TIME COURSE OF NEUROMUSCULAR EFFECTS AND PHARMACOKINETICS OF ROCURONIUM BROMIDE (ORG 9426) DURING ISOFLURANE ANAESTHESIA IN PATIENTS WITH AND WITHOUT RENAL FAILURE


SUMMARY
We have studied the onset and duration of action and pharmacokinetics of rocuronium bromide (Org 9426) during anaesthesia with nitrous oxide, fentanyl and isoflurane after a single bolus dose of rocuronium 0.6 mg kg⁻¹ in nine patients with chronic renal failure requiring regular haemodialysis, and in nine healthy control patients. Blood samples were collected over 390 min and concentrations of rocuronium and its putative metabolites measured using HPLC. Onset time for maximum block, duration of clinical relaxation (T₁₂) and recovery index, were 61 (SD 25.0) s and 65 (16.4) s, 55 (26.9) min and 42 (9.3) min and 28 (12.3) min and 19 (8.8) min, respectively, for patients with and without renal failure. The time for TOF ratio to return spontaneously to 0.7 was 99 (41.1) min and 73 (24.2) min, respectively, in the two groups. None of these differences was significant. The pharmacokinetic data were best described by a three-exponential equation. There were significant differences between patients with and without renal failure in the rates of clearance (2.5 (1.1) ml kg⁻¹ min⁻¹ and 3.7 (1.4) ml kg⁻¹ min⁻¹, respectively) and the mean residence times (97.1 (48.7) min and 58.3 (9.6) min) (P < 0.05). The differences in other kinetic parameters were not significant. We conclude that the effects of rocuronium may be prolonged in patients with renal disease, because of a decreased clearance of the drug. (Br. J. Anaesth. 1993; 71: 222-226)

KEY WORDS

Rocuronium (Org 9426) is a new monoquaternary aminosteroidal neuromuscular blocking drug, with a duration of action similar to that of vecuronium but with a more rapid onset of action [1-3]. Initial animal studies suggested that, as with vecuronium, it is excreted primarily in the bile [4]. However, it became apparent that the pharmacokinetics of vecuronium were affected in the presence of renal disease [5, 6]. In this study we compared the neuromuscular effects and measured the blood concentrations of rocuronium after a single bolus dose administered to normal patients and those with renal failure.

PATIENTS AND METHODS
After obtaining written informed consent and Ethics Committee approval, we studied nine patients with normal renal function (ASA I or II) undergoing elective dental or ophthalmic surgery, and nine patients with chronic renal failure requiring regular haemodialysis (ASA III or IV) and undergoing construction of arterio-venous fistulae. Any patient who was receiving medication known to interfere with neuromuscular transmission was excluded, except in the case of patients with renal failure, who were permitted to continue receiving corticosteroids, beta-adrenoceptor antagonists and calcium entry blocking drugs when these were essential medical therapy. Patients who were more than 35 % or less than 20 % of their ideal weight or had abnormal hepatic function were excluded from study. All patients with renal failure had undergone haemodialysis within 2 days before surgery.

After premedication with oral temazepam 20 mg 60 min before operation, anaesthesia was induced with fentanyl 2-3 μg kg⁻¹ and thiopentone 3-5 mg kg⁻¹ and maintained with 66% nitrous oxide in oxygen and 0.5—1.0% isoflurane (inspired concentration). Ventilation was assisted to maintain the end-tidal carbon dioxide concentration at 4.5-5.5 %. Additional increments of fentanyl were administered, if required, throughout the procedure.

Heart rate, non-invasive arterial pressure, oxygen saturation and temperature were monitored routinely. Skin temperature over adductor pollicis was kept greater than 32 °C throughout the study period by wrapping the arm in cotton wool.

Neuromuscular monitoring was commenced after


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induction of anaesthesia using transcutaneous supramaximal stimuli of 0.2 ms duration to the ulnar nerve at the wrist in a train-of-four (TOF) mode at 2 Hz every 12 s. The resultant force of contraction of adductor pollicis was measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd). After stabilization of control responses, rocuronium 0.6 mg kg$^{-1}$ (2 x ED$_{95}$ dose) was administered as a fast bolus injection. The times to greater than 5% depression of T1 (lag time) and its maximum depression (onset time) were recorded. Tracheal intubation was performed after the onset of maximum neuromuscular block. The times for spontaneous recovery of T1 to 25, 75 and 90% of control and to a TOF ratio of 0.7 were recorded as measures of the recovery characteristics of this bolus dose.

