Pharmacodynamics and pharmacokinetics of rocuronium in intensive care patients†


Summary
We have studied dose requirements, recovery times and pharmacokinetics of rocuronium in 32 intensive care patients. After an initial dose of 50 mg, rocuronium was administered as maintenance doses of 25 mg whenever two responses to train-of-four (TOF) stimulation reappeared (bolus group; n=27) or by continuous infusion to maintain one response in the TOF (infusion group; n=5). Median requirements for rocuronium were 27.4 (range 14.5–68.3) mg h⁻¹ and 43.7 (30.9–50.3) mg h⁻¹ in patients in the bolus and infusion groups, respectively. Median total duration of rocuronium administration was 29.0 (12.4–95.5) h and 63.4 (24.0–140.3) h, respectively. Median time from administration of the last bolus dose and end of infusion to recovery of the fourth twitch in the TOF was 100 (45–300) min and 60 (15–155) min, respectively. Arterial blood samples were obtained for up to 10 h after cessation of rocuronium administration, and concentrations of the parent compound and its putative metabolites were measured using high pressure liquid chromatography (HPLC). The plasma concentration profile (n=12) was described adequately by a two-compartment model. Mean plasma clearance (Cl), steady-state distribution volume (Vss), mean residence time (MRT) and elimination half-life (T1/2) were 3.16 (SD 1.15) ml kg⁻¹ min⁻¹, 769 (334) ml kg⁻¹, 262 (120) min and 337 (163) min, respectively. Recovery times, Vss, MRT, and T1/2 differed from previously published data obtained after rocuronium infusion of moderate duration in surgical patients. (Br. J. Anaesth. 1997; 78: 267–273).

Key words

Rocuronium (Org 9426) is a new aminosteroidal, non-depolarizing neuromuscular blocking agent which has an intermediate time course of action and is related chemically to vecuronium (2-morpholino, 3-desacetyl, 16-N-allypyrrolidino derivative). Several maintenance doses of rocuronium did not result in an increase in duration of action. In surgical patients the pharmacokinetics of rocuronium given as a single bolus dose followed by a continuous infusion have been shown to be similar to those obtained after a single bolus dose. The main route of elimination of rocuronium appears to be the hepatobiliary pathway and, unlike vecuronium, rocuronium does not appear to be metabolized in the liver. This may be an advantage of rocuronium in comparison with vecuronium, which has a pharmacologically active 3-OH metabolite. This metabolite is thought to contribute to cumulative characteristics of vecuronium after usual clinical doses given to healthy volunteers and after long-term administration in critically ill patients with concomitant renal failure.

Neuromuscular blocking agents are used occasionally to facilitate mechanical ventilation in intensive care patients, although their use has declined over the past 5 yr, partly because a growing number of reports on delayed recovery from neuromuscular block have appeared. One important factor contributing to prolonged neuromuscular block may be absolute and relative overdoses of the neuromuscular blocking agent, which may be attributable to the lack of regular monitoring of the patient’s neuromuscular function during drug administration.

This first study of rocuronium in intensive care patients aimed to determine the dose of rocuronium required to facilitate smooth mechanical ventilation in conditions of adequate analgesia and sedation and to ascertain recovery time and pharmacokinetics.

Patients and methods
We studied 32 patients admitted to the intensive care unit (ICU) because of acute respiratory failure, or multiple trauma or blunt brain trauma, or both, necessitating mechanical ventilation for an anticipated...
period of at least 24 h. After approval by the Ethics Committee of the Medical Faculty at the University of Innsbruck, written informed consent was obtained from the patients’ closest relatives or, whenever this was impossible, from the attending intensivist who was not involved in the study. Exclusion criteria were known alcohol or drug abuse, severe hepatic, renal or cardiac disease, neuromuscular disease, pregnancy, age less than 18 or more than 70 yr on admission, and administration of vecuronium within 4 h before the study. On admission, an acute physiological and chronic health evaluation (APACHE) II score and, if applicable, an injury severity score (ISS) were calculated.

