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Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anaesthesia

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Summary

The neuromuscular effects of intravenous rocuronium bromide, 0.6 mg.kg^{-1} or 0.9 mg.kg^{-1}, were studied in four groups of 10 patients during anaesthesia with or without halothane (0.5–0.75% inspired concentration). Neuromuscular block was monitored using mechanomyography and train-of-four stimulation. The mean times to onset of complete neuromuscular block were 58 and 59 s using the 0.6 mg.kg^{-1} dose in patients anaesthetised with fentanyl and halothane respectively. The times of 34 min and 33 min for 25% recovery of T1 (first response in the train of four), 54 min and 52 min for 90% recovery of T1, 55 min and 60 min for a train of four ratio of 0.7, and 13 and 13 min respectively for the recovery index (25–75% recovery of T1) were not significantly different in these groups. Complete block with the 0.9 mg.kg^{-1} dose occurred in 47 s and 44 s respectively in the fentanyl and halothane groups. T1 recovered to 25% in 51 min and 58 min, and to 90% in 77 min and 86 min respectively in the two groups. The recovery indices and the times to spontaneous recovery of the train of four ratio to 0.7 were 17 min and 19 min, and 83 min and 93 min respectively. All the parameters were significantly different between the 0.6 mg.kg^{-1} and 0.9 mg.kg^{-1} doses. Halothane in the concentrations used did not influence the neuromuscular effects. It is concluded that rocuronium is a rapidly acting non-depolarising muscle relaxant with a duration of action similar to that of vecuronium and may be a useful alternative to suxamethonium for rapid tracheal intubation.

Key words

Neuromuscular relaxants; rocuronium (Org 9426).
Anaesthesia; halothane, fentanyl.
Anaesthetics, volatile; halothane.
Analgesics; fentanyl.

The introduction of atracurium and vecuronium provided anaesthetists with muscle relaxants with distinct advantages over other agents in terms of an intermediate duration of action and relative lack of side effects. However, both are relatively slow in onset of effect unless used in large doses which may give rise to side effects or prolonged block. Desacetoxy derivatives of pancuronium and vecuronium have been shown in animal studies to be associated with a fast onset of neuromuscular block [1,2]. Preclinical studies with rocuronium (Org 9426), a desacetoxy analogue of vecuronium have confirmed these findings [2,3]. Studies in humans have also shown the agent to have a faster onset of action but a similar duration of clinical relaxation to vecuronium [4–6].

The present study examines the time-course of neuromuscular block following two different doses of rocuronium during anaesthesia with or without halothane supplementation.

Patients and methods

Forty adult patients between the ages of 18 and 65 years, conforming to ASA grades 1 and 2 were included in the study following approval by the Regional Ethics Committee. All patients gave written informed consent and were undergoing elective surgery. None was receiving any medication known to interact with neuromuscular blocking agents. Patients who were above 35% or below 20% of their ideal weight were not studied.

Following premedication with oral temazepam (10–20 mg), anaesthesia was induced with thiopentone (3–5 mg.kg^{-1}) and fentanyl (2–3 μg.kg^{-1}). It was maintained in one group of 20 patients with 67% nitrous oxide in oxygen and further increments of fentanyl and/or thiopentone as required; the other group of 20 received 0.5–0.75% halothane in addition. Ventilation was assisted so as to maintain the end-tidal carbon dioxide concentration between 4.6 and 6.0 kPa. Skin temperature over the adductor pollicis muscle was maintained above 32°C.

The ulnar nerve was stimulated percutaneously at the wrist with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 12 s, the resultant force of contraction of the adductor pollicis muscle being measured and recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Ltd). Following stabilisation of control

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Table 1. Physical characteristics. Values are mean (SD) (range). There were 10 patients in each group.

	Fentanyl		Halothane	
Dose (mg.kg^{-1})	0.6	0.9	0.6	0.9
Age; years	38 (9) (30–58)	41 (15) (21–63)	44 (11) (19–58)	39 (8) (26–50)
Weight; kg	56 (7)	67 (8)	66 (8)	62 (11)
Height; cm	159 (7)	164 (8)	165 (9)	160 (5)
Sex (m/f)	1/9	3/7	3/7	1/9

responses, patients received rocuronium in a dose of 0.6 mg.kg^{-1} (n = 20, and 0.9 mg.kg^{-1} (n = 20), as a single fast intravenous bolus. Tracheal intubation was carried out once maximum block had supervened.

