Pharmacokinetics and pharmacokinetic–dynamic modelling of rocuronium in infants and children


Summary
We have determined the pharmacokinetics and pharmacokinetic–pharmacodynamic relationship of rocuronium in infants and children. We studied infants (n=5, 0.1–0.8 yr) and children (n=5, 2.3–8 yr), ASA II, in the ICU while undergoing artificial ventilation under i.v. anaesthesia with an arterial cannula in situ and the EMG of the adductor pollicis muscle was monitored. Rocuronium 0.06 (infants) and 0.09 (children) mg kg\(^{-1}\) min\(^{-1}\) was given i.v. over 5 min until 85% neuromuscular block was obtained. Arterial blood samples were obtained over 240 min. Plasma concentrations were measured by HPLC. Pharmacokinetic–dynamic variables were calculated using the Sheiner model and the Hill equation. Statistical analysis was performed using the Mann–Whitney U test (P<0.05). The mean administered dose was 0.32 (sd 0.08) mg kg\(^{-1}\) and 0.4 (0.1) mg kg\(^{-1}\) for infants and children, respectively. Infants differed from children in plasma clearance (4.2 (0.4) vs 6.7 (1.1) ml min\(^{-1}\) kg\(^{-1}\)), distribution volume at steady state (231 (32) vs 165 (44) ml kg\(^{-1}\)), mean residence time (56 (10) vs 26 (9) min), concentration in the effect compartment at 50% block (1.2 (0.4) vs 1.7 (0.4) mg litre\(^{-1}\)) and the slope of the concentration–effect relationship (5.7 (1.3) vs 3.9 (0.5)). Calculated mean ED\(_{90}\) values were 0.26 and 0.34 mg kg\(^{-1}\) for infants and children, respectively. The time course of neuromuscular block after equipotent doses did not differ. (Br. J. Anaesth. 1997; 78: 690–695).

Key words Neuromuscular block, rocuronium. Infants. Children. Pharmacokinetics, rocuronium. Pharmacodynamics.

Rocuronium is an intermediate-acting non-depolarizing neuromuscular blocking agent that has a faster onset of action than other non-depolarizing neuromuscular blocking agents.\(^1\) There are only two studies comparing the neuromuscular effects of rocuronium in infants with those in children.\(^2,3\) These investigators obtained different results in that Woelfel and colleagues found that a fixed dose of rocuronium 0.6 mg kg\(^{-1}\) had a longer neuromuscular blocking effect and a slower recovery in infants than in children.\(^4\) Taivainen and colleagues administered individually determined ED\(_{95}\) doses of rocuronium to infants, children and adults and found a similar duration of effect and recovery rate of neuromuscular function in all three age groups.\(^3\) These apparently conflicting results may be explained by the pharmacokinetics of rocuronium. However, pharmacokinetic data currently available for rocuronium in infants are limited and cannot be used to explain the above pharmacodynamic differences.\(^3\) We designed a study to analyse the pharmacokinetics and pharmacodynamic–kinetic relationship of rocuronium in infants and children in order to rationalize these apparently conflicting results in the literature and to contribute to the development of rational dose regimens.

Patients and methods
After obtaining institutional Ethics Committee approval and parental written informed consent, we studied five infants and five children, ASA II, in the intensive care unit during stable recovery from elective tracheal or cardiovascular surgery, that is in a state of haemodynamic stability without supportive medication, normal peripheral (>32.5°C) and core (>36.5°C) temperatures, and normal values for blood chemistry, plasma proteins and packed cell volume. All patients were studied in the same intensive care unit. This site was chosen to guarantee stable cardiovascular and respiratory status of the patients, in the absence of surgical manipulations or bleeding during the study period, to allow an arterial cannula for arterial sampling to obtain reliable plasma concentrations for modelling. Surgical procedures in the patients are listed in table 1. Patients receiving medications or with diseases known to affect neuromuscular function, or patients with signs of hepatic or renal dysfunction were excluded.

