British Journal of Anaesthesia 1992; **69**: 269–273

COMPARISON OF INTUBATING CONDITIONS AFTER ADMINISTRATION OF ORG 9426 (ROCURONIUM) AND SUXAMETHONIUM

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SUMMARY

We have assessed intubating conditions after administration of Org 9426 (rocuronium) 600 μg kg^{-1} at 60 or 90 s in groups of 20 patients anaesthetized with thiopentone, nitrous oxide in oxygen and small doses of fentanyl, and compared the data with those obtained after suxamethonium 1 mg kg^{-1} in similar groups of patients. The influence of prior suxamethonium administration on the potency of Org 9426 was studied also by constructing a dose–response curve. Intubating conditions after Org 9426 were found to be clinically acceptable (good or excellent) in 95% of patients at 60 s and in all patients at 90 s and in all patients at both times after suxamethonium. The average time for the onset of block following Org 9426 at this dose was 89 s (which is shorter than with any of the currently available non-depolarizing neuromuscular blocking drugs); the duration of clinical relaxation (25% recovery of twitch height) 30 min. Prior administration of suxamethonium did not appear to influence the potency of Org 9426.

KEY WORDS

Anaesthesia: intubating conditions. Neuromuscular relaxants: suxamethonium, Org 9426 (rocuronium).

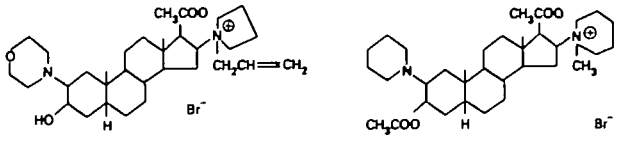
Suxamethonium is currently the only available neuromuscular blocking drug with an onset of action that makes it useful for rapid tracheal intubation. However, it has several side effects, some of which are inconvenient, while others may be harmful [1, 2]. In addition, its use may be contraindicated in some situations. Atracurium and vecuronium are associated with an onset which is relatively slow, particularly when compared with suxamethonium [3–8]. Although various methods, such as the use of the "priming" (divided dose) technique and the use of larger doses of atracurium and vecuronium, have been tried in an attempt to reduce the onset time of these neuromuscular blockers, these methods have either proved unsuccessful and hazardous to the patient, as in the case of the priming technique [9–11], or resulted in a long duration of action as with the use of larger doses [5, 8]. A non-depolarizing neuromuscular blocker with a rapid onset of action, and preferably a shorter duration that could be used for rapid tracheal intubation, is thus desirable.

Desacetoxy derivatives of pancuronium and vecuronium have been shown in experimental studies to have an onset of action which is considerably faster than that of vecuronium [12, 13]. Initial clinical studies in man have confirmed that Org 9426 (rocuronium) (fig. 1), a newly developed desacetoxy derivative of vecuronium, has a faster onset of action than its parent compound [14, 15]. The present study was designed to compare the tracheal intubating conditions after administration of Org 9426 and suxamethonium. It was also planned to assess the onset and duration of clinical relaxation it produced and examine the influence of prior administration of suxamethonium on the potency of Org 9426.

PATIENTS AND METHODS

After obtaining informed patient consent and approval of the Regional Ethics Committee, we studied 80 adult patients aged 18–65 yr, ASA grades I and II, undergoing elective surgery. None had any renal or hepatic dysfunction or were receiving any medication known to interact with neuromuscular blocking agents. All patients with potential airway problems were excluded.

After premedication with oral temazepam 10–20 mg, anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and fentanyl 1–3 μg kg^{-1} and maintained with 67% nitrous oxide in oxygen and further increments of fentanyl, thiopentone or both, as required. ECG, indirect arterial pressure, end-tidal carbon dioxide concentration and oxygen saturation



Org 9426 (rocuronium) Vecuronium

FIG. 1. Structural formulae of Org 9426 (rocuronium) and vecuronium.

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TABLE I. *Scoring of intubating conditions. Total score of 8–9 = excellent; 6–7 = good; 3–5 = fair; 0–2 = poor*

Score	Jaw relaxation (laryngoscopy)	Vocal cords	Response to intubation
0	Poor (impossible)	Closed	Severe coughing or bucking
1	Minimal (difficult)	Closing	Mild coughing
2	Moderate (fair)	Moving	Slight diaphragmatic movement
3	Good (easy)	Open	None

were monitored routinely in all patients. Ventilation was assisted using a non-rebreathing circuit and the end-tidal partial pressure of carbon dioxide maintained at 4.7–6.0 kPa. Skin temperature over the adductor pollicis muscle was measured and maintained greater than 32 °C. The ulnar nerve was stimulated percutaneously at the wrist after induction of anaesthesia, with supramaximal stimuli of 0.2 ms duration at a frequency of 0.1 Hz. The resultant force of contraction of the adductor pollicis muscle was measured and recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer Ltd).