The time from the end of injection of the muscle relaxant to the first measurable reduction in the height of the first response of the TOF (T1) (lag time), and the time to maximum block (onset time) were measured. Recovery from neuromuscular block was allowed to occur spontaneously and the times for the recovery of the T1 to 25, 75 and 90% of control were recorded. The recovery index (time for recovery of T1 from 25 to 75%) and the time to the appearance of a TOF ratio of 0.7 were also recorded. The study was terminated at this stage and anaesthesia and further relaxation if necessary were maintained as appropriate for surgery using further smaller doses of rocuronium or vecuronium.

Heart rate (from the electrocardiograph), noninvasive arterial blood pressure, end-tidal carbon dioxide concentration and oxygen saturation were routinely monitored in all patients. Any signs of histamine release, either localised or systemic, following rocuronium administration were recorded.

The results were analysed using analysis of variance followed by Student's t-tests with Bonferroni correction for intergroup comparisons.

Results

The four groups of 10 patients were similar in respect of age, weight, height and sex distribution (Table 1). The high proportion of females in the study was due to the use of patients undergoing gynaecological surgery.

All patients attained complete block following rocuronium. The neuromuscular results are given in Table 2. The lag times averaged from 24 to 29 s and were not significantly different among the groups. The onset of complete block in individual patients ranged between 42 and 90 s with the 0.6 mg.kg^{-1} dose. The average times for maximum block were 58 and 59 s during fentanyl and halothane anaesthesia respectively. These times were reduced to 47 and 44 s in the groups receiving 0.9 mg.kg^{-1} of rocuronium with individual values ranging between 31 to 61 s. There were no significant differences within each dose between the two anaesthetic techniques but the 0.9 mg.kg^{-1} doses were associated with a significantly faster onset of block ($p < 0.05$).

The clinical duration (time to recovery of T1 in the TOF to 25% of control) was significantly longer ($p < 0.05$) in patients receiving the 0.9 mg.kg^{-1} doses (51 and 58 min in the fentanyl and halothane groups respectively) in comparison to those receiving the 0.6 mg.kg^{-1} doses (34 and 33 min respectively). The differences between fentanyl and halothane groups given either dose of rocuronium were again not significant. The overall total recovery times (T1 to 90%) were also dose-related being 54 and 52 min respectively with the 0.6 mg.kg^{-1} dose during fentanyl and halothane anaesthesia and 77 and 86 min with the 0.9 mg.kg^{-1} dose. Spontaneous recovery of the TOF ratio to 0.7 occurred in 55 and 60 min at the low dose, and 83 and 93 min at the high dose, in the fentanyl and halothane groups respectively. The recovery indices averaged from 13 to 20 min across the groups.

Table 2. Mean (SD) onset and duration of action of rocuronium during fentanyl or halothane anaesthesia.

	Fentanyl (mg.kg^{-1})		Halothane (mg.kg^{-1})	
	0.6	0.9	0.6	0.9
Time to maximum block; s	58 (10.6)	47 (7.0)	59 (15.3)	44 (8.1)
$T_{25\%}$; min	34 (7.4)	51 (10.7)	33 (4.4)	58 (7.8)
$T_{75\%}$; min	47 (13.1)	68 (14.9)	46 (7.4)	78 (11.4)
$T_{90\%}$; min	54 (17.4)	77 (21.0)	52 (10.6)	86 (14.7)
$T_{0.7\,TOF}$; min	55 (12.6)	83 (24.4)	60 6.9)	93 (11.7)
Recovery index; min	13 (6.7)	17 (5.4)	13 (4.4)	20 (4.0)

$T_{25\%}$, $T_{75\%}$, $T_{90\%}$ and $t_{0.7\%\,TOF}$ indicate times of recovery of T1 to 25, 75 and 90% of control and to recovery of TOF ratio to 0.7. Recovery index = time from recovery of T1 from 25 to 75%. All times are significantly different between groups receiving 0.6 and 0.9 mg.kg^{-1} within each anaesthetic technique.

