Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia


Summary
We have studied the pharmacokinetics of a single bolus of rocuronium (Org 9426), followed by an infusion, in eight patients during anaesthesia with halothane and nitrous oxide in oxygen. Neuromuscular block was monitored using train-of-four (TOF) stimulation and recording the force of contraction of the adductor pollicis muscle. Rocuronium was administered as an initial bolus dose of 0.45 mg kg\(^{-1}\) followed by an infusion adjusted manually to maintain T1 (first response in the TOF) at 10 % of control. Mean onset time and time to recovery of T1 to 10 % were 72 (SD 19.6) s and 27 (9.6) min, respectively. The infusion rates were stable in 19.8 (6.5) min. The mean requirement for rocuronium for steady state 90 % block of T1 was 528 (163.3) µg kg\(^{-1}\)h\(^{-1}\). After cessation of surgery the infusion was stopped and patients were allowed to recover spontaneously. The times to attain a T1 of 90 % and a TOF ratio of 0.7 were 31 (11.7) min and 36 (7.3) min, respectively. Blood samples were collected for 390 min after cessation of infusion and concentrations of rocuronium and its putative metabolites measured using HPLC. A two-exponential equation was used to describe the pharmacokinetic data. The rate of clearance, mean residence time and volume of distribution at steady state were 3.3 (0.77) ml kg\(^{-1}\) and 36 (7.3) ml kg\(^{-1}\), respectively. These values were not significantly different from previously published data for a single bolus dose [9].

Patients and methods
After obtaining informed consent and approval of the Regional Ethics Committee, we studied eight adult patients, aged 18–65 yr, ASA I and II, undergoing elective surgery lasting more than 1 h. These patients were part of a larger study assessing the use of rocuronium by continuous infusion. None had a renal or hepatic dysfunction or was receiving any medication known to interact with neuromuscular blocking agents. Any patient above 35 % or below 20 % of their ideal body weight was excluded.

Before premedication with oral temazepam 10–20 mg, anaesthesia was induced with fentanyl 2–3 µg kg\(^{-1}\) and thiopentone 3–5 mg kg\(^{-1}\), and maintained with 66 % nitrous oxide and 0.5 % halothane (inspired) in oxygen and additional doses of fentanyl. Heart rate (from ECG), non-invasive arterial pressure, end-tidal carbon dioxide concentration, oxygen saturation and temperature were monitored routinely. Ventilation was adjusted to maintain end-tidal carbon dioxide concentration at 4.5–5.5 %. Skin temperature over the adductor pollicis muscle was maintained above 32 °C.

Rocuronium is a new monoquaternary amino-steroidal non-depolarizing neuromuscular blocking drug with an intermediate duration of action similar to that of vecuronium but with a much faster onset of effect [1–4]. Blockers with an intermediate duration of action, such as vecuronium and atracurium, have previously been shown to be suitable for administration by continuous infusion [5, 6]. Because of its rapid onset and intermediate duration of action, rocuronium has also been found to be suitable for use by continuous infusion [7, 8]. Previous pharmacokinetic studies after single bolus doses have shown the clearance and elimination half-life of rocuronium to be 2.5–3.97 ml kg\(^{-1}\) min\(^{-1}\) and 104–131 min, respectively [2, 9]. Blockers used over longer periods by infusion may show a progressive decrease in the drug infusion rate because of accumulation of drug in the distribution compartments [10, 11]. In the present study we have therefore estimated the pharmacokinetics of rocuronium when administered as a bolus followed by continuous infusion. The results were compared with previously published data for a single bolus dose [9].
The kinetic characteristics are given in table 3. Mean $V_{ss}$, $Cl$, $T_{1/2}^\beta$ and MRT were 212.5 ml kg$^{-1}$, 3.3 ml kg$^{-1}$ min$^{-1}$, 85.6 min and 67.2 min, respectively. The values were not significantly different from those obtained previously using a single bolus dose of rocuronium [9]. No metabolites were detected in the plasma of any patient.

**Results**

Mean age, weight and height of the eight patients (seven male, one female) were 35 (range 18–59) yr, 67 (sd 8.4) (54–80) kg and 167 (4.9) (158–175) cm, respectively.

**PHARMACODYNAMIC EFFECTS**

Onset time (time from the end of injection to maximum effect) was 72 (sd 19.6) s and all patients attained complete block. The time to recovery of T1 to 10 % was 27 (9.6) min.

The mean rates of infusion required to maintain T1 at 10 %, recorded every 10 min, are given in table 1. There were large individual variations, as demonstrated by the large sd values. The rate was initially high but stabilized at 450–600 $\mu$g kg$^{-1}$ h$^{-1}$ in a mean time of 19.8 (6.5) min. The infusion rate showed a reduction from 70 min onwards but there were only two patients in the study beyond this time. The mean infusion rate for all patients over the entire period was 328 (163) $\mu$g kg$^{-1}$ h$^{-1}$. The mean duration of the infusions was 74 (45.1) min (range 40–176 min) and the mean total dose of rocuronium administered was 1.0 (0.18) (0.66–1.18) mg kg$^{-1}$.

The speed of recovery after the infusions were stopped is shown in table 2. Mean times for recovery of T1 to 25 %, 75 % and 90 % of control were 9.1 (6.3), 26.0 (10.2) and 31.4 (11.7) min, respectively. Recovery index was 17 (6.2) min and the time to recovery of the TOF ratio to 0.7 was 36.4 (10.2) min.

