Pharmacodynamics and pharmacokinetics of an infusion of Org 9487, a new short-acting steroidal neuromuscular blocking agent


Summary
We have evaluated in 10 anaesthetized patients the time course of action, infusion requirements, reversibility and pharmacokinetics of Org 9487. Org 9487 was administered as a bolus dose of 1.5 mg kg⁻¹, followed by an infusion to maintain a block of 75–85% for 60 min. After recovery from the bolus dose, a mean dose of Org 9487 3.4 (± 1.0) mg kg⁻¹ h⁻¹ was administered to maintain a mean neuromuscular block of 83% (± 3%). During the final 15 min of infusion, the infusion requirements were 2.5 (± 1.1) mg kg⁻¹ h⁻¹. In the five patients who were allowed to recover spontaneously, a TOF ratio of 0.7 was reached 37.9 (± 12.4) min after stopping the infusion of Org 9487. In the five patients who received neostigmine, a TOF ratio of 0.7 was reached after 14.5 (± 6.1) min. Plasma clearance was 8.5 (± 30%) ml kg⁻¹ min⁻¹. Volume of distribution at steady state was 293 (± 55%) ml kg⁻¹. Terminal half-life and mean residence time were 71.7 (± 34%) and 33.4 (± 31%) min, respectively. The concentration of the 3-OH metabolite remained relatively low. Urinary excretion of Org 9487 and its metabolites was 22% in 24 h. In conclusion, a 1-h infusion of the short-acting drug Org 9487 changed its time course characteristics gradually from that of a short-acting neuromuscular blocking agent to that of a neuromuscular blocker with an intermediate duration of action. (Br. J. Anaesth. 1994; 73: 331-335)

Key words Neuromuscular block. Org 9487. Pharmacokinetics. Org 9487.

Org 9487, the 16-N-allyl, 17-β-propionate analogue of vecuronium, is a new steroidal neuromuscular blocking agent. In clinical studies, Org 9487, in a dose 1.3 × ED₉₀ (1.5 mg kg⁻¹), produced neuromuscular block with a fast onset, good to excellent tracheal intubating conditions at 1 min and a duration until recovery to a train-of-four (TOF) ratio of 0.7 of approximately 25 min [1, 2]. This profile resembles that of suxamethonium as the clinical duration, that is time until 25% twitch recovery of control, is similar, but the time to clinically adequate recovery, that is a TOF ratio of 0.7, is longer [1]. Because of its fast spontaneous recovery, the duration of action of Org 9487 could be shortened by early antagonism with neostigmine, thereby increasing the margin of safety, for example in failed intubation [1]. In a preliminary pharmacokinetic study using an intubating dose of Org 9487 1.5 mg kg⁻¹, the terminal half-life was 88 (± 19) min [2]. The 3-OH metabolite was present in plasma, with concentrations varying from 10:1 (parent compound:metabolite) at the beginning of the measuring period to 1:10 at the end [2]. Theoretically, prolonged administration of Org 9487 may increase recovery time of the neuromuscular block because of reduction of net distribution clearance in time. Another mechanism which may prolong recovery time is formation of metabolites with intrinsic neuromuscular blocking activity. Although the potency of the 3-OH metabolite in the cat is less than that of the parent compound, it may still contribute to the neuromuscular blocking effect if the rate of formation exceeds that of elimination.

In this study we have evaluated the time course of action, infusion requirements, reversibility and pharmacokinetics of an infusion of Org 9487.

Patients and methods
After approval by the hospital medical Ethics Committee, we studied 10 ASA I–II patients, aged 18–65 yr, undergoing elective surgery. Written informed consent was obtained. After premedication with midazolam 0.1–0.15 mg kg⁻¹ orally, approximately 45 min before the expected start of anaesthesia, anaesthesia was induced with fentanyl 1–3 μg kg⁻¹ and propofol 2–3 mg kg⁻¹. Anaesthesia was maintained with increments of fentanyl 50 μg and 1.0% end-tidal concentration of isoflurane in a mixture of 65% nitrous oxide in oxygen.