In all patients analgesia and sedation were provided by continuous infusion of sufentanil 0.3–1.8 μg kg\(^{-1}\) h\(^{-1}\) or fentanyl 2–12 μg kg\(^{-1}\) h\(^{-1}\) and midazolam 0.2–0.8 mg kg\(^{-1}\) h\(^{-1}\) to maintain the patient comfortable and free of agitation at any time. Combined parenteral and enteral nutritional support was standardized and included carbohydrates (up to 4 g kg\(^{-1}\) day\(^{-1}\)), amino acids (up to 2 g kg\(^{-1}\) day\(^{-1}\)) and lipids (up to 2 g kg\(^{-1}\) day\(^{-1}\)). Depending on the predisposing disease, other drugs were administered concurrently (i.e. dopamine, dobutamine, phenylephrine, adrenaline, noradrenaline, nitroglycerin, amrinone, frusemidne, ranitidine and sucralfate, and antibiotics (β-lactam antibiotics, aminoglycosides, ciprofloxacin, metronidazole, polymyxin, sulbactam and vancomycin)).

A range of laboratory values, including tests of liver function and calculated creatinine clearance, were obtained daily. Haemodynamic, pulmonary gas exchange and other variables were monitored as part of routine clinical management and were not evaluated further in this study.

**MODES OF ROCURONIUM ADMINISTRATION**

Rocuronium was administered i.v. as an initial bolus dose of 50 mg. In 27 of 32 patients (bolus group) neuromuscular block was maintained with repeat doses of rocuronium 25 mg given each time the second response in the indirectly evoked train-of-four (TOF) was detectable by tactile or visual assessment (i.e. approximately 80% neuromuscular block).\(^{12}\) In the remaining five patients (infusion group) continuous infusion of rocuronium was started at an initial rate of 0.25 mg kg\(^{-1}\) h\(^{-1}\) at the time of recovery of the first response in the TOF (T1) after the initial bolus dose. The infusion rate was then adjusted to maintain T1 (i.e. approximately 95% neuromuscular block).\(^{12}\)

**NEUROMUSCULAR MONITORING**

Using a constant-current nerve stimulator (Digistim, Neuro Technology Inc, Houston, TX, USA) in the TOF mode, the ulnar nerve was stimulated at the wrist every 15 min. The number of visual and tactile responses of the thumb was recorded by trained medical students throughout administration of the drug. After cessation of administration of the neuromuscular blocking agent, the time from the last bolus dose and the end of rocuronium infusion, respectively, to the reappearance of all four twitches in the TOF mode was recorded. In addition, in 15 patients the time to attain a TOF ratio of 0.7 was determined by a new neuromuscular transmission monitor based on accelerometry (TOF Guard, Biometer, Denmark), as this device became available in the course of this study.

**PHARMACOKINETICS**

In 16 of 32 patients (11 in the bolus group and five in the infusion group) plasma concentrations of rocuronium and its putative metabolites were measured in arterial blood samples. A blank blood sample was obtained either before the first bolus dose or at least 3 days after cessation of rocuronium administration, preferably before the patient was discharged from the ICU. In patients in the bolus group blood samples were obtained approximately every 6 h, just before a repeat dose was administered. In patients receiving rocuronium by continuous infusion, blood samples were obtained at 2, 4, 7, 12, 20, 40 and 60 min after administration of the bolus dose and just before and 1 h after the start of infusion. Furthermore, before and 1 h after a change in the infusion rate, additional samples were obtained. After the last repeat dose, or after cessation of the infusion, samples were obtained at 5, 10, 20, 40, 60, 90, 150, 240, 360, 480 and 600 min. Blood was collected in lithium-heparinized tubes. Plasma was separated within 240 min after withdrawal. Sodium dihydrogen phosphate (NaH\(_2\)PO\(_4\) \(1\) mol litre\(^{-1}\)) solution was added to plasma (0.2 ml of acid to each 1.0 ml of plasma). Samples were stored at \(-18^\circ\)C until analysis.