Patients were routinely sedated and their lungs ventilated with the aid of i.v. bolus doses of

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morphine and midazolam. Before calibration of the neuromuscular device patients received thiopentone 2–6 mg kg\(^{-1}\) and alfentanil 20–80 \(\mu\)g kg\(^{-1}\) to guarantee a sufficient level of anaesthesia during the period of neuromuscular block. Standard monitoring included ECG, pulse oximetry, continuous core and palmar skin temperature monitoring, and invasive arterial pressure measurement.

**NEUROMUSCULAR MONITORING AND SEQUENCE OF EVENTS**

The arm opposite to the arm with the arterial cannula was used for neuromuscular measurements, that is adductor pollicis muscle electromyography (Relaxograph, Datex, Finland) after supramaximal train-of-four (TOF) stimulation (4 stimuli at a frequency of 2 Hz every 10 s). Surface stimulating electrodes were attached over the ulnar nerve on the wrist and recording electrodes over the adductor pollicis muscle, over the proximal volar surface of the index finger and at the radial side of the wrist distal to the stimulating electrodes.\(^8\) Palmar skin temperature was obtained from the same hand. A stable calibration signal of the electromyographic trace was awaited before rocuronium was administered. Neuromuscular block was defined as percentage depression of the first EMG twitch response (T1) of the TOF compared with the baseline calibration response. After infusion of rocuronium, neuromuscular function was recorded in every patient until full spontaneous recovery of the EMG response had occurred. The stable twitch response after recovery (Tc) was used as a reference value to calculate EMG recovery data. The time of maximal neuromuscular block after rocuronium infusion and times from maximum block until recovery of T1 to 25% and 75% of Tc and to a train-of-four ratio (T4/T1) of 0.7 (DUR\(_{0.7}\)) were calculated. The recovery index (RI\(_{55-79\%}\) time of T1 recovery from 25% to 75% of Tc) was derived from these data.

Rocuronium was administered by a continuous infusion joined by a needle to a rubber attachment of a steadily running central venous cannula. In five infants rocuronium, diluted in physiological saline to a concentration of 0.1 mg ml\(^{-1}\), was infused end to side to a running peripheral venous cannula at a rate of 0.06 mg kg\(^{-1}\) min\(^{-1}\) until a decrease in twitch height of 85% was obtained. The infusion was then stopped to prevent occurrence of complete block. In five children, rocuronium, diluted in physiological saline to a concentration of 0.3 mg ml\(^{-1}\), was infused via a peripheral venous cannula at a rate of 0.09 mg kg\(^{-1}\) min\(^{-1}\) also until 85% block was obtained.

Blood samples (0.5 ml) were obtained from an arterial cannula at the following times: one blank sample immediately before administration of rocuronium; five samples during onset of neuromuscular block at various degrees of block, that is at 1 and 2 min after the start of infusion and at approximately 20, 50, and 80% of block; one sample at maximum block; three samples at approximately 20%, 55% and 90% recovery of T1; and at 30, 45, 60, 90, 120, 180 and 240 min after disconnection of the infusion. Total sampling volume was restricted to less than 2% of the circulating blood volume of infants and to less than 1% of the circulating blood volume of children. Samples were stored in lithium heparinized tubes at room temperature until centrifugation, which took place within 4.5 h after the start of sampling. Plasma samples were stored at \(-20^\circ\)C after centrifugation. After completion of the study all samples were transported on dry ice to the analytical laboratory and stored at \(-18^\circ\)C until analysis.

**SAMPLE ANALYSIS**

Concentrations of rocuronium (Org 9426) and its putative derivatives, 17-desacetyl-rocuronium (Org 9943) and 16-N-desallyl-rocuronium (Org 20860), were analysed by HPLC as described previously.\(^7\) Using this method precision was almost independent of concentration and was 8%, 7% and 12% for rocuronium (10–20 000 ng ml\(^{-1}\)), Org 9943 (20–20 000 ng ml\(^{-1}\)) and Org 20860 (20–20 000 ng ml\(^{-1}\)), respectively. The accuracy for rocuronium, expressed as percentage recovered of the added amount, was 86%, 103%, 107% and 98% at concentrations of 10, 1000, 5000 and 10 000 ng ml\(^{-1}\), respectively. At 20 and 200 ng ml\(^{-1}\), accuracy was 92% and 106% for Org 9943, and 93% and 111% for Org 20860, respectively. The lower limit of quantification, defined as the lowest concentration that could be determined with a precision and accuracy greater than 15%, was 10, 20 and 20 ng ml\(^{-1}\) for rocuronium, Org 9943 and Org 20860, respectively.