ECG, oxygen saturation, end-tidal Pco₂ and central and peripheral temperatures were monitored continuously (Cardiocap, Datex, Finland) and recorded. Non-invasive arterial pressure was measured every 1 min from induction until 10 min

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after administration of Org 9487 and then every 3 min. After induction, patients' lungs were ventilated to maintain end-tidal $P_{\text{CO}_2}$ at 4.0-4.6 kPa. Central and peripheral temperatures were maintained with a warming mattress and arm-cover above 36.5 °C and 32.5 °C, respectively.

PHARMACODYNAMIC PROCEDURES

After induction of anaesthesia, single twitch contractions of the adductor pollicis muscle at a preload of 200-400 g were measured with the Relaxometer [3]. Through surface electrodes, square wave stimuli of 0.2-ms duration at 0.1 Hz were delivered to the ulnar nerve at the wrist. The resultant force of thumb adduction was quantified by a force displacement transducer and recorded online and displayed continuously on a monitor. Single twitch contractions ($T_w$) at 0.1 Hz were recorded for at least 5 min before administration of the neuromuscular blocker. After administration of Org 9487, neuromuscular transmission was monitored by continuous $T_w$ stimulation at 0.1 Hz and TOF stimulation (four consecutive stimuli at 2 Hz) at 25% and 90% recovery of $T_w$ and thereafter at 3-min intervals until the TOF ratio was at least 0.7. After antagonism by neostigmine, neuromuscular transmission was monitored by $T_w$ at 0.1 Hz and TOF just before and 2, 5, 8 and 10 min after administration of neostigmine and thereafter at 3-min intervals. From the recorded $T_w$ and TOF the following onset variables were calculated: time from end of injection of Org 9487 until the first depression of $T_w$ (lag time); magnitude of the neuromuscular block 1 min after administration of Org 9487; maximal neuromuscular block; time from the end of administration of Org 9487 until maximum depression of $T_w$ (onset time). Also, duration variables were calculated: time from the end of the infusion of Org 9487 until 25% recovery of $T_w$ ($\text{DUR}_{25}$); recovery time from $T_w$ 25% to $T_w$ 75% (recovery index, RI); time from the end of the infusion of Org 9487 until 90% recovery of $T_w$ ($\text{DUR}_{90}$); time from the end of the infusion of Org 9487 until recovery to a TOF ratio of 0.7 ($\text{DUR}_{\text{TOF} < 0.7}$).

After stabilization of anaesthesia and twitch response, that is within approximately 10 min after induction, patients received Org 9487 1.5 mg kg$^{-1}$ (1.3 × ED$_{90}$), based on corrected body weight (CBW):

$$\text{CBW (kg)} = \frac{(\text{length (cm)} - 100) + \text{weight (kg)}}{2}$$

The blocker was administered over 10 s into a rapidly running infusion, located in a vein on the foot. Approximately 1-2 min after the end of injection, the trachea was intubated. After recovery of $T_w$, a continuous infusion of Org 9487 5 mg kg$^{-1}$ h$^{-1}$ was started. The rate of infusion was adjusted to maintain a constant neuromuscular block of approximately 75-85%. The infusion requirement was calculated as the amount of the infused dose of Org 9487 for the total period of infusion and for the final 15 min of infusion. The mean neuromuscular block produced during infusion was calculated. In five patients, neuromuscular block was antagonized by neostigmine 40 μg kg$^{-1}$, combined with methyl-atropine 7 μg kg$^{-1}$, administered 50 min after the end of administration of the intubating dose of Org 9487, whereby constant infusion of Org 9487 was maintained for 10 min and the neuromuscular blocking effect of Org 9487 was assumed to remain unchanged during the last 10 min of infusion, that is during antagonism. Sixty minutes after the end of administration of the intubating dose of Org 9487, the infusion of Org 9487 was stopped in all patients and recovery was awaited until a TOF ratio of at least 0.7 was obtained.