Concentrations of rocuronium and its potential metabolites, 17-desacetyl-rocuronium (Org 9943) and 16-N-desallyl-rocuronium (Org 20860), were measured using high pressure liquid chromatography (HPLC) with 3,17-didesacetyl vecuronium as the internal standard. The precision (reproducibility) of the method was 8% over the range 10–100 000 ng ml\(^{-1}\) for rocuronium, 7% over 10–25 000 ng ml\(^{-1}\) for 17-desacetyl rocuronium and 12% over 10–25 000 ng ml\(^{-1}\) for desallyl rocuronium. The lower limits of detection were 3, 5 and 15 ng for rocuronium, 17-desacetyl rocuronium and desallyl rocuronium, respectively.\(^{13}\)

The plasma concentration–time data were analysed using the program MultiFit (JH Proost, University Centre for Pharmacy, Groningen, The Netherlands). This program has been used in several pharmacokinetic studies with rocuronium.\(^{2–4}\) The parameters of a two- and three-exponential function were fitted to the logarithm of the measured plasma concentration, assuming a constant relative error and using the Marquardt algorithm for minimization of the residual sum of squares.\(^{14}\) Initial estimates of the parameters were obtained from the plasma concentration–time data after the last bolus dose or after the end of the last infusion period. The fitting procedure took into account each plasma concentration measurement and each rocuronium bolus dose administration and, for the infusion group, dose rate, time of start.
and time of change of each subsequent rocuronium infusion. To test if a three-exponential function fitted better to the data than a two-exponential function, the F test was applied.\textsuperscript{15} The volume of the central compartment \( (V_C) \), steady-state volume of distribution \( (V_{ss}) \), plasma clearance \( (C_l) \) and mean residence time \( (MRT) \) were calculated using standard equations,\textsuperscript{16} assuming that elimination takes place from the central compartment.

STATISTICAL ANALYSIS

Descriptive statistics were applied to patient data, dose requirement for rocuronium, total dose of rocuronium administered, duration of treatment, neuromuscular and kinetic variables. The data were summarized by means of sample size, median, mean \((\text{SD})\), minimum and maximum values. For each patient the mean amount of rocuronium administered per hour was calculated separately. Linear regression analysis was applied to recovery times \( vs \) duration of treatment, total dose of rocuronium administered, creatinine clearance and tests of liver function (aminotransferases, bilirubin), respectively.

Results

The 32 intensive care patients (30 males) were given a median APACHE II score of 18 (range 11–39). Median age, weight and height of these patients were 29 (16–65) yr, 80 (60–105) kg and 180 (165–195) cm. Twenty-seven of 32 patients were trauma patients with a median injury severity score (ISS) of 30 (5–59); the remaining five were non-trauma patients. Median creatinine clearance was 110.5 (27.0–186.0) ml min\(^{-1}\). Median values for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were 22.0 (5–78) iu litre\(^{-1}\) and 30.0 (5–93) iu litre\(^{-1}\), respectively, and median total bilirubin concentration was 25.1 (3.9–194.4) \(\mu\text{mol litre}^{-1}\). Conditions precipitating admission to the ICU are summarized in table 1. Twenty-five of the 32 patients recovered from their illness and were discharged from the ICU at 2–40 days after admission. Of the seven patients (22\%) who died because of the severity of their illness, four died within 1 week after administration of rocuronium had been stopped and three died 2–7 weeks later.

Table 1  Summary of conditions precipitating admission to the ICU. ALI = acute lung injury; ARDS = acute respiratory distress syndrome

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Cause of admission (associated conditions)</th>
</tr>
</thead>
</table>
| Trauma patients | 12  Head trauma + multiple trauma  
|                 | 8   Multiple trauma  
|                 | 7   Head trauma  |
| Non-trauma patients | 3   ALI or ARDS (pneumonia, HIV infection; acute necrotizing pancreatitis; empyema of pleura, sepsis)  
|                    | 2   Acute respiratory failure (heart failure intraoperatively; chronic lung disease) |