**PHARMACOKINETIC ANALYSIS**

Pharmacokinetic analysis was based on iterative, non-linear, least-squares regression analysis by the computer program Multitfit using the Marquardt minimizing algorithm.\(^8\) Initial estimates were obtained by a stripping procedure. For each individual patient the parameters of a two- or three-exponential equation were fitted to the logarithm of the plasma concentration–time data pairs, assuming a constant relative error. The choice between a two- or three-compartment model was made on the \(P\) test, accepting a more complex model as significantly better fitting if \(P<0.05\). Relevant pharmacokinetic variables were calculated using standard equations, assuming the elimination to take place from the central compartment.\(^9\)

**PHARMACOKINETIC–DYNAMIC MODELLING**

The concentration–effect data were analysed using the computer program PkPdFit, the T1 data of the EMG and the values of the coefficients and exponents of a multiequivalent equation, describing the concentration vs time data in plasma. For each individual patient the variables of the model of Sheiner and colleagues,\(^10\) that is the rate constant between plasma and effect compartment (\(k_{eo}\)), the concentration in the effect compartment at 50% block (EC\(_{50}\)) and the sigmoidicity coefficient of the Hill equation (\(\gamma\)) were fitted to the effect using equal weight for each measurement. The fit was optimized with Simplex as the minimizing algorithm,\(^11\) using sets of
initial estimates obtained from previous fits. From these data individual ED$_{90}$ values, that is individual bolus doses resulting in 90% block, were derived.

**STATISTICAL ANALYSIS**

All data are presented as mean (sd), [range] and {median} unless otherwise stated. Comparisons between data obtained in infants and children were made using the Mann–Whitney $U$ test. Pharmacokinetic–dynamic variables were related to age and weight by linear regression. $P$<0.05 was considered as an indicator of statistically significant difference.

The computer programs Multifit and PkPdFit were written by one of the authors (J. H. P.).

**Results**

**PHARMACODYNAMICS**

Patient data are shown in table 1. Tracheal resections had been performed 7 and 11 days before the study while other procedures had been finished 3–20 h before the start of the modelling study. All open heart surgical procedures were performed under normothermic conditions with a mean duration of extracorporeal perfusion of 33 (13) min. Mean time between the end of extracorporeal perfusion and initiation of this study was 7.9 h. The interval between the last dose of intraoperative neuromuscular blocking agent and the start of the modelling study was always more than 10 times the elimination half-life of the blocker given during operation. None of the patients had infusions of vasoactive drugs. Core and palmar skin temperatures did not differ between the groups during the study and averaged 36.9 (0.3) $^\circ$C and 34.6 (1.5) $^\circ$C, respectively. Mean duration of calibration was 16 (8) min. In infants, 0.32 (0.08) mg kg$^{-1}$ of rocuronium established 96.9 (2.9) % block in 6.6 (1.6) min. In children, these values were 0.4 (0.1) mg kg$^{-1}$, 96.5 (0.7)% and 5.9 (1.4) min, respectively (ns). RI$_{25–75\%}$ and DUR$_{0.7}$ were 9.1 (4.7) and 21.5 (11.8) min in infants, and 0.32 (0.08) mg kg$^{-1}$, 96.5 (0.7)% and 5.9 (1.4) min, respectively (ns). RI$_{25–75\%}$ and DUR$_{0.7}$ were 9.1 (4.7) and 21.5 (11.8) min in infants, and 6.3 (0.7) and 14.0 (1.1) min in children, respectively (ns).

**PHARMACOKINETICS**

The duration of rocuronium infusion was 5.3 (1.4) and 4.5 (1.1) min in infants and children, respectively. The dose administered was 1.21 (0.06) times the individual ED$_{90}$ dose (calculated using individual PK/PD data) for infants and children, respectively. For all patients a three-compartment model fitted the plasma concentration vs time data significantly better than a two-compartment model. The residual coefficient of variation of the three-compartmental fits showed ranges and median values of [4.2–7.7%] {5.9%} and [7.7–20.9%] {13.1%} for infants and children, respectively. A representative example is presented in figure 1.