PHARMACOKINETIC PROCEDURES

Central venous blood samples from the superior cava were obtained just before and 10, 20, 30, 40, 50 and 60 min after the end of administration of the intubating dose of Org 9487 in a vein on the dorsum of the foot. After stopping the infusion of Org 9487, venous blood samples were obtained after 2, 5, 10, 20, 40, 60, 120, 180 and 240 minutes, and at 75%, and 90% recovery of $T_w$ and at recovery of the TOF ratio to 0.7. Blood was acidified immediately with 1 ml of NaH$_2$PO$_4$ 1 mol litre$^{-1}$ to prevent spontaneous deacetylation and stored at room temperature to prevent haemolysis. Plasma was separated by centrifugation within 4 h after collection of the sample and stored at −18 °C until analysis. Urine was collected in fractions during the first 24 h, either via a urinary catheter from a collection bag to which 1 ml of NaH$_2$PO$_4$ 1 mol litre$^{-1}$ was added before each sampling period, or from voluntary produced portions. These portions were acidified immediately with 1 ml of NaH$_2$PO$_4$ 1 mol litre$^{-1}$. From each fraction, the total amount was measured and a well mixed aliquot (10 ml) obtained and stored at −18 °C until analysis.

The concentrations of Org 9487 and its three putative metabolites, 3-OH Org 9487 and 17-OH Org 9487, were determined by high-pressure liquid chromatography (HPLC) with a diode array detector (DAD), and 3-OH Org 9487 and 17-OH Org 9487 were determined by high-pressure liquid chromatography (HPLC) with a diode array detector (DAD) or by measurement of rocuronium [4] and has been adapted and validated in our analytical laboratory for Org 9487 and its putative metabolites [2].

Pharmacokinetic analysis was based on iterative linear least square regression analysis by the computer program MULTIFIT, using Marquardt as the minimizing algorithm. Initial estimates were obtained by a stripping procedure (ESTRIP). MULTIFIT provides all relevant pharmacokinetic variables which are calculated using standard equations [5]. Concentration vs time data were fitted for each patient to both bi- and triexponential equations.

The effective plasma concentrations of Org 9487 and 3-OH Org 9487 at $T_w$ of 75% and 90% block and at a TOF ratio of 0.7 were calculated ($EC_{T_w < 0.7}$, $EC_{T_w < 0.9}$ and $EC_{\text{TOF} < 0.7}$ respectively) in patients who were allowed to recover spontaneously from neuromuscular block.
PHARMACODYNAMICS

The results with respect to time course of action variables are presented in table 1. The infusion of Org 9487 was started 8.2 (2.0) min after the end of administration of the intubating dose. For a mean neuromuscular block of 83 (3) % for 60 min, the infusion requirement of Org 9487 was 3.4 (1.0) mg kg⁻¹ h⁻¹ during the time of infusion. During the final 15 min of infusion, the infusion requirement was 2.5 (1.1) mg kg⁻¹ h⁻¹. Although the infusion rate was diminished progressively immediately after the start, the neuromuscular block could easily be maintained at the desired level. In the five patients in whom spontaneous recovery was awaited, Tw at the end of infusion of Org 9487 was 19 (5) %. In the five patients in whom neuromuscular block was antagonized by neostigmine during a constant infusion of Org 9487, that is 10 min before the infusion was stopped, Tw and TOF increased within 10 min from 15 (2) % and 0.01 (0.03) to 81 (24) % and 0.39 (0.09), respectively.

PHARMACOKINETICS

In nine patients, pharmacokinetic analysis was performed. In one patient, plasma concentration analysis failed, most probably because of a drug or the metabolite of a drug, administered in the study period, interfering with the determination of Org 9487. Plasma concentration decay of Org 9487 was significantly better described by a triexponential equation in only two patients. A typical plasma concentration decay curve is presented in figure 1. The pharmacokinetic variables, based on biexponential equations for all nine patients, are presented in table 2.

