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# *First Human Exposure of Org 25969, a Novel Agent to Reverse the Action of Rocuronium Bromide*

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***Background:*** **Acetylcholinesterase inhibitors are widely used for the reversal of neuromuscular blocking agents. However, acetylcholinesterase inhibitors have several side effects and are not effective during profound block. Org 25969 is a modified γ-cyclodextrin that encapsulates the neuromuscular blocking agent, rocuronium bromide (Esmeron®/Zemuron®, NV Organon, Oss, The Netherlands), forming a tightly bound complex with an association constant of approximately $10^7$ $M^{-1}$. Chemical encapsulation of rocuronium promotes dissociation of rocuronium from the acetylcholine receptor, thereby reversing the neuromuscular block without the side effects associated with acetylcholinesterase inhibitors.**

***Methods:*** **Twenty-nine healthy male volunteers were enrolled to investigate the safety, pharmacokinetics, and efficacy of Org 25969. In part 1, Org 25969 or placebo was administered to 19 subjects during one to three treatment periods each. In part 2, a further 10 subjects received general anesthesia on two separate occasions, using an intubating dose of 0.6 mg/kg rocuronium. Three minutes after rocuronium administration, Org 25969 or placebo was given in random order. Six doses of 0.1–8.0 mg/kg Org 25969 were evaluated. Neuromuscular block was measured using an acceleromyograph, the TOF-Watch-SX® (NV Organon, Oss, The Netherlands).**

***Results:*** **All adverse events related to Org 25969 treatment were of limited duration and mild intensity, except for a period of paresthesia, seen in one patient receiving 8 mg/kg Org 25969, which was of moderate intensity. No adverse events required any treatment, and all subjects recovered from them. When 8 mg/kg Org 25969 was given, the train-of-four ratio returned to 0.9 within 2 min after its administration. No signs of recurarization were observed.**

***Conclusions:*** **Org 25969 was both well tolerated and effective in reversing neuromuscular block induced by rocuronium in 29 human volunteers.**

NEUROMUSCULAR blocking agents (NMBAs), which produce muscle relaxation during surgery, are an essential adjunct to anesthesia. However, rapid reversal of their effects, particularly in cases of profound block, has proved difficult. Recently, a novel fast-acting agent, Org 25969, a modified γ-cyclodextrin, has been developed to routinely reverse rocuronium bromide (Esmeron®/Zemuron®; NV Organon, Oss, The Netherlands)–induced neuromuscular block (NMB).[1] Cyclodextrins are cyclic oligosaccharides, well known for their capability to encapsulate lipophilic guest molecules.[2] The advantage of using cyclodextrins as NMB reversal agents is that they are generally very water soluble, have no endogenous targets, and are therefore unlikely to cause major side effects.[3] Org 25969 was designed to have an optimal affinity for rocuronium, and its hydrophobic interior was tailored to fully encapsulate the hydrophobic steroid skeleton of rocuronium (fig. 1).[4] Once the Org 25969–rocuronium interaction has been established, it prevents the binding of rocuronium to nicotinic receptors in the neuromuscular junction and hence results in cessation of NMB *in vivo*.[5] In addition, in the guinea pig *in vivo*, Org 25969 was found to increase plasma and urine concentrations of rocuronium,[6] indicating that Org 25969 increases the clearance of rocuronium by the kidney. Thus, Org 25969–rocuronium interaction leads to a shift of rocuronium into the plasma, reducing the level of free rocuronium availability at the neuromuscular junctions.

Eriksson *et al.*[7] and Kopman *et al.*[8] clearly showed that recovery from NMB to a train-of-four (TOF) ratio of 0.9 or greater was predictive of the recovery of pharyngeal muscles, striated muscles of the upper esophagus, the masseter muscle, and the extraocular muscles. This finding suggests that there may be a substantial risk of aspiration at TOF ratios below 0.9. Furthermore, after the use of NMBAs of intermediate duration, such as rocuronium, and using a TOF ratio of 0.9 as the criterion for adequate recovery, Debaene *et al.*[9] showed a 45% incidence of postoperative residual curarization in patients arriving in the recovery room.

Anticholinesterases, such as neostigmine, are routinely used as reversal agents for NMBAs. However, the use of anticholinesterases as reversal agents has major drawbacks regarding safety and efficacy. They nonspecifically activate both nicotinic and muscarinic synapses by competitively inhibiting the breakdown of acetylcholine, rather than acting as true reversal agents. Their use leads to bradycardia, hypersalivation, and bronchoconstriction, which are reduced by using anticholinergics such as atropine and glycopyrrolate. In addition, anticholinesterases have little effect against profound block and show considerable interindividual variation in efficacy.

This article is featured in "This Month in Anesthesiology." Please see this issue of Anesthesiology, page 5A.

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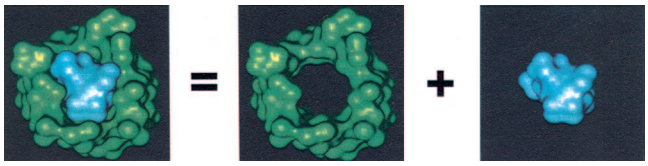

**Fig. 1. X-ray crystal structures of Org 25969 (*green*) and rocuronium (*blue*) with filled van der Waals surface, showing that the two structures have many close contacts and are highly complementary to each other.**

If neostigmine is administered before a partial recovery (≥ 10% twitch activity) of NMB is reached, the total time to reach 90% recovery of NMB is not shortened.[10] Reversal of NMB by an acetylcholinesterase inhibitor is therefore usually done by waiting until recovery of twitch height to 10–25%, which takes approximately 30 min when a bolus of 0.6 mg/kg rocuronium is given.

To ensure the greatest patient safety possible, many anesthesiologists routinely use acetylcholinesterase inhibitors to reverse NMB.[11] In a study performed by Baurain *et al.*,[12] TOF values were approximately 0.9 (range, 0.71–0.99) 15 min after neostigmine (40 μg/kg) at a T1 twitch of 25%, in the absence of the use of halogenated anesthetic agents, such as halothane or sevoflurane. Therefore, it can take 15 min or more to reach TOF 0.9 after neostigmine administration, which may explain why postoperative residual curarization is so frequently observed in the recovery room.[13]

Here, we report the first administration of the novel agent Org 25969 to human volunteers. Our primary objective was to explore the safety and tolerability of Org 25969 in man. In addition, we investigated the pharmacokinetics and efficacy in reversing the action of rocuronium.

## Materials and Methods

The study consisted of two parts: Part 1 evaluated the safety and tolerability of increasing doses of Org 25969, and part 2 was a pilot efficacy study.

### *Subject Recruitment*

After obtaining institutional review board approval (Stuivenberg Hospital, Antwerp