![Representative example of a three-compartmental fit of plasma concentration decay of rocuronium in an infant.](image)

**Table 1** Patient data and surgical procedures. (number or mean (sd) [range]).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical procedure ($n$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal resection</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Aortic valvulotomy</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Aortic coarctation resection</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Ventricular septum closure</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.5 [0.1–0.8]</td>
<td>5.4 [2.3–8.0]</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>6.0 (2.1)</td>
<td>19.1 (4.9)</td>
</tr>
<tr>
<td></td>
<td>[4.7–9.6]</td>
<td>[13.8–27]</td>
</tr>
</tbody>
</table>

1.2 (0.05) times the individual ED$_{90}$ dose (calculated using individual PK/PD data) for infants and children, respectively.
In infants, there was a significantly larger volume of distribution at steady state ($V^{ss}$), lower plasma clearance ($Cl_{pl}$), and consequently a longer mean residence time ($MRT_{iv}$) (table 2). The volume of the central compartment was similar in both age groups (table 2). There was a significant positive relationship for age (yr) and $Cl_{pl}$ (ml min$^{-1}$ kg$^{-1}$) ($Cl_{pl}$ = 0.403 age + 4.25; $P$ = 0.005), whereas there were significant inverse relationships for age and $V^{ss}$ (ml kg$^{-1}$) ($V^{ss}$ = −14.1 age + 239; $P$ = 0.0019), and age and $MRT_{iv}$ (min) ($MRT_{iv}$ = −5.20 age + 55.8; $P$ = 0.0012). Similar relationships existed for body weight (kg) and $Cl_{pl}$ ($Cl_{pl}$ = 0.142 BW + 3.65; $P$ = 0.019), body weight and $V^{ss}$ ($V^{ss}$ = −5.30 BW + 264; $P$ = 0.0041) and body weight and $MRT_{iv}$ ($MRT_{iv}$ = −2.00 BW + 65.7; $P$ = 0.0018). Potential metabolites of rocuronium in plasma were not detected.

PHARMACOKINETIC–PHARMACODYNAMIC MODELLING

The goodness of the PK/PD fits ($r^2$) showed ranges and median values of [0.9912–0.9980] {0.9971} and [0.9925–0.9951] {0.9942} for infants and children, respectively. The ranges and median values of the residual SD, expressed as percentage twitch height depression, were [1.5–3.4] {1.9} and [2.2–2.9] {2.4} for infants and children, respectively. A representative example is presented in figure 2.

![Figure 2](image-url)  
*Figure 2* Example of a pharmacodynamic–pharmacokinetic fit in an infant. A: Effects actually measured (■) with the curve fitted to them. B: Concentration–effect (logit scale) relationship in the effect compartment (■, onset □, offset).

The results of the modelling are presented in table 2. There was a significant inverse correlation for age and $\gamma$ ($\gamma = -0.30$ age + 5.71; $P$ = 0.030), and for BW and $\gamma$ ($\gamma = -0.13$ BW + 6.45; $P$ = 0.013).

**Discussion**

This study was carried out under conditions that may differ from those in the operating theatre and in postoperative cardiac surgery patients. Although this may create limitations, we believe that the data may well be valid for developing dose regimens for general anaesthetic practice for the following reasons. (1) Our time course results were in agreement with those of other investigators, obtained in comparable age groups. (2) Our simulations with the PK/PD data predicted findings obtained previously for infants and children (see below). (3) Our patients were in a stable cardiovascular state without supportive medication and had normal values for blood chemistry, plasma proteins and packed cell volume. (4) The study was not commenced before at least 10 half-lives of the neuromuscular blocking agent used during operation had elapsed.

PHARMACODYNAMICS

We found a similar time course of neuromuscular recovery after an ED95 dose of rocuronium administered by infusion in infants and children. This result supports the study of Taivainen and colleagues. Why, then, did Woelfel and colleagues find that after a constant dose of rocuronium 0.6 mg kg$^{-1}$, infants showed recovery times twice as long as those of children? Our pharmacokinetic–pharmacodynamic data allowed us to model a pharmacokinetic–dynamic relationship in each individual patient for any dose of rocuronium. We simulated the time course of action of an individual ED90 and of a fixed dose of 0.6 mg kg$^{-1}$ in infants and children (fig. 3).