Table 1 Mean (sd) pharmacodynamic variables of Org 9487 after a bolus dose of 1.5 mg kg⁻¹ administered in a vein located on the foot followed by an infusion to obtain 75–85 % neuromuscular block for 1 h in anaesthetized patients; five patients received neostigmine 40 μg kg⁻¹ and methyl-atropine 7 μg kg⁻¹ after 50 min of infusion

Table 2 Mean (cv %) pharmacokinetic variables of Org 9487 after a bolus dose of 1.5 mg kg⁻¹ followed by an infusion in anaesthetized patients (n = 9) and after a bolus dose of 1.5 mg kg⁻¹ (n = 3) in a previous study [2]. P, A and B = coefficients of the biexponential or triexponential function describing the plasma concentration decay of Org 9487; T1, T2 and T3 = initial distribution, redistribution and terminal half-lives, respectively; V1 = apparent volume of the central compartment; V2 = apparent volume of distribution at steady state; CL = total plasma clearance; CLini = initial plasma clearance; MRT = mean residence time; k12, k21, and k10 = intercompartmental and elimination rate constants, respectively.
appearance for the 3-OH metabolite (table 3, fig. 1). The plasma concentrations of Org 9487 and 3-OH Org 9487 at Tw of 75 % (EC\textsubscript{75}) and 90 % (EC\textsubscript{90}) and at a TOF ratio of 0.7 (EC\textsubscript{TOF-0.7}) are presented in table 3. Both the 17-OH and 3,17-diOH metabolites were not detected in plasma.

Urinary excretion of Org 9487 and its metabolites during the first 8 h were 11.7 (28) % and 4.9 (25) %, respectively, and during the first 24 h, 14.6 (20) % and 7.5 (17) %, respectively, of the amount administered. In all patients, the 3-OH metabolite showed a secondary increase in the amount excreted, 12–24 h after administration, while traces of the 3,17-diOH metabolite could be detected in urine from 6 h onwards.

Discussion

PHARMACODYNAMICS

We found a fast onset of neuromuscular block and an easily adjustable neuromuscular block after administration of Org 9487. However, lag time and onset time were longer and neuromuscular block at 1 min was smaller (maximum neuromuscular block unchanged) compared with those obtained in a previous study [1]. As the anaesthetic technique and monitoring of neuromuscular block were identical, this most probably results from differences in the locus of administration of Org 9487. The factors involved in the dynamic profile, in particular with respect to the fast onset of Org 9487, were discussed previously [1].

Spontaneous recovery from Tw of 25 % to a TOF ratio of 0.7 after stopping the infusion of Org 9487 was longer than spontaneous recovery from Tw of 25 % to a TOF ratio of 0.7 after an intubating dose [1]: 35.2 vs 16.1 min, respectively. Also, neostigmine-induced recovery time seems to be longer after infusion than after an intubating dose [1].

Three mechanisms may explain both the longer spontaneous and longer neostigmine-induced recovery from neuromuscular block produced by an infusion of Org 9487. First, prolonged administration of Org 9487 shifts the period of recovery of neuromuscular block to a phase characterized by a slower plasma concentration decay because of diminished contribution of distribution to plasma clearance in time. For similar reasons, spontaneous recovery of neuromuscular block induced by an infusion of pancuronium [6], vecuronium [7] and rocuronium [8] is prolonged compared with recovery after an intubating dose of twice the ED\textsubscript{90} value. This is in contrast with results of studies with atracurium [7] and mivacurium [9], suggesting almost unaltered recovery after continuous infusion compared with that after single bolus administration, as recovery from neuromuscular block of these drugs appears to be governed primarily by elimination processes.

As reversal of neuromuscular block is the result of the antagonistic effect of neostigmine and disappearance from plasma of the neuromuscular blocker [10], recovery after neostigmine may also be expected to last longer after prolonged infusion. Comparison of recovery with that of vecuronium [unpublished data] obtained under identical circumstances, that is neostigmine 10 min before stopping the infusion at similar degrees of neuromuscular block, revealed similar time profiles. For vecuronium (n = 5), a DUR\textsubscript{TOF-0.7} value of 16.4 (4.7) min was calculated.

These results suggest that Org 9487 is suitable for short administration, that is intubation and short surgical procedures (less than 30 min) and that prolonged administration (longer than 1 h) of Org 9487 changes the time course of the drug progressively from that of a short-acting agent into that of an intermediate-acting agent.

