Spontaneous or neostigmine-induced recovery after maintenance of neuromuscular block with Org 9487 (rapacuronium) or rocuronium following an initial dose of Org 9487

K. C. McCourt¹, R. K. Mirakhur¹*, D. W. Lowry¹, M. T. Carroll¹ and H. J. Sparr²

¹Department of Anaesthetics, The Queen’s University of Belfast, Whita Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK. ²Department of Anaesthesia, Leopold-Franzens-Universität, Innsbruck, Austria

*Corresponding author

We have examined spontaneous and neostigmine-induced recovery after an initial dose of Org 9487 1.5 mg kg⁻¹ followed by three repeat doses of Org 9487, a 30-min infusion of Org 9487 or two incremental doses of rocuronium. Mean clinical duration after incremental doses of Org 9487 0.5 mg kg⁻¹ increased from 12.3 (SD 3.4) min to 14.0 (4.0) and 15.9 (5.9) min (P<0.01), and after rocuronium from 14.4 (5.2) min to 19.2 (5.9) min (P<0.01). Times for spontaneous recovery from a T1 of 25% to a TOF ratio of 0.8 after the last bolus dose of Org 9487 and after a 30-min infusion were 72.4 (16.5) and 66.1 (26.9) min compared with 36.7 (15.8) min in the group receiving rocuronium. These times were significantly reduced to 9.9 (4.5), 8.6 (6.1) and 5.7 (2.5) min, respectively, after neostigmine administration at a T1 of 25% (P<0.05). We conclude that administration of Org 9487 by repeat bolus doses or infusion was associated with slow spontaneous recovery but neostigmine administration resulted in adequate recovery in less than 10 min.


Keywords: neuromuscular block, Org 9487; neuromuscular block, rocuronium; pharmacodynamics; antagonists neuromuscular block, neostigmine

Accepted for publication: January 12, 1999

Org 9487 is a new aminosteroidal neuromuscular blocking agent with a rapid onset of action which may possibly be antagonized when block is still profound.¹ In a previous study, van den Broek and colleagues reported that recovery after a 60-min infusion of Org 9487 was prolonged compared with recovery after a single dose.² It has also been shown that duration of action of some neuromuscular blocking drugs may be altered by prior administration of another blocker.³ The aim of this study was to examine spontaneous and neostigmine-induced recovery using a bolus and three maintenance doses of Org 9487, a bolus dose and a 30-min infusion of Org 9487, or a bolus dose of Org 9487 followed by two maintenance doses of rocuronium. The rocuronium groups were included to examine the feasibility of using another rapidly acting drug for maintenance if the use of Org 9487 was found to be associated with prolonged recovery, even when used only for a 30-min period for maintenance of block.

Methods and results

We studied 90 adult patients in a two-centre study, after obtaining informed consent and approval from the Ethics Committees. Pregnant patients, patients receiving concurrent treatment with drugs known to interfere with neuromuscular transmission, or those with significant hepatic, renal or neuromuscular disorders were excluded.

Patients were anaesthetized with propofol 1.5–2.5 mg kg⁻¹ and alfentanil 30 µg kg⁻¹, followed by infusions of propofol 6–10 mg kg⁻¹ h⁻¹ and alfentanil 30 µg kg⁻¹ h⁻¹, and 66% nitrous oxide in oxygen. Standard monitoring was applied and the lungs were ventilated to normocapnia. Skin temperature over the adductor pollicis muscle was maintained greater than 32°C by wrapping the arm in cotton wool. The ulnar nerve was stimulated in a train-of-four (TOF) mode every 12 s and the force of thumb adduction recorded.

Patients received, by random allocation, an initial dose of Org 9487 1.5 mg kg⁻¹ followed by: three maintenance doses of Org 9487 0.5 mg kg⁻¹ every time T1 recovered to 25% (groups 1 and 2); infusion of Org 9487 for 30 min after recovery of T1 to 5% after the bolus dose, at an initial rate of 4.0 mg kg⁻¹ h⁻¹ and adjusted to maintain neuromuscular block at 90±10% (groups 3 and 4); or two maintenance doses of rocuronium 0.15 mg kg⁻¹ at recovery of T1 to 25% (groups 5 and 6). Neuromuscular block in groups 1, 3 and 5 was allowed to recover spontaneously while patients in groups 2, 4 and 6 received neostigmine 0.05 mg kg⁻¹ with glycopyrrolate.
0.01 mg kg⁻¹ on recovery of T1 to 25% after the final bolus dose of blocker or after infusion. Times to various recovery end-points were recorded.