PHARMACODYNAMICS

Dose requirements, total dose and duration of treatment

In the 27 patients in the bolus group the median dose of rocuronium required to maintain approximately 80\% neuromuscular block was 27.4 (median 14.5–68.3) mg h\(^{-1}\) and 0.34 (0.18–0.85) mg kg\(^{-1}\) h\(^{-1}\), respectively. Median duration of treatment was 29.0 (12.4–95.5) h, and the total dose of rocuronium administered was 875 (375–5775) mg. Evaluation of the amount of rocuronium administered per hour to individual patients revealed a significant time effect, which was investigated further. Dose requirements of rocuronium per hour were fitted to a model using weighted non-linear regression in order to compensate for the decrease with time in the number of patients treated. The dose requirement \( vs \) time relationship is described by the following equation: mean dose \( (t) = 0.3793 \times 0.5314 \times e^{-0.755 \times t} \). From this equation it can be calculated that the mean amount of rocuronium needed for neuromuscular block decreases from 0.63 to 0.38 mg kg\(^{-1}\) h\(^{-1}\) during the first 6–9 h and remains constant thereafter (fig. 1).

In the five patients in the infusion group one response to TOF (i.e. approximately 95\% neuromuscular block) was maintained by a median rocuronium dose of 43.7 (range 30.9–50.3) mg h\(^{-1}\) and 0.54 (0.52–0.63) mg kg\(^{-1}\) h\(^{-1}\), respectively. In this group of patients median duration of treatment was 63.4 (24.0–140.3) h and the total dose administered was 2014 (965–7051) mg. Because of the relatively small number of patients in the infusion group no attempt was made to analyse dose requirements over time as was done in the bolus group.

Recovery of neuromuscular function

Recovery data could not be obtained from all patients because some required further neuromuscular block (with vecuronium or pipecuronium) after the study period. The speed of recovery is summarized in table 2. The total dose of rocuronium administered, duration of treatment (fig. 2) and creatinine clearance and tests of liver function (ALT,
the mean residual coefficient of variation (cv) was 16% (range 10–26%), which is not markedly higher than the measurement error in the rocuronium plasma concentration assay (10–15%). In general, standard errors of estimated individual pharmacokinetic variables were relatively small; the mean value of the relative standard error was 5 (range 2–17%) for clearance, 28 (8–66%) for Vss, 14 (7–38%) for V1, 11 (5–23%) for MRT and 19 (5–38%) for terminal half-life. The main pharmacokinetic variables in the bolus (n = 8) and infusion (n = 4) groups are summarized in table 3 together with data from two previous studies in surgical patients where rocuronium was administered as a single bolus dose followed by continuous infusion to maintain 90% neuromuscular block for a period of approximately 2 h.23

Discussion
Knowledge of pharmacodynamics and pharmacokinetics of neuromuscular blocking agents acquired in the course of studies in surgical patients, who were given rather small doses during a short period, may not be directly applied to intensive care patients. This consideration is supported by the main findings of this first study on effect-controlled administration of rocuronium in intensive care patients.

First, the dose required to maintain neuromuscular block decreased during the first 6–9 h and remained constant thereafter. Second, recovery time after administration of rocuronium for more than 24 h was prolonged moderately in comparison with administration up to 3 h in surgical patients. Third, in intensive care patients the volume of distribution at steady state was increased and terminal half-life

Table 3  Main pharmacokinetic variables of rocuronium obtained from ICU patients (bolus and infusion) in the present study, and from two previous studies in surgical patients after rocuronium infusion of moderate duration (mean (st) [range]; unless otherwise stated). Vss (ml kg–1) = Volume of distribution at steady state; T1/2β (min) = terminal half-life; Cl (ml kg–1 min–1) = clearance; MRT (min) = mean residence time (*Data from Sparr, Khuenn-Brady and Eriksson; **data from McCoy and colleauge)