Second, the plasma concentration of the 3-OH metabolite increased during the infusion. After stopping the infusion, the 3-OH Org 9487 plasma concentration decreased more slowly than that of Org 9487 (table 3). Assuming identical potency ratios of Org 9487 and 3-OH Org 9487 in cat and humans, that is 1:0.5, the contribution of 3-OH Org 9487 to the neuromuscular block of Org 9487 at the end of infusion, that is at Tw of 19 (5) %, should be approximately 6 % (table 3). At clinically adequate recovery, that is at a TOF ratio of 0.7, this contribution to residual neuromuscular block should be increased to 27 % (table 3). These values demonstrate that the metabolite could contribute to neuromuscular receptor occupancy after 1 h of neuromuscular block.

Third, another factor which might have increased the recovery time is the use of isoflurane as the volatile anaesthetic. In this study, recovery from Tw of 25 % to a TOF ratio of 0.7 took place after more than 1 h with an end-tidal concentration of isoflurane.

Table 3 Org 9487 and 3-OH Org 9487 plasma concentrations during and after stopping the infusion of Org 9487 (ng ml\textsuperscript{-1}) (mean (Cv%)) and relative contribution of 3-OH Org 9487 to the neuromuscular or residual block (%), assuming identical potency ratios of Org 9487 and 3-OH Org 9487 in cat and humans, that is 1:0.5.

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>Org 9487</th>
<th>3-OH Org 9487</th>
<th>Relative contribution of 3-OH Org 9487 to the block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = 10 min</td>
<td>10</td>
<td>5979 (38%)</td>
<td>340 (30%)</td>
<td>3</td>
</tr>
<tr>
<td>t = 60 min</td>
<td>10</td>
<td>5029 (47%)</td>
<td>650 (31%)</td>
<td>6</td>
</tr>
<tr>
<td>Stop infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t = at EC\textsubscript{Tw-75}</td>
<td>5</td>
<td>1597 (26%)</td>
<td>490 (20%)</td>
<td>13</td>
</tr>
<tr>
<td>t = at EC\textsubscript{Tw-90}</td>
<td>5</td>
<td>1010 (41%)</td>
<td>489 (23%)</td>
<td>20</td>
</tr>
<tr>
<td>t = at EC\textsubscript{TOF-0.7}</td>
<td>5</td>
<td>606 (24%)</td>
<td>452 (25%)</td>
<td>27</td>
</tr>
<tr>
<td>t = 240 min</td>
<td>10</td>
<td>89 (46%)</td>
<td>205 (27%)</td>
<td></td>
</tr>
</tbody>
</table>
of 1%. It has been demonstrated that isoflurane potentiated the effects of neuromuscular blocking agents, which may become maximal 45-60 min [8, 11] after the start of administration of the volatile agent.

PHARMACOKINETICS

A bolus dose of Org 9487 1.5 mg kg⁻¹ produced a plasma concentration decay described best as a triexponential equation [2] (table 2). The results of the pharmacokinetic analysis of the current study are in agreement with those of that study [2]. The absence of a rapid distribution phase (τ) may be explained easily by absence of sampling in the first 20 min after bolus administration. The somewhat lower values derived for volume of distribution (Vₚ) and clearance (Cl) in the current study resulted in a mean residence time identical to that found after a single bolus dose.

The terminal half-life of Org 9487 was only slightly shorter than those of vecuronium (108 and 116 min [12, 13]) and rocuronium (94 and 97 min [14, 15]), which were studied using identical pharmacokinetic analysis and fitting. The shorter duration of action after an intubating dose of Org 9487 [1, 2] compared with those of vecuronium [16] and rocuronium [17] seems therefore to be primarily a result of a higher rate of (initial) clearance.

Ten minutes after administration of the bolus dose of Org 9487, the plasma concentration of 3-OH Org 9487 was approximately 6% of that of Org 9487 (table 3). As the vials contained only 1% maximal 3-OH Org 9487, plasma concentrations of the 3-OH metabolite are primarily the result of degradation of Org 9487 after its administration.

Renal excretion of Org 9487 appears to be of minor importance, as approximately 17% of the administered dose is excreted in urine during the first 8 h (parent compound and 3-OH metabolite). In the following 16 h only approximately 5% is additionally excreted. These values are similar to those obtained for vecuronium [13] and rocuronium [15]. Under the current study conditions, recovery from neuromuscular block induced by Org 9487 seems therefore relatively independent of renal function.

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References