After a stabilization period of approximately 10 min, 40 patients were allocated randomly to receive either suxamethonium 1 mg kg^{-1} or Org 9426 600 μg kg^{-1}, administered rapidly in a fast flowing i.v. infusion. The dose of suxamethonium is that used commonly for facilitating tracheal intubation and the dosage of Org 9426 was approximately twice its ED_{95} of 305 μg kg^{-1} using the single twitch stimulation [16]. Within each of these two groups, 20 patients each were allocated randomly to intubation at 60 s and at 90 s. All intubations were carried out by the same experienced anaesthetist (R.C.). The intubating conditions were graded using a modification of the methods described previously [17, 18] (table I). This takes into consideration the ease of laryngoscopy, condition of the vocal cords and the response to tracheal intubation. These are scored on a four-point scale (0–3) and the total scores added together to give an overall intubation score for each patient. If intubation was not successful, it was re-attempted at 60-s intervals, but the assessment was based on the first attempt. A score of 8–9 was considered excellent, 6–7 good, 3–5 poor and 0–2 bad; good and excellent were taken as clinically acceptable. No fentanyl or thiopentone was administered during the 5 min before administration of the neuromuscular blockers and carrying out tracheal intubation.

The time from administration of the neuromuscular blocker to the development of the first measurable effect (lag time) and the time from injection until occurrence of maximum block (onset time) were recorded in all patients. The time of recovery of the twitch height to 25 % of control (duration of clinical relaxation) was recorded in those receiving Org 9426 and time to 90 % recovery in those receiving suxamethonium.

Potency estimation of Org 9426 was carried out in patients given suxamethonium to assess the influence of prior administration of the drug. These 40 patients were allocated to five groups of eight patients each and received Org 9426 100, 150, 200, 250 or 300 μg kg^{-1} at 90 % recovery from suxamethonium. An additional group of eight patients received Org 9426 350 μg kg^{-1} after administration of suxamethonium and 90 % recovery from it (because a previous study had shown that the average degree of block with Org 9426 300 μg kg^{-1} was less than 95 % [16]). Maximum block after administration of Org 9426 was allowed to occur in these patients. The twitch height data after administration of Org 9426 were subjected to arc–sine transformation and regression analysis. A dose–response curve was constructed and the ED_{50}, ED_{90} and ED_{95} estimated and compared with values obtained previously in the absence of prior suxamethonium [16].

Bradycardia, tachycardia or signs of histamine release were recorded. Results were analysed statistically using analyses of variance with Tukey modification, Wilcoxon rank sum, Kruskall–Wallis and *t* tests as appropriate.

RESULTS

The four groups of 20 patients were comparable in age, weight, height and sex distribution (table II).

After suxamethonium, intubating conditions were excellent or good in all patients at both 60 and 90 s (fig. 2). Intubating conditions after Org 9426 were acceptable in 19 of 20 (95 %) patients at 60 s, being excellent in 13. The conditions were acceptable in all patients at 90 s, with 17 of 20 (85 %) being graded as excellent. In one patient receiving Org 9426 the trachea could not be intubated at 60 s because of closed vocal cords, but intubation was possible 60 s later. There was no significant difference in acceptable intubating conditions between suxamethonium and Org 9426. The degree of neuromuscular block with Org 9426 was 89 (SD 15.2) % at 60 s and 98 (3.0) % at 90 s.