The changes in heart rate and mean arterial pressure are shown in Table 3. No signs of histamine liberation were observed in any patients following rocuronium administration.

Discussion

The present study shows that rocuronium is a neuromuscular blocking drug with a rapid onset of action approaching that of suxamethonium. Rapid onset of effect with Org 9426 has been reported previously by other workers also [4–6]. The time to complete block of 58 s with a dose of 600 μg.kg^{-1}, is quicker than a time of 89 s reported in a previous study using a similar dose and a similar anaesthetic technique [6]. This is probably due to the use of a TOF mode of stimulation in the present study in contrast to the use of single twitch in the other study. It has been shown before that the onset time for intermediate duration neuromuscular blocking drugs is faster using a TOF mode of stimulation [7,8]. The observation of rapid onset of action with rocuronium confirms the hypothesis

Table 3. Mean (SD) values of heart rate (HR) (beat.min^{-1}) and mean arterial pressure (MAP) (mmHg) before and after induction of anaesthesia and rocuronium administration.

	Fentanyl		Halothane	
Group	MAP	HR	MAP	HR
Pre-induction	89 (11)	81 (14)	97 (13)	88 (17)
Postinduction	84 (11)	83 (14)	85 (13)	84 (16)
Prerelaxant	78 (12)	75 (14)	82 (11)	77 (17)
Postrelaxant	86 (14)	80 (12)	74 (14)	85 (16)
+10 min	82 (15)	76 (12)	79 (11)	77 (13)

put forward by Bowman and his colleagues and found to be true in animal studies that a relatively low potency non-depolarising relaxant with a steroid structure would be associated with a relatively rapid onset of effect [1,2]. The usefulness of the rapid onset of action of rocuronium has been shown by the demonstration of intubating conditions which are generally similar to those obtained with the use of suxamethonium [6].

The present study shows, not unexpectedly, that increasing the dose results in a faster onset of neuromuscular block. This has been reported with other non-depolarising relaxants [10,11] as well as with Org 9426 [12]. The onset time was reported to decrease from 186 to 72 s when the dose was increased from 0.3 $mg.kg^{-1}$ to 0.9 $mg.kg^{-1}$ (1 to $3 \times ED_{95}$) during anaesthesia with enflurane [12]. The present study and a study carried out by us previously [13] shows a reduction in average onset time from 102 s with 0.3 $mg.kg^{-1}$ to 59 s with 0.6 $mg.kg^{-1}$ and 45 s with a 0.9 $mg.kg^{-1}$ employing the TOF mode of stimulation. The duration of clinical relaxation of rocuronium is similar to those of atracurium and vecuronium, being in the range of 25–35 min using equipotent doses ($2 \times ED_{95}$) [10,11,14–16]. The rate of recovery (recovery index) of rocuronium is also similar to that of atracurium and vecuronium. The increase in the duration of action which was observed in the present study by increasing the dose is known to occur with all relaxants and rocuronium is no different from them.

Halothane did not significantly affect the time to onset of block or the duration of action of rocuronium. It is no different from agents like vecoronium or atracurium in this respect [17–19]. Enflurane and isoflurane potentiate the effect of nondepolarising relaxants. The same has also been reported with rocuronium [20,21] and would occur by the same mechanisms.

The present study, which was not specifically designed to assess the cardiovascular effects of rocuronium, did not show changes in heart rate or arterial pressure of any clinical significance. Detailed studies of cardiovascular effects in humans are not yet available. Animal studies have shown no significant cardiovascular effects with up to $3 \times ED_{95}$ doses of rocuronium although a dose $5 \times ED_{95}$ was reported to cause a 13% increase in heart rate [22].

In conclusion, rocuronium appears to be a rapidly acting nondepolarising relaxant with an onset of action which approaches that of suxamethonium and may be a suitable replacement for suxamethonium for rapid tracheal intubation and studies to confirm this are indicated. The duration of action, however, resembles that of intermediate duration compounds such as vecuronium and atracurium.

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