<table>
<thead>
<tr>
<th></th>
<th>ICU patients (n = 12)</th>
<th>Surgical patients (i.v. anaesthesia; n = 7)*</th>
<th>Surgical patients (halothane anaesthesia; n = 8)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of rocuronium administration (h)</td>
<td>39.38</td>
<td>2.16</td>
<td>1.23</td>
</tr>
<tr>
<td>Median total dose (mg)</td>
<td>937.5</td>
<td>195.7</td>
<td>67.0</td>
</tr>
<tr>
<td>Cl (ml kg–1 min–1)</td>
<td>3.16 (1.15) [1.39-5.07]</td>
<td>4.50 (1.95) [2.80-8.61]</td>
<td>5.30 (0.77) [1.97-4.55]</td>
</tr>
<tr>
<td>Vss (ml kg–1)</td>
<td>160 (88) [40-291]</td>
<td>146 (56) [71-238]</td>
<td>62 (8) [48-71]</td>
</tr>
<tr>
<td>T1/2β (min)</td>
<td>769 (334) [314-1351]</td>
<td>310 (80) [205-408]</td>
<td>213 (40) [152-303]</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>262 (120) [89-460]</td>
<td>78 (36) [41-132]</td>
<td>67 (19) [47-97]</td>
</tr>
<tr>
<td>T1/2β (min)</td>
<td>337 (163) [125-686]</td>
<td>108 (37) [64-163]</td>
<td>86 (18) [54-109]</td>
</tr>
</tbody>
</table>
and mean residence time were prolonged compared with surgical patients with normal hepatic and renal function who received rocuronium for an intermediate duration.

A median dose of rocuronium of 27.4 mg h⁻¹ administered to patients in the bolus group was sufficient for smooth mechanical ventilation in ICU patients under adequate sedation and analgesia. In patients in the bolus group the next maintenance dose was not given before the second response in the TOF had reappeared. It occurred several times that three responses to TOF stimulation were detectable when the next bolus dose was given. Mean neuromuscular block in the bolus group was therefore approximately 80%,¹² Higher doses of rocuronium were administered to patients in the infusion group to maintain one response to TOF stimulation (i.e. 95% neuromuscular block). The median dose requirement in the infusion group (43.7 mg h⁻¹) in this study was comparable with that necessary in surgical patients for 90% neuromuscular block under i.v. anaesthesia.²¹¹⁸

In patients in the bolus group, evaluation of dose requirements for rocuronium over time revealed a significant time effect (fig. 1). In addition, the doses of rocuronium administered to patients in both groups differed greatly from case to case. Therefore, monitoring of neuromuscular function is mandatory in ICU patients in order to adjust the dose to the individual needs of each patient and to avoid overdosing. Monitoring of neuromuscular function, however, does not eliminate prolonged weakness and myopathy in intensive care patients receiving neuromuscular blocking agents.¹⁰¹⁸ The results of this study suggest that a block of approximately 80%, which corresponds to that provided in the bolus group, may be sufficient to facilitate mechanical ventilation under adequate sedation and analgesia, even though some of the patients needed high levels of positive end-expiratory pressure and inversed-ratio ventilation for appropriate oxygenation. If, however, full relaxation of the diaphragm is desired, additional doses of rocuronium may be necessary to establish complete neuromuscular block of the diaphragm,²⁰ for example to prevent coughing on tracheal suction in patients with severe head injury.²¹ The optimal level of neuromuscular block and the mode of administration of neuromuscular blocking agent (repeated bolus injections or continuous infusion) should be adapted to the individual needs of ICU patients.

None of the patients receiving rocuronium in this study showed prolonged recovery from neuromuscular block, if the definition given by Segredo and colleagues²³ is applied (i.e. failure to recover any response to ulnar nerve stimulation within 2 h after administration of the last dose of a neuromuscular blocking agent). However, recovery of neuromuscular function was moderately delayed in ICU patients compared with surgical patients who received an infusion of rocuronium for up to 3 h duration.²² In this study recovery time was not related to the total dose of rocuronium given, duration of treatment, creatinine clearance or tests of liver function (aminotransferases, bilirubin). In 47% of patients in this study the time to attain a T4/T1 ratio of 0.7 was assessed using a small accelerometer (TOF Guard) designed for routine monitoring. The validity of TOF values obtained in the ICU setting using this device has not been investigated. In surgical patients, however, it was demonstrated that the limits of agreement are wide between TOF values obtained using this particular acceleration monitor and a mechanomyographic monitor, which is why these two monitoring systems should not be used interchangeably.²⁵