**PHARMACOKINETICS**

Figures 1 and 2 show the plasma concentrations of rocuronium in individual patients and the average for the group during the bolus dose and infusion maintenance, and in the post-infusion period. The plasma concentration decay was fitted (using the whole data set) to a simpler two-rather than a three-exponential equation as there was no significant difference between the two (mean coefficients of variance of 22 % and 17 % for the two- and three-exponential fits, respectively).

The kinetic characteristics are given in table 3. Mean $V_{ss}$, $Cl$, $T_{1/2}^\beta$ and MRT were 212.5 ml kg$^{-1}$, 3.3 ml kg$^{-1}$ min$^{-1}$, 85.6 min and 67.2 min, respectively. The values were not significantly different from those obtained previously using a single bolus dose of rocuronium [9]. No metabolites were detected in the plasma of any patient.
The present study has confirmed that rocuronium is a neuromuscular blocking drug with a rapid onset of action, thought to be a result of its low potency, and is in keeping with other reports of its rapid onset of effect \[1, 3, 4, 17\]. This is obviously an advantage for rapid control of the level of block when the drug is used by infusion and this has been shown in the present and previous studies \[7, 8\]. Administration of neuromuscular blocking drugs by continuous infusion provides for greater stability of drug concentrations, and ensures greater consistency in the degree of paralysis \[18\]. When appropriately titrated to individual patient requirements, infusion techniques have the potential to avoid periods of both inadequate and excessive drug effects \[10\].

The times to recovery of neuromuscular function were not unduly prolonged after the infusions. The mean recovery index of 17 min after stopping the infusion was slightly less than that reported after single bolus doses of rocuronium. This may have resulted from the fact that the patients in the present study were recovering from a level of block of 90%.
maintained by infusion rather than from a complete block using a bolus dose. In the latter situation more drug is redistributed during recovery from the peripheral to the central compartment, which then tends to slow the plasma concentration decay and elimination during the recovery phase [11].

Controlled infusions titrated to effect, minimize the transfer of drug to compartments other than the effect compartment. Use of blockers in this manner, therefore, results in a faster recovery than that resulting after a similar period of block using incremental maintenance doses. However, recovery may be prolonged, with an increased recovery index, after prolonged infusions because of saturation of the distribution compartments. In this situation, distribution of the blocker from plasma to the peripheral compartments contributes progressively less and less to reduction in plasma concentrations [11]. This was not the case in the present study where the duration of infusions was relatively short.

In the present study, no metabolites were detected in plasma in any patient. Metabolites in plasma or urine in humans have been found to be either absent or below the level of detection after 0.6 or 1.0 mg kg\(^{-1}\) bolus dose administration [2, 9]. Cooper and colleagues reported values of 207 ml kg\(^{-1}\), 3.7 ml kg\(^{-1}\) min\(^{-1}\) and 97.2 min, respectively, for steady state volume of distribution, rate of clearance and elimination half-life with 0.6 mg kg\(^{-1}\) in patients with normal renal function during isoflurane anaesthesia [9]. Values using a dose of 1 mg kg\(^{-1}\) were reported as 270 ml kg\(^{-1}\), 4.0 ml kg\(^{-1}\) min\(^{-1}\) and 131 min, respectively [2]. In the present study, mean steady state volume of distribution and elimination half-life were 212 ml kg\(^{-1}\) and 85.6 min, respectively, after a bolus dose followed by infusion. These variables are similar to those reported by Cooper and colleagues in normal patients after a bolus dose of 0.6 mg kg\(^{-1}\), although lower than those reported by Szentháradzy and colleagues who were studying patients undergoing renal transplantation [9, 19]. The rate of clearance was also similar to that reported in the previous study of single bolus dose administration [9]. Rocuronium concentrations were 1287 ng ml\(^{-1}\) at 25 % recovery of T1 and had decreased to 711 ng ml\(^{-1}\) on recovery of the TOF ratio to 0.7, which were similar to those after single bolus doses of 0.6–1.0 mg kg\(^{-1}\) [2, 9].

The use of venous samples in the present study was based on convention. Although data obtained from arterial sampling may yield different and more accurate values, in particular for \(V_{1s}\) in the present study we used venous sampling to allow comparison with the results obtained from the previous single dose study based on venous sampling [9].

Although patients in the present study were anesthetized with halothane compared with isoflurane in the study of Cooper and colleagues [9] with which the results from the present study have been compared, it has been shown that there are no significant differences in the kinetics of rocuronium during anaesthesia with these two agents [20].

Studies in the cat showed that less than 10 % of rocuronium was excreted in urine and, as with vecuronium, most was excreted in bile [21]. However, previous work in healthy patients and those with renal failure has suggested a considerable role for renal clearance, with approximately 30 % of rocuronium being recovered unchanged from urine [2, 9]. This was associated with greater inter-individual variability of effect in patients with renal disease and the possibility of a longer duration of action of rocuronium in such patients [9]. It is likely that a similar trend will be observed after the use of rocuronium by infusion.

In conclusion, the present study indicates that rocuronium is suitable for infusions of moderate duration in patients with normal hepatic and renal function, with little difference in recovery and kinetic characteristics compared with single bolus doses. The absence of detectable metabolites is in keeping with previous work with single bolus dose administration and indicates minimal metabolism even with a total dose of 1.0 mg kg\(^{-1}\). These results, however, do not preclude possible prolonged recovery with alteration in the kinetics of the drug after a much longer period of administration or in patients with significant renal or hepatic dysfunction, or both.

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