Figure 3 demonstrates clearly how infants show a duration of effect of rocuronium twice as long as that of children after a constant dose of 0.6 mg kg$^{-1}$, despite similar time courses after an individual ED90. If a dose of 0.6 mg kg$^{-1}$ is replaced by an intubating dose of twice the mean ED90 values in infants and children, the difference becomes less pronounced but is still clinically relevant. Dur$^{25\%}$ of intubating doses ($2 \times$ ED90, i.e. 0.52 mg kg$^{-1}$ for infants and 0.67 mg

![Figure 3](image-url)  
*Figure 3* Simulated time course of action in infants (open symbols) and children (closed symbols) of an ED90 dose (■) and of a dose of 0.6 mg kg$^{-1}$ (△) of rocuronium using the model according to Sheiner and colleagues and the fitted values for the variables obtained in this study.
characteristics of different doses of rocuronium in infants and children are supported in studies in which pharmacodynamic parameters of muscular function in infants after a large bolus dose or repeated doses, as demonstrated by the modelling results shown in figure 3.

We observed a negative correlation for weight-normalized volume of distribution at steady state and age and body weight. In contrast, O’Kelly and colleagues found that volume of distribution increased slightly with age and weight, whereas Vuksanaj and Fisher did not find a significant trend in their study in children aged 4–11 yr. One can only speculate on the reason for these differences. It is possible that the different methodologies in the three studies may have created the observed differences. Comparing our results with weight-normalized volume of distribution at steady state in adults \( (205 \text{ ml kg}^{-1}) \), \( V_{\text{ns}} \) it may be concluded that in children aged 4–8 yr, \( V_{\text{ns}} \) is lower than in adults. In contrast, \( V_{\text{ns}} \) in infants is higher than in adults and children.

The larger plasma clearance and lower volume of distribution in children compared with both infants and adults resulted in a markedly lower mean residence time and a shorter duration of neuromuscular block. A short duration of action of an intubating dose of rocuronium has been observed in children compared with infants and adults.

Other non-depolarizing neuromuscular blocking agents do not seem to show similar correlations between pharmacokinetic variables and patient characteristics in children. All existing studies support the concept that the volume of distribution of a neuromuscular blocking agent is larger in infants than in children, in accordance with the larger percentage of extracellular fluid. For plasma clearance the situation is different. Studies with atracurium revealed that plasma clearance is larger in infants than in children. This may be explained by the organ-independent elimination rate in combination with the larger volume of distribution. A study with vecuronium showed similar plasma clearance in both age groups, and studies with d-tubocurarine indicated that plasma clearance may be smaller in infants compared with children. The latter finding may result from the relatively large contribution of renal clearance in elimination, compared with vecuronium.

**Figure 4** Relationship between plasma clearance and age in infants and children \( (\square) \). The solid line represents the regression line \( (C_{\text{pl}} = 0.40 \times \text{age} + 4.25) \). The dotted line was calculated from the results of O’Kelly and colleagues (range 0.25–8 yr) and the dashed line was calculated from the results of Vuksanaj and Fisher (range 4–11 yr).
PHARMACOKINETIC–PHARMACODYNAMIC RELATIONSHIP

Our results showed that infants needed a lower concentration of rocuronium in the effect compartment than children in order to produce the same degree of neuromuscular block. This result corroborates data available for d-tubocurarine and vecuronium.18–20 The lower effective concentrations in infants may be because of their potentially lower quantal content of acetylcholine, as shown in newborn rats, the larger because of their potentially lower quantal content of plasma proteins in infants.19–21 The slope of the concentration–response relationship based on the Hill equation was steeper in infants than in children. This finding supports the previous study of dose–response curves of rocuronium in infants, children and adults which showed the steepest slope in infants. This steeper slope in infancy may be a unique characteristic of rocuronium as this phenomenon has not been seen with other neuromuscular blocking agents.18,20,22

References


