Reports of Investigation

Comparison of vecuronium with ORG 9487 and their interaction

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Purpose: To compare the pharmacodynamic behaviour of vecuronium with that of ORG 9487, we measured the time-course of action of equipotent doses of ORG 9487 and vecuronium and investigated their mutual interaction when given in succession.

Methods: Sixty ASA I-II patients were anaesthetized with thiopentone, fentanyl, halothane and nitrous oxide and assigned randomly to four groups. Each patient received an initial dose (ID) of either vecuronium (V) or ORG 9487 (O) followed by maintenance doses (MD_n) of either V or O (ID/MD: O/O, V/O, O/V, and V/V). The time course of action was measured mechanomyographically, determining the duration until 25% recovery of the single twitch (DUR_{25}).

Results: The onset time of an ID of ORG 9487 was shorter than that of an ID of vecuronium (96 *vs* 203 sec, $P < 0.001$). The DUR_{25} of the ID of ORG 9487 was less than half that of vecuronium (10.7 ± 2.8 *vs* 28.8 ± 6.1 min, $P < 0.001$). The DUR_{25} of MD_1 and MD_2 of ORG 9487 were shorter than those of vecuronium (O/O: 7.3 ± 2.8 and 8.5 ± 2.4 min; V/O: 12.7 ± 3.3 and 11.5 ± 3.5 min, *vs* O/V: 16.4 ± 4.5 and 20.6 ± 4.7 min; V/V: 18.8 ± 3.0 and 20.1 ± 3.8 min, respectively, $P < 0.05$). An ID of vecuronium prolonged the DUR_{25} of MD_1 and MD_2 of ORG 9487 ($P < 0.05$).

Conclusion: ORG 9487 is a muscle relaxant with a shorter duration of action than vecuronium. Maintenance doses of ORG 9487 are also shorter acting than roughly equipotent maintenance doses of vecuronium, irrespective of which relaxant is given initially.

Objectif : Dans le but de comparer le comportement pharmacodynamique du vécuronium avec celui de l'ORG 9487, nous avons mesuré le décours temporel de l'activité de deux doses équipotentes d'ORG 9487 et de vécuronium et étudié leur interaction mutuelle lorsqu'ils sont administrés successivement.

Méthodes : Soixante patients ASA I et II anesthésiés au thiopental, fentanyl, halothane et protoxyde d'azote ont été répartis aléatoirement en quatre groupes. Chaque patient recevait une dose initiale (DI) de vécuronium (V) ou d'ORG 9487 (O) suivi par des doses d'entretien (DE) de V ou de O (DI/DE : O/O, V/O, O/V et V/V. Le décours temporel de l'activité était mesuré par mécanomyographie en déterminant l'intervalle de récupération de 25% du twitch (DUR_{25}).

Résultats : Le début d'action d'une DI d'ORG 9487 était plus court qu'une DI de vécuronium (96 *vs* 203 s, $P < 0,001$). La DUR_{25} de la DI d'ORG 9487 était la moitié de celle du vécuronium (10,7 ± 2,8 *vs* 28,8 ± 6,1 min, $P < 0,001$). La DUR_{25} de la DE_1 et de la DE_2 de l'ORG 9487 était plus courte que celle du vécuronium (respectivement, O/O : 7,3 ± 2,8 et 8,5 ± 2,4 min ; V/O : 12,7 ± 3.3 et 11,5 ± 3,5 min *vs* O/V : 16,4 ± 4,5 et 20,6 ± 4,7 min ; V/V : 18,8 ± 3,0 et 20,1 ± 3,8 min, $P < 0,05$). Une DI de vécuronium prolongeait la DUR_{25} de la DE_1 et de la DE_2 de l'ORG 9487 ($P < 0,05$).

Conclusion : Le myorelaxant ORG 9487 possède une durée d'action plus courte que le vécuronium. Les doses d'entretien de l'ORG 9487 ont une durée d'action plus courte que des doses à peu presque équipotentes de vécuronium quel que soit le myorelaxant initial administré.

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RAPID onset and offset of neuromuscular block is a desirable property for muscle relaxants used for intubation and for short surgical procedures. The 16-N-allyl, 17-ß-propionate analogue of vecuronium, ORG 9487 is a new short-acting, non-depolarizing steroidal relaxant.