Between-group comparisons were made using analysis of variance followed by pairwise tests. Page’s test for ordered alternatives and the Wilcoxon signed rank test were used to analyse the duration of action of maintenance doses of the blockers within each group. The Hochberg–Bonferroni procedure was used to adjust for multiple testing as appropriate. P<0.05 was taken to represent a significant difference.

Data from two patients were excluded because of major study violations. Mean time to T1 recovery of 5% in patients receiving the Org 9487 infusion (groups 3 and 4) was 11.9 (sd 4.4) min, and to 25% recovery of T1 in the other four groups (groups 1, 2, 5 and 6), 16.3 (4.3) min. Time to 25% recovery of T1 after the maintenance doses of Org 9487 increased from 12.3 (3.4) min to 14.0 (4.0) and 15.9 (5.9) min with the three repeat doses (P<0.01), and after the maintenance doses of rocuronium from 14.4 (5.2) to 19.2 (5.9) min (P<0.01). Median infusion rate of Org 9487 for 90±10% block was 2.72 (range 1.08–4.58) mg kg⁻¹ h⁻¹.

Times for recovery of T1-25%–TOF 0.7, T1-25%–TOF 0.8 and T1-25%–75% recovery indices are shown in Table 1. These were significantly longer in the spontaneously recovering groups receiving Org 9487 for maintenance than in the rocuronium maintenance group (P<0.05). Administration of neostigmine resulted in a significant reduction in these times (P<0.05).

Bronchospasm and/or increased airway pressure, and an erythematous rash were observed in four and three patients, respectively, after administration of the initial dose of Org 9487; none required treatment.

**Comment**

Our results showed that spontaneous recovery after maintenance with increments or an infusion of Org 9487 was relatively long. The clinical duration (25% recovery of T1) of 16.3 min after the initial bolus dose of Org 9487 was similar to that reported recently by Kahwaji and colleagues. Prolonged spontaneous recovery has been described previously after a 60-min infusion of Org 9487 and may be a result of saturation of the redistribution sites, reduced clearance of the drug or accumulation of active metabolites. The concentration of the 3-desacetyl metabolite of Org 9487 increases with time and it is more potent than Org 9487 in its neuromuscular blocking effect, with a longer duration of action and slower recovery. Administration of neostigmine, however resulted in a significant reduction in all recovery times.

Duration of action of the rocuronium increments was only marginally longer than that of the Org 9487 increments. However, T125%–TOF 0.7 and 0.8 in the spontaneously recovering rocuronium maintenance group were nearly twice as fast as in the corresponding Org 9487 groups, possibly because of cumulation of the metabolite in the latter groups. Times T125%–TOF 0.7 and T125%–TOF 0.8 were recorded to allow comparison with results from previous studies where a TOF ratio of 0.7 was reported, and to conform to more recent guidelines.

In summary, we have shown that repeat bolus administration or a 30-min infusion of Org 9487 was associated with slow spontaneous recovery but that block was antagonized rapidly by neostigmine 0.05 mg kg⁻¹ when administered at 25% recovery of T1. Administration of rocuronium may be preferable if neuromuscular block is needed after the initial dose of Org 9487.

**Acknowledgements**

We thank Organon Teknika for supplies of Org 9487, financial support and statistical analysis (Mr H. Reitbergen). Dr M. Hollenstein-Zacke helped with the study in Innsbruck.

**References**

1 Wierda JMKH, van den Broek L, Proost JH, Verbaan BW, Hennis PJ. Time course of action and endotracheal intubating conditions of Org 9487, a new short-acting steroidal muscle relaxant; a comparison with succinylcholine. Anesth Analg 1993; 77: 579–84