Anaesthesia was stopped and tracheal extubation performed at the end of surgery. The patients were observed over the next 1 h in the recovery area for any signs of residual muscle weakness.

Venous blood samples (4 ml) were obtained either from a dedicated peripheral cannula or from a central venous catheter before the administration of rocuronium (time zero), and at 1, 3, 5, 10, 15, 30, 60, 90, 150, 210, 270, 330 and 390 min after administration; at 25% recovery of T1 ($T_{1/25}$) and when the TOF ratio was 0.7. The samples were collected in lithium heparinized tubes and centrifuged within 4 h. The plasma was mixed with sodium dihydrogen phosphate buffer solution (0.2 ml to each 1.0 ml of plasma) and stored at −18°C until required for analysis.

Analysis of rocuronium and its putative metabolites, 17-desacetyl rocuronium and 16 N-desallyl rocuronium was carried out using high pressure liquid chromatography (HPLC) by a method previously described for vecuronium [7] but modified and validated for rocuronium and using 3,17-didesacetyl vecuronium (Org 7402) as the internal standard. After extraction of rocuronium and its putative derivatives from the sample, the compounds were separated by HPLC and the concentrations determined by fluorimetric detection after post-column ion-pair extraction. The precision (reproducibility) of the method is 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 limit of quantification with a precision better than 15% of this HPLC method was 10 ng ml$^{-1}$ for rocuronium and 20 ng ml$^{-1}$ for its putative derivatives, from a 1-ml sample of plasma.

Concentration vs time data were fitted for individual patients to both two- and three-exponential equations using a computer program for non-linear curve fitting (Multifit, JH Proost, University of Groningen in the Netherlands). This program allows estimation of parameters of various compartmental models using various minimizing algorithms [8]. It uses standard procedures and pharmacokinetic formulae derived from the literature [9]. The method has been validated using datasets and results from other available programs. The appropriate model was determined for each patient by the $F$ test. The volume of the central compartment ($V_c$), steady-state distribution volume ($V^\infty$), plasma clearance ($Cl_p$), elimination half-life ($T_P$) and mean residence time (MRT) were calculated using standard equations.

Data were subjected to Mann–Whitney $U$ test for determination of statistical significance. This test was chosen because of the wide scatter of the results, particularly in patients with renal failure. $P < 0.05$ was considered statistically significant.

### Results

The patients in the two groups were similar in average ages, weights, heights and sex distribution (table I).

The onset and duration of action of rocuronium are given in table II. Neuromuscular block was evident in about 30 s and the onset of maximum block was present in just over 1 min in both groups. The block was complete in all but one patient in the renal failure group and one patient in the control group, in whom the maximum blocks attained were 97% and 96%, respectively. Times to recovery to $T_{1/2}$ were 55 and 42 min, to $T_{1/2}$ 84 and 60 min and to $T_{1/2}$ 101 and 69 min, respectively, in renal failure and normal patients. Times for the TOF ratio to recover to 0.7 were 99 and 73 min, respectively, with recovery indices (times for recovery of T1 from 25% to 75% of control ($T_{1/25-75}$)) of 28 and 19 min. Although the times for all these end-points were longer in patients with renal failure, the differences did not attain statistical significance ($P > 0.05$).