ORG 9487 (1.5 mg·kg^{-1}, based on the bromide salt) and succinylcholine (1.0 mg·kg^{-1}) showed similar onset times and intubating conditions at one minute after administration.[1] In the same study neuromuscular block has been shown to be rapidly reversible when 40 µg·kg^{-1} neostigmine was given two minutes after administration of 1.5 mg·kg^{-1} ORG 9487. A train-of-four (TOF) ratio of 0.7 was achieved within 10 min. However, spontaneous recovery after an intubating dose followed by a continuous infusion of ORG 9487 for 50 minutes was almost identical to the recovery from vecuronium following the same period of relaxation.[2] The purpose of this study was to compare the time courses of vecuronium and ORG 9487 and to study their interaction when these drugs were given in succession.

Methods

Patients and anaesthetic technique

After approval by the hospital medical Ethics Committee, we studied 60 ASA I-II patient undergoing elective surgery with an expected duration of approximately 60 min. Patients receiving medication interfering with neuromuscular function or suffering from any neuromuscular, renal and/or hepatic disease were excluded. Written, informed consent was obtained. Premedication with 7.5–15 mg midazolam *po* was given 30–60 min before the expected start of anaesthesia, which was induced with 4–6 mg·kg^{-1} thiopentone *iv* and 1–3 µg·kg^{-1} fentanyl *iv*. Anaesthesia was maintained with increments of 50–100 µg fentanyl *iv* and halothane (0.7% ET) in a mixture of nitrous oxide and oxygen (2:1). The ECG, oxygen saturation and heart rate were monitored throughout the procedure (Cardiocap®, Datex, Finland) and recorded. The $P_{ET}CO_2$ was kept between 4.0 and 4.6 kPa. Peripheral temperature was maintained > 32.5°C. Systemic arterial pressure was measured non-invasively every three to five minutes. The patients were assigned randomly to four groups, differing in the sequence of administration of the relaxants (Table I).

TABLE I Relaxant administration scheme. The initial dose and maintenance dose of vecuronium (V) and Org 9487 (O) are equipotent.

	Initial dose	
	Org 9487 (1.5 mg·kg^{-1})	Vecuronium (0.07 mg·kg^{-1})
Maintenance dose		
Org 9487 (0.55 mg·kg^{-1})	Group O/O n = 15	Group V/O n = 15
Vecuronium (0.025 mg·kg^{-1})	Group O/V n = 15	Group V/V n = 15

Neuromuscular monitoring and measurements

Neuromuscular blockade was monitored mechanomyographically using the Relaxometer (Groningen, The Netherlands).[3] After induction of anaesthesia and positioning of the arm, the ulnar nerve was stimulated supramaximally (30–60 mA) at the wrist through surface electrodes with square wave stimuli of 0.2 msec duration.

Neuromuscular monitoring was commenced after induction allowing a period of five minutes for calibration and stabilization. The supramaximal current was then redetermined and twitch response set at 100% before the administration of the relaxant. Neuromuscular blockade was monitored continuously with single twitch (ST) stimulation at 0.1 Hz and, at intervals during the recovery period only, with train of four (TOF) stimulation. Following randomisation, patients received an initial bolus dose of 0.07 mg·kg^{-1} vecuronium or 1.5 mg·kg^{-1} ORG 9487 into a rapidly running infusion in the forearm. Tracheal intubation was attempted one minute after administration of ORG 9487 or at 75% block after the administration of vecuronium. Relaxation was maintained with bolus doses of 0.55 mg·kg^{-1} ORG 9487 or 0.025 mg·kg^{-1} vecuronium, administered at spontaneous twitch recovery of 25%, according to the randomisation code. Neuromuscular block was reversed with 40 µg·kg^{-1} neostigmine and 7 µg·kg^{-1} methylatropine at ST recovery of 75% near the end of surgery. Monitoring of neuromuscular function was continued until the TOF had recovered to a ratio of ≥0.7. The following variables were calculated from the recordings: (1) time from the end of administration of the initial dose until first depression of the ST (lag-time); (2) time from the end of administration until maximum ST depression (onset time); (3) the maximum depression of ST after the initial dose (maximum block); (4) time from the end of administration of the initial dose (ID) until 25% recovery of ST (clinical duration, DUR_{25}); (5) time from the end of administration of the maintenance dose (MD) until 25% recovery of the ST (duration of the maintenance dose, DUR_{25} MD_n, n=nth MD); (6) time from the end of administration of the initial dose until ST recovery of 25% following the last maintenance dose (clinical relaxation time, CRT); and (7) time from 25% until 75% recovery of the ST (recovery index, RI).