In this study the pharmacokinetic variables of individual patients of both groups were analysed together, as the two different modes of rocuronium administration (single bolus dose vs continuous infusion) were not expected to produce different results. None of the putative metabolites of rocuronium was detected in any of the patients. In most subjects, the plasma concentration profile followed a two-exponential decay after the end of rocuronium administration, and no sign of non-linear kinetics were observed. However, in intensive care patients it is questionable if processes of drug distribution and elimination are linear and invariable in time. Therefore, the pharmacokinetics can be described only in global terms. It may be of more importance to take into account intra-individual variability as a result of (patho-) physiological changes such as diurnal rhythms, changes in organ perfusion and organ function, changes in the ratio between extravascular fluid content, and number of receptors. Up-regulation of receptors may lead theoretically to an increased level of rocuronium necessary to achieve the same degree of neuromuscular block. In this study there was no evidence of resistance to rocuronium, as the requirement for rocuronium was constant after more than 6–9 h of administration. Concomitantly administered drugs may interfere with the pharmacodynamics of rocuronium and possibly also with drug clearance.

The main pharmacokinetic variables of rocuronium in ICU patients were different compared with surgical patients,²³ that is volume of distribution at steady state was increased, plasma clearance was decreased and terminal half-life and mean residence time were prolonged. These pharmacokinetic variables may differ because of true differences between ICU and surgical patients. Clearance, for example, might be diminished as a result of impaired renal or hepatic function. Differences in pharmacokinetic variables may, however, be artefacts and result from differences in total duration of administration, total dose, plasma concentrations and sampling schedule. Plasma concentrations during the terminal phase were markedly higher after long-term administration, either by infusion or by repeated bolus doses, than after short-term administration. Therefore, plasma concentrations remained above the limit of quantification much longer than after short-term administration. As a result, the apparent half-life may be longer, even if the “true” half-life is similar. Consequently, the calculated volume of distribution at steady state also increased, and the calculated plasma clearance decreased.
Figure 3 Simulation of the plasma concentration profile of rocuronium after stopping a BET infusion producing a constant plasma concentration of 2000 µg litre⁻¹ over a period of 2 h (closed symbols) and 40 h (open symbols) in ICU patients (■, ○) and surgical patients (□, △), respectively. The dashed line at 750 µg litre⁻¹ indicates the level at which 10% neuromuscular block was reached.

Appendix

In order to investigate the consequences of the differences in drug disposition between ICU and surgical patients, the time course of the plasma concentration profile was simulated for both types of patients. To clarify the influence of duration of drug administration, the plasma concentration was simulated after stopping an infusion lasting 2 and 40 h, respectively (Fig. 3).

These time values were chosen because they represent typical values of the duration of a rocuronium infusion in surgical patients² and in the ICU patients in this study, respectively.

For surgical patients the pharmacokinetic data of rocuronium were derived from a study in which rocuronium was administered as a bolus dose of 600 µg kg⁻¹ followed by a continuous infusion to maintain twitch height at 10% of control². The mean pharmacokinetic variables of a two-exponential model were: clearance 4.51 ml kg⁻¹ min⁻¹, intercompartmental clearance 1.77 ml kg⁻¹ min⁻¹, Vss 146 ml kg⁻¹ and Vp 310 ml kg⁻¹.

For ICU patients the mean pharmacokinetic data of this study were used.

For both types of patients the plasma concentration profile was maintained at a constant level of 2000 µg litre⁻¹ by means of bolus administration followed by an infusion with a continuously decreasing infusion rate according to the BET scheme.¹² After 2 and 40 h, respectively, the infusion rate was stopped, and the plasma concentration profile was followed for 8 h.

The plasma concentration profiles after stopping the infusion are depicted in figure 3. After 2 h of infusion, the plasma concentration decay in ICU patients was less rapid than that in surgical patients. However, the decay over the concentration range from 2000 to 750 µg litre⁻¹, which corresponds to approximately 90% and 10% neuromuscular block, was only slightly retarded in the ICU patients compared with the surgical patients.

In contrast, after 40 h of infusion, the decay after stopping the infusion was much slower in the ICU patients, and the time necessary to reach 750 µg litre⁻¹, or 90% recovery, was 160 min compared with 40 min in surgical patients. Simulations over a longer period of time resulted in approximately the same profiles as shown in figure 3, indicating that steady state had been reached.

As shown by the simulations, both duration of treatment and altered pharmacokinetics may be responsible for the alteration in the recovery profile in ICU patients compared with surgical patients.

Acknowledgements

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References