The lag and onset times of 23 s and 60.4 s, respectively, for suxamethonium were significantly faster than the corresponding times of 25.8 s and

TABLE II. *Physical characteristics of patients (mean (range or SD))*

	Suxamethonium		Org 9426	
	60 s	90 s	60 s	90 s
n	20	20	20	20
Age (yr)	38 (19–63)	33 (18–63)	32 (18–55)	35 (19–63)
Weight (kg)	67 (13.3)	65 (11.9)	66 (8.9)	67 (12.7)
Height (cm)	164 (10.4)	163 (10.4)	163 (7.0)	166 (8.8)
Sex (M/F)	9/11	9/11	8/12	12/8

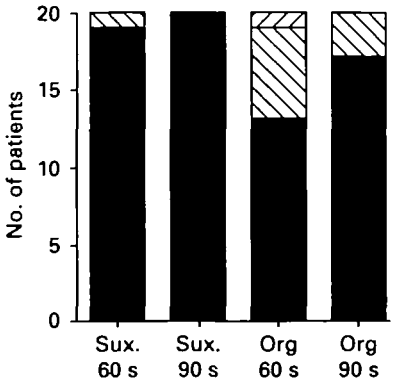

FIG. 2. Intubating conditions after Org 9426 and suxamethonium. Sux. = Suxamethonium; Org = Org 9426; 60 s = 60-s intubation; 90 s = 90-s intubation. □ = Poor; ▨ = fair; ▧ = good; ■ = excellent.

TABLE III. *Onset and duration of action (mean (SD)). * P < 0.05 between groups. † 90% recovery; § 25% recovery*

	Suxamethonium		Org 9426
n	40		40
Lag time (s)	23.0 (5.4)	*	25.8 (6.2)
Onset time (s)	60.4 (22.4)	*	88.9 (36.9)
Duration (min)	13.3 (4.6)†		30.5 (7.5)§

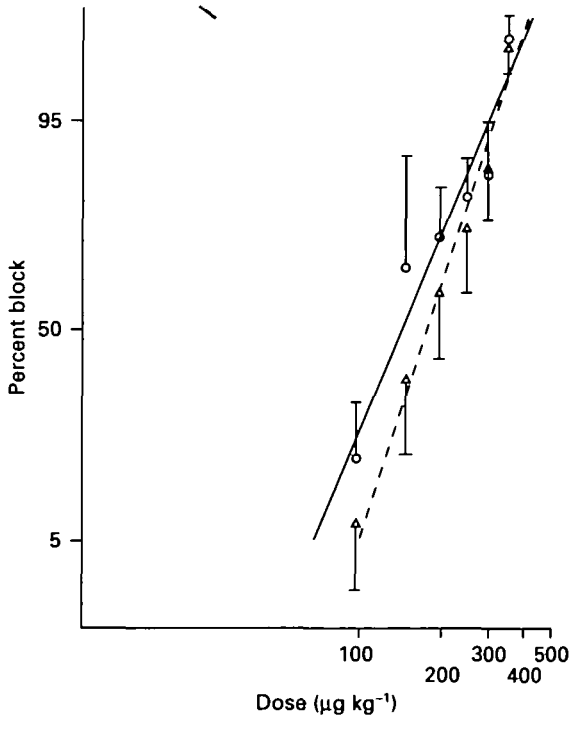

FIG. 3. Dose–response curves for Org 9426 with (– – –) and without (——) prior suxamethonium. The curve for the group without suxamethonium is taken, with permission, from Cooper and colleagues [16].

TABLE IV. *Estimated potency of Org 9426 (with 95% confidence limits) with or without prior suxamethonium. † Includes the additional group of eight patients given Org 9426 350 μg kg⁻¹*

	Without prior suxamethonium [16]	After suxamethonium†
ED_{50} (μg kg^{-1})	147 (130–165)	183 (173–193)
ED_{90} (μg kg^{-1})	272 (243–304)	292 (272–313)
ED_{95} (μg kg^{-1})	305 (269–346)	318 (294–343)

88.9 s for Org 9426 ($P < 0.05$). Ninety per cent recovery from suxamethonium block occurred in 13.3 min, whereas the duration of clinical relaxation (time to 25% recovery) of Org 9426 was 30.5 min (table III).

The dose–response curve after administration of different doses of Org 9426 after prior suxamethonium is shown in figure 3 and estimated ED_{50}, ED_{90} and ED_{95} values are given in table IV. These also show, for comparison, the data obtained previously without prior administration of suxamethonium. The dose–response curves and estimated ED_{50}, ED_{90} or the ED_{95} values did not differ significantly between the groups.

There were no significant changes in heart rate or arterial pressure and there was no evidence of any histamine release.