Statistical analysis

A sample size estimation with respect to the difference in duration of the first maintenance dose was performed and indicated a group size of 15 patients. The Wilcoxon rank sum test was used to compare data between two groups. The Kruskal-Wallis test was used to compare more than two groups, e.g., demographic data and DUR_{25} of MD_n of all four groups, followed by the Dunn test to determine differences between groups. Sex and ASA class were compared using the Fisher exact test. Results were considered to be statistically significant at a P value <0.05. Data are presented as mean ± SD.

Results

Fifty-four ASA class I and 6 ASA class II patients were investigated. There were no differences among the four groups with respect to age (range 19–64 yr), height (range 154–197 cm), weight (range 51–98 kg) and sex distribution (39 male, 21 female).

Onset characteristics, maximum block and duration until 25% single twitch recovery after the initial dose of ORG 9487 and of vecuronium are presented in Table II. The onset time and DUR_{25} of the initial dose of ORG 9487 were shorter than those of vecuronium ($P < 0.001$).

The DUR_{25} of the initial and maintenance doses of all evaluable subjects are presented in Figure 1a–1d.

The CRT was similar for all four groups [61.1 ± 5.0, 62.3 ± 10.6, 60.0 ± 12.5, and 68.4 ± 12.9 min for groups O/O, O/V, V/O and V/V, respectively].

For the statistical analysis of the DUR_{25} of the first and second maintenance doses only patients (n=51) who received at least two maintenance doses were compared (Table III).

The DUR_{25} of the first and second maintenance doses of ORG 9487 were shorter after an initial dose of ORG 9487 than those of vecuronium after an initial dose of ORG 9487 ($P < 0.001$). The DUR_{25} of the first and second maintenance doses of ORG 9487 were also shorter than those of vecuronium administered after an initial dose of vecuronium ($P < 0.001$).

TABLE II Lag time, onset time, maximum block (Max. block), and clinical duration (DUR_{25}) after an initial dose of 1.5 mg·kg^{-1} Org 9487 (O) or 0.07 mg·kg^{-1} vecuronium (V). Mean ± SD, NS = not significant.

	Group O	*Group V*	*P*
	(n = 30)	(n = 30)	
Lag time (sec)	34 ± 8	51 ± 15	< 0.001
Onset time (sec)	96 ± 29	203 ± 46	< 0.001
Max. block (%)	99.6 ± 1.0	99.8 ± 0.9	NS
DUR_{25} (min)	10.7 ± 2.8	28.8 ± 6.1	< 0.001

TABLE III Clinical duration (DUR_{25}) after maintenance doses (MD_1 and MD_2) of Org 9487 (O) or vecuronium (V). Subgroups O/O(O) and V/O(O) received Org 9487 after an initial dose of Org 9487 or vecuronium, respectively. Groups O/V(V) and V/V(V) received vecuronium after an initial dose of Org 9487 or vecuronium, respectively. For statistical data the reader is referred to the text. Mean ± SD).

Number of patients	*Subgroup*	*DUR_{25} MD_1*	*Subgroup*	*DUR_{25} MD_2*
		min		min
15	O/O	7.3 ± 2.8	O/OO	8.5 ± 2.4
12	V/O	12.7 ± 3.3	V/OO	11.5 ± 3.5
15	O/V	16.4 ± 4.5	O/VV	20.6 ± 4.7
9	V/V	18.8 ± 3.0	V/VV	20.1 ± 3.8

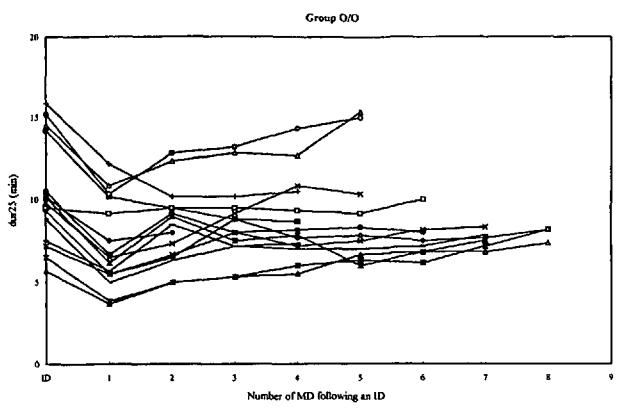

FIGURE 1A Clinical duration of the initial dose and maintenance doses of Org 9487 on the y-axis and the number of the subsequently administered maintenance doses of Org 9487 on the x-axis. Shorter duration leads to an increased number of maintenance doses. NB: different scaling of the Y-axis.

