor pollicis muscle in all children at the time of intubation (Table 1). Two minutes after giving the relaxant acceleration of the thumb was markedly decreased.

Relaxation of the adductor pollicis muscle correlated significantly \((P<0.0001)\) with intubation score. When acceleration of the thumb was suppressed by less than 20%, intubation conditions were considered ‘acceptable’ in only 48% of the children. In contrast, when thumb acceleration was depressed by 50% or more, intubation conditions were acceptable in 97% of the children.

**Neuromuscular recovery**

Time to recovery of the TOF ratio to 0.8 increased significantly with increasing rocuronium dosage, that is from 12 (7) min after rocuronium 0.1 mg kg\(^{-1}\) to 50 (22) min following 0.6 mg kg\(^{-1}\) (Table 1, Fig. 1).

**Cardiovascular stability**

Despite anaesthesia with 8% sevoflurane inspired with 60% nitrous oxide, systolic arterial pressure did not change significantly between loss of the eyelash reflex (103 (15) mm Hg) and tracheal intubation (98 (13) mm Hg). Heart rate increased from 109 (21) beats min\(^{-1}\) before test drug injection to 128 (26) beats min\(^{-1}\) \((P<0.05)\) at time of intubation with no differences between groups.

**Discussion**

During inhalation induction of anaesthesia with sevoflurane in children, small doses of rocuronium which depress but do not abolish contraction of the adductor pollicis muscle optimize intubation conditions but allow rapid recovery. The optimal rocuronium dose for intubation within 2 min in this study during inhalation induction with 8% sevoflurane in 60% nitrous oxide, and oxygen was 0.29 mg kg\(^{-1}\) [CI 0.23–0.38].

We assessed intubation conditions using the score proposed by Magorian and colleagues,\(^{11}\) which is commonly used in paediatric anaesthesia.\(^{14}\) In accordance with a consensus panel,\(^{12}\) ‘excellent’ and ‘good’ intubating conditions were considered ‘clinically acceptable’, while ‘poor’ and ‘inadequate’ conditions were considered ‘clinically not acceptable’. To study the different effects of low-dose rocuronium on jaw relaxation, position of the vocal cords, and reaction to intubation, we also assessed these variables on a four-point rating scale.

We measured neuromuscular block by accelerometry of the adductor pollicis muscle which is a new, clinically applicable method used in children.\(^{14}\) We did not perform a prolonged period of signal stabilization after the automatic start-up-procedure of the TOF-Watch\(^{10}\) monitor, as this would have delayed drug injection for at least 3 min.\(^{12}\) As in clinical practice, we administered the test drug immediately after loss of the eyelash reflex, that is 64 (11) s after the first sevoflurane exposure.

Intubating conditions are influenced by both the anaesthetic technique and the degree of muscle relaxation.\(^{15}\) When using sevoflurane and nitrous oxide without muscle relaxants, the time to reach a clinical end-point for intubation averages more than 4 min.\(^{3}\) For a combination of sevoflurane and rocuronium, intubation conditions will depend on the time interval between drug administration and the intubation attempt,\(^{2}\) especially when small doses of relaxant are given. We chose to assess intubation conditions 2 min after relaxant injection, as a short time interval to tracheal intubation is clinically desirable.

However, in our study even after injection of the largest doses of rocuronium maximum neuromuscular block was not established at the time of intubation. Increasing slightly the time interval between relaxant injection and tracheal intubation may have reduced further the dose of rocuronium required for acceptable intubation conditions, albeit with an increased exposure to high concentrations of sevoflurane.

Meeting the three main criteria required for easy intubation required different doses of rocuronium. While
jaw relaxation improved with the lowest rocuronium dose, relaxation of the vocal cords and inhibiting the reaction to intubation required larger doses. This supports the view that intubating conditions cannot be predicted from the degree of jaw relaxation during laryngoscopy. Additional clinical variables, more reliably predicting acceptable intubation, would be helpful in practice.

Two minutes after rocuronium 0.15–0.3 mg kg$^{-1}$, intubation conditions were considered clinically acceptable in the majority of the children, but the twitch height in the adductor pollicis muscle was depressed by only 30–40% at that time. The larger relaxant doses required to fully abolish the response of the adductor pollicis did not further improve intubation conditions, but prolonged recovery. The data are in accordance with the results of a previous study, reporting a 95% probability of acceptable intubation conditions when the twitch height using mechanomyography is depressed by 50%. Quantitative neuromuscular monitoring of the adductor pollicis muscle may, therefore, be useful to predict intubation conditions.

When rocuronium is given during steady-state sevoflurane anaesthesia, lower doses are required for intubation (ED$_{95TI}$: rocuronium 0.25 mg kg$^{-1}$ vs 0.29 mg kg$^{-1}$ in our study). This difference may be explained by greater augmentation of neuromuscular block after prolonged exposure to volatile anaesthetics, which is not evident on induction of anaesthesia.

Rocuronium is an ‘intermediate’ acting muscle relaxant when $2 \times$ ED$_{95}$ (0.6 mg kg$^{-1}$) is given. In our study, rocuronium 0.15 mg kg$^{-1}$ improved intubation conditions and also allowed a rapid recovery of the TOF ratio to 0.7 after 14 (5) min. This is comparable with recovery following shorter acting drugs such as mivacurium. Mivacurium is the only available neuromuscular blocking drug which shows a comparable neuromuscular recovery to small doses of rocuronium while improving intubation conditions 90 s after a dose of 0.2 mg kg$^{-1}$. The recovery time after mivacurium is even shorter than that after the optimal rocuronium dose of 0.29 mg kg$^{-1}$ determined in this study. Mivacurium may be preferable when rapid intubation is required for surgery of less than 20 min duration in children. Rocuronium 0.29 mg kg$^{-1}$ may be used for surgery of very short duration when given in conjunction with an anticholinesterase (e.g. neostigmine), which has been shown to decrease recovery time by 30–40%.

In conclusion, 2 min after injection of a low dose of rocuronium 0.29 mg kg$^{-1}$, intubation conditions are improved markedly in children during inhalation induction of anaesthesia with 8% sevoflurane in 60% nitrous oxide, and cardiovascular stability is maintained. When thumb acceleration is depressed by 50% or more, the clinician can expect acceptable intubation conditions in the majority of patients.

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