DISCUSSION

We have found that intubating conditions after administration of Org 9426 600 μg kg^{-1} were clinically acceptable in more than 95% of patients, which is similar to that observed after a commonly used dose of suxamethonium 1 mg kg^{-1}. This is similar to the reports of other workers using Org 9426 in doses of 500–600 μg kg^{-1} [14, 19–21]. Conditions are better at 60 s when compared with those produced with an approximately equipotent dose of vecuronium, which were described as acceptable in only 40% of patients, and none was excellent [5]. With Org 9426, the conditions were excellent in 65% of patients at 60 s. Although there appears to be no difference between the incidence of acceptable intubations between vecuronium and Org 9426 at 90 s, it is clear that the quality of intubation was superior with Org 9426 at this stage, being excellent in 85% of subjects, in contrast with only about 25% of patients using vecuronium. Conditions also appeared to be superior to those reported after atracurium [8]. Intubating conditions with suxamethonium were acceptable in all patients, which is consistent with clinical experience.

The degree of block present after Org 9426 600 μg kg^{-1} in the present study was about 89% and 98%, respectively, at 60 and 90 s. This is greater than the degree of block observed by other workers at similar times after administration of vecuronium or atracurium [7]. Although previous studies have shown that complete block of the adductor pollicis muscle is not required for the provision of good intubating conditions [5, 8, 22], the greater speed of action of Org 9426 must contribute to the good intubating conditions it provides at 60–90 s. Another possible reason could be the earlier occurrence of block in the vocal cords with Org 9426, in contrast with onset of block in the adductor pollicis muscle [23].

The time to maximum block of approximately 90 s with Org 9426, while significantly longer than a time of about 60 s with suxamethonium, was still faster than the onset times reported for either atracurium or vecuronium in equipotent doses [5, 7, 8] and is similar to that reported by other workers [15, 19, 24]. The reason for this rapid onset of neuromuscular block has been suggested to be the low potency of

Org 9426, which results in a higher molecular load being present at the neuromuscular junction, producing an initial high concentration gradient and transfer of molecules of the drug to the biophase [12]. However, the times reported in this study are considerably shorter than those reported by other workers [14, 25]. The difference may be caused by the observation of a biphasic type of block by these workers, who reported an initial rapid phase followed by a slower secondary phase. We did not observe a significant slow phase in the present study, in which the average time for the complete block itself was about 90 s. Only five patients in the present study had not attained complete block in the present study by 2 min. Hence we feel that the slower phase may be caused by individual variation and some resistance observed in some patients. It is worth noting that Wierda and colleagues [14] studied only 11 patients who were given a dose of Org 9426 500 $\mu g\ kg^{-1}$, and Booij and Knape [25] studied only five patients who were given a dose of 500 $\mu g\ kg^{-1}$ or more of the drug. In each case the biphasic block must favour good early intubating conditions with Org 9426, as the degree of block that is usually necessary for facilitating good tracheal intubating conditions is obtained much more rapidly—usually within 1 min of administration of this drug. In terms of the duration of clinical relaxation (25% recovery of the twitch height), Org 9426 does not differ appreciably from equipotent doses of vecuronium or atracurium. It is possible that the duration to 25% recovery is slightly longer with the use of Org 9426. This duration of clinical relaxation is similar to that reported previously [14, 15]. However, the present study was not designed to assess the total duration of action and recovery characteristics of Org 9426.

Although the present study was not designed to assess the influence of prior administration of suxamethonium on the neuromuscular properties of Org 9426, it was considered useful to use the groups who received suxamethonium to assess the influence of suxamethonium administration on the estimated potency of Org 9426. Using a well defined technique of single dose administration and construction of a dose–response curve, we were not able to find any significant difference in the potency of Org 9426 administered after recovery from suxamethonium block compared with a previous study using the same methodology with the exception of prior administration of suxamethonium [16]. There was no difference in the estimated ED_{50}, ED_{90} and ED_{95} values with or without prior suxamethonium, indicating no potentiation of the effect of Org 9426 by suxamethonium. This differs from vecuronium, with which a nearly 50% reduction was attained in the ED_{50} by prior administration of suxamethonium [26]. However, the investigators in that study were using a cumulative dose–response technique—a method which has subsequently been considered inappropriate for assessing potency and dose–response relationships of intermediate acting drugs.

There was no evidence of any significant cardiovascular effects or histamine liberation. However, more detailed studies of the haemodynamic effects of Org 9426 are necessary to confirm this.

ACKNOWLEDGEMENT

Supplies of Org 9426 and financial assistance were received from Organon Teknika BV, Belgium.

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