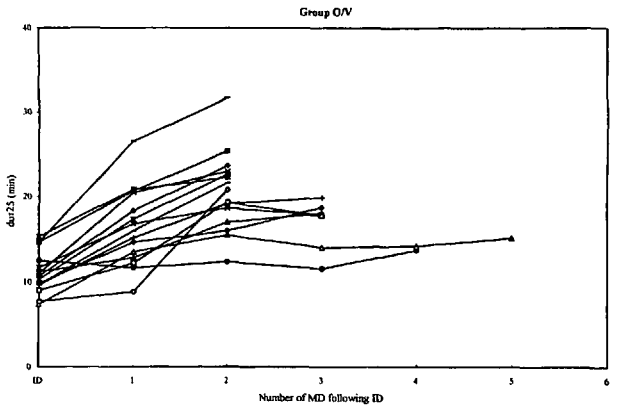

FIGURE 1B Clinical duration of the initial dose of Org 9487 and maintenance doses of vecuronium on the y-axis and the number of the subsequently administered maintenance doses of vecuronium on the x-axis. Shorter duration leads to an increased number of maintenance doses.

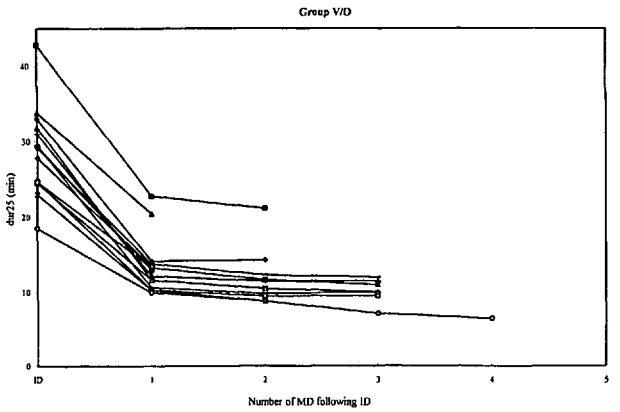

FIGURE 1C Clinical duration of the initial dose of vecuronium and maintenance doses of Org 9487 on the y-axis and the number of the subsequently administered maintenance doses of Org 9487 on the x-axis. Shorter duration leads to an increased number of maintenance doses.

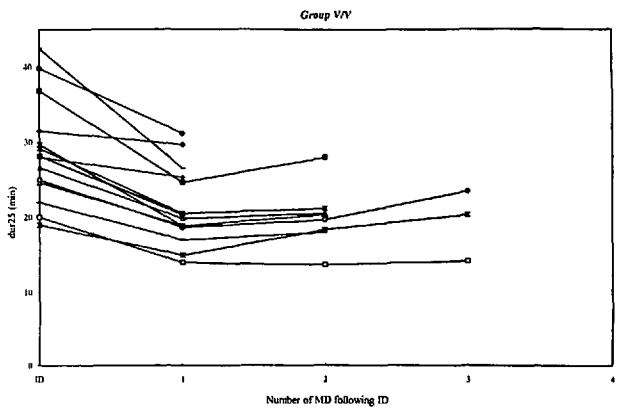

FIGURE 1D Clinical duration of the initial dose and maintenance doses of vecuronium on the y-axis and the number of the subsequently administered maintenance doses of vecuronium on the x-axis. Shorter duration leads to an increased number of maintenance doses.

The DUR_{25} of the first and second maintenance doses of ORG 9487 were shorter after an initial dose of ORG 9487 than those after an initial dose of vecuronium ($P < 0.001$ for MD_1 and $P < 0.05$ for MD_2).

The DUR_{25} of the first and second maintenance doses of vecuronium were not significantly affected by the initial dose whether it was ORG 9487 or vecuronium ($P = 0.18$ for MD_1 and $P = 0.78$ for MD_2).