Figure 1 shows the mean plasma concentrations of rocuronium over the period of sampling. The data from one patient from each group were excluded: the patient from the control group had received a further increment of rocuronium which interfered with the fitting of the data and the patient from the renal failure group had received metoclopramide which interfered with the analysis of rocuronium. For 14 of 16 patients, the three-exponential equation provided

### Table I. Physical and biochemical characteristics (mean (SD) [range]) of the two groups. **Significant difference between groups (P < 0.01)

<table>
<thead>
<tr>
<th></th>
<th>Renal failure (n = 9)</th>
<th>Normal renal function (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>51 [22–61]</td>
<td>46 [27–64]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 (18.8) [42–91]</td>
<td>69 (13.0) [53–94]</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (11.0) [145–182]</td>
<td>164 (12.7) [153–185]</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>5/4</td>
<td>4/5</td>
</tr>
<tr>
<td>Urea (mmol litre$^{-1}$)</td>
<td>22.2 (9.6) [14.2–46.0]</td>
<td>** 4.9 (1.1) [3.4–6.4]</td>
</tr>
<tr>
<td>Creatinine (mmol litre$^{-1}$)</td>
<td>777 (168) [426–940]</td>
<td>** 79 (10.5) [71–95]</td>
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TABLE II. Characteristics of neuromuscular block (mean \(\pm SD\) [range]). * Significant difference between groups (\(P < 0.05\))

<table>
<thead>
<tr>
<th></th>
<th>Renal failure patients</th>
<th>Normal patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lag time (s)</td>
<td>(n = 9)</td>
<td>29 (7.4) [22-41]</td>
</tr>
<tr>
<td>Onset time (s)</td>
<td>(n = 9)</td>
<td>61 (25.0) [43-124]</td>
</tr>
<tr>
<td>Time to recovery (min)</td>
<td>(n = 9)</td>
<td>55 (26.9) [35-115]</td>
</tr>
<tr>
<td>to (T_{1/2})</td>
<td>(n = 8)</td>
<td>84 (36.7) [54-158]</td>
</tr>
<tr>
<td>to (T_{10})</td>
<td>(n = 7)</td>
<td>101 (47.4) [64-182]</td>
</tr>
<tr>
<td>Time to TOF ratio 0.7 (min)</td>
<td>(n = 8)</td>
<td>99 (41.1) [62-174]</td>
</tr>
<tr>
<td>Recovery index (min)</td>
<td>(n = 8)</td>
<td>28 (12.3) [12-43]</td>
</tr>
<tr>
<td>Plasma concn (ng ml(^{-1})) at TOF ratio 0.7</td>
<td>(n = 9)</td>
<td>1229 (308) [843-1657]</td>
</tr>
<tr>
<td></td>
<td>(n = 9)</td>
<td>669 (237) [441-1047]</td>
</tr>
</tbody>
</table>

**Fig. 1.** Plasma concentrations (mean, \(\pm SD\)) after administration of rocuronium 0.6 mg kg\(^{-1}\). O = Patients with renal failure; ▲ = patients with normal renal function. Significant difference between groups from 15 min onwards (\(P < 0.05\)).

The mean pharmacokinetic data for each group are given in table IV. \(V_c\) (51.0 ml kg\(^{-1}\) and 38.5 ml kg\(^{-1}\)) in the renal failure and normal patients, respectively, \(V''\) (211.7 ml kg\(^{-1}\) and 207.1 ml kg\(^{-1}\)) and \(T_f\) (104.4 min and 97.2 min) did not differ significantly between the groups. MRT (97.1 min and 58.3 min) was significantly longer and the \(Cl\) (2.5 ml kg\(^{-1}\) min\(^{-1}\)) was significantly smaller.
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ml kg⁻¹ min⁻¹ and 3.7 ml kg⁻¹ min⁻¹) significantly less (both P < 0.05) in patients with renal disease. The plasma concentrations of rocuronium at T₁/₂₆₆₉ were 1229 and 891 ng ml⁻¹, and at TOF ratio 0.7 were 669 and 441 ng ml⁻¹ respectively, in patients with and without renal failure (TOF ratio—P < 0.05).

There was a significant negative correlation between the rate of clearance and the time to the spontaneous recovery of TOF ratio to 0.7 (r = -0.64; P < 0.01) (fig. 2).

There were large between-patient differences in both clinical response and kinetic parameters, particularly in patients with renal disease. No metabolites were detected in plasma in patients from either group.