The recovery indices following approximately 60 min of relaxation were similar (14.9 ± 6.2, 15.1 ± 6.6, 13.0 ± 5.1, and 16.2 ± 6.1 min for the groups O/O, O/V, V/O, and V/V, respectively). Neuromuscular blockade was easily reversed with neostigmine in all groups reaching a TOF-ratio of 0.7 within two to five minutes after its administration.

Discussion

This study compared the pharmacodynamic behaviour of approximately equipotent doses of vecuronium and ORG 9487 and also their mutual interaction when administered consecutively. It showed that ORG 9487 is a short-acting muscle relaxant suitable for induction and maintenance of block in patients undergoing short surgical procedures. Maintenance doses of ORG 9487 provided relaxation of shorter duration than maintenance doses of vecuronium after an initial dose of ORG 9487 as well as after an initial dose of vecuronium. This shorter duration of action of ORG 9487 increases the flexibility of neuromuscular block, particularly during short surgical procedures or near the end of surgery. In contrast, such benefit was not reported for a maintenance dose of vecuronium following a pancuronium induced neuromuscular blockade because the duration of action resembled that of a maintenance dose of pancuronium.[4] Also, Kay *et al.*[5] found a prolonging effect of an initial dose of 55 $\mu g \cdot kg^{-1}$ pancuronium on the duration of action of the first two maintenance doses of 25 $\mu g \cdot kg^{-1}$ vecuronium. More recently, Erkola *et al.*[6] investigated the influence of pancuronium-induced relaxation on the duration of action of subsequently administered mivacurium and Kim *et al.*[7] investigated the influence of an initial dose of vecuronium or rocuronium on the duration of action of subsequent doses of mivacurium. Both studies revealed a marked prolongation of duration of action of the maintenance doses of mivacurium following the initially applied relaxant. This influence of an initially administered relaxant on the duration of action of a subsequently administered relaxant has been reported by several other authors for a variety of relaxants and for various sequences of administration.[8–11] We also found the DUR_{25} of the first and second maintenance doses of ORG 9487 to be longer after an initial dose of vecuronium compared that after an initial dose of ORG 9487. However, a maintenance dose of ORG 9487 was always significantly shorter acting than a maintenance dose of vecuronium irrespective of the initially applied relaxant. A likely explanation for the interaction of relaxants is based on the theory of the "margin of safety," described by Paton and Waud.[12] Before the twitch response starts to fade, in healthy individuals, usually >75–80% of the postjunctional receptors must be occupied by a non-depolarizing neuromuscular blocking agent. Consequently, maintenance of a clinical neuromuscular block means that more than 80% of these receptors are still occupied by the first

administered relaxant when the maintenance dose of a second relaxant is administered. In this case only 20% of the endplate receptors will be available for the relaxant given for maintenance of relaxation. Twitch recovery will therefore still largely depend on the removal of the initially administered relaxant from the junction and consequently be predominantly determined by its plasma clearance of the first administered relaxant. Different relaxant-receptor dissociation rates may also play a role, as suggested by Fawcett *et al.*[13] in isolated forearm experiments with pancuronium, vecuronium and rocuronium.

Our results are consistent with the difference in plasma clearances between ORG 9487 and vecuronium, i.e., 8.5–11.1 $ml \cdot kg^{-1} \cdot min^{-1}$ and 4.0 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively.[2,14,15]

Synergism would offer an alternative explanation for the influence of the first relaxant on the subsequently administered relaxants. Among others Lebowitz *et al.*,[16] Waud *et al.*,[17–18] Naguib *et al.*[19–21] and Ferres *et al.*[22] studied several combinations of chemically related and unrelated drugs. In general, these studies resulted in synergism when combinations of chemically unrelated drugs were administered simultaneously, and in an additive effect for chemically related drugs. Synergism may be the consequence of different receptor binding sites for benzylisoquinolines (mivacurium, atracurium, *d*-tubocurarine) and aminosteroids (ORG 9487, vecuronium, rocuronium). Recently, the effects of various combinations of relaxants were extensively reviewed.[23] In conclusion, ORG 9487 is a short-acting muscle relaxant which is suitable for induction and/or maintenance of neuromuscular block during procedures lasting less than one hour.

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