DISCUSSION

We have shown that rocuronium was a rapidly acting agent with an onset time just greater than 1 min after a bolus of 0.6 mg kg⁻¹ in patients with or without renal failure. This is similar to the findings of Szenohradszky and colleagues [10] using the same dose of rocuronium in patients with renal failure and observed by us in a previous study in healthy patients [11]. Onset of neuromuscular block with rocuronium in renal failure appears to be unlike that after other myoneural blockers such as vecuronium, atracurium and tubocurarine, which have been reported by some workers to show a delayed onset of effect compared with healthy patients [12, 13].

The duration of clinical relaxation (T₁/₂₆₉) after rocuronium was prolonged (55 min) in patients with renal disease compared with that in patients with normal renal function (42 min). Because of the relatively large degree of variability present, especially among patients with renal failure, these prolonged recovery characteristics failed to attain statistical significance; it is likely that analysis of results from a larger number of patients may have produced significant findings. This was a first study undertaken in a group of ill patients which has suggested that a longer duration of action of rocuronium is likely in them. Szenohradszky and colleagues [10]; the duration of action in both groups of patients in the present study was also longer than those we have observed in a previous study [11]. The difference is likely to reflect the use of isoflurane in the present study, in contrast with the use of balanced or halothane-supplemented anaesthesia in the earlier study [11]. Some prolongation of recovery with rocuronium during isoflurane and enflurane anaesthesia has been reported previously [14]. The duration of clinical relaxation is, however, much more prolonged in patients with marked hepatic dysfunction [15].

Studies on the excretion of rocuronium suggest that the main mechanism is hepatic uptake and biliary excretion [4, 15]. However, the results from the present study suggest a considerable role for renal clearance. The rates of clearance in patients with normal renal function in the present study are similar to those reported by Wierda and colleagues [16]. The reduced rates of clearance in patients with renal failure are in keeping with findings in cats in which renal pedicle ligation resulted in a smaller rate of clearance [4]. This study in cats suggested that only about 10 % of an administered dose of rocuronium was excreted in urine. However, our findings of an approximately 30–40 % increase in the indices of duration of action of rocuronium in patients with renal failure would suggest a greater dependence upon renal excretion in man. That this is the case is supported by the findings of Wierda’s group, who were able to recover 33 % of unchanged rocuronium from urine [16]. Observation of a significant negative correlation between the rate of clearance and the time to spontaneous recovery of TOF ratio to 0.7 would suggest the decreased clearance to be the responsible factor for a somewhat longer duration of action of rocuronium.

The steady-state volume of distribution for rocuronium is smaller (211.7 ml kg⁻¹ and 207.1 ml kg⁻¹, respectively, in patients with and without renal failure) compared with that reported by Bencini and colleagues [13] for vecuronium (471 ml kg⁻¹ and 510 ml kg⁻¹). This may be a result of the greater fat solubility of vecuronium [16]. For rocuronium, which has a greater dependence on hepatic uptake and biliary excretion [4, 15], it is in hepatic dysfunction that both the kinetics and dynamics show the greatest changes. However, there are to date no published studies which have measured the biliary excretion of rocuronium in humans. Absence of any detectable metabolites would indicate minimal metabolism, which is supported by results from animal studies [4].

The plasma concentrations of rocuronium during recovery from neuromuscular block were greater in patients with renal failure, significantly so at the point of recovery of TOF ratio 0.7 (table II). This may indicate altered sensitivity of the receptor in patients with renal failure. However, this remains speculative, as steady-state plasma concentrations at a particular degree of neuromuscular block (such as Cₚ<sub>50</sub>) were not determined in the present study. Because of the very rapid onset of block, it is difficult to obtain sequential samples after a bolus of rocuronium 0.6 mg kg⁻¹. The present study was not, therefore, designed as a pharmacokinetic–pharmacodynamic modelling study which would have yielded such information.

In conclusion, the results from the present study suggest some prolongation of the effect of a single 0.6-mg kg⁻¹ dose of rocuronium in patients with renal failure, and demonstrated that they show greater between-patient variability than patients with normal renal function. This may be even more significant with larger or repeated doses. The results suggest that the drug should be used with caution in patients with significant renal disease, and that monitoring of neuromuscular block in this group of patients is essential.

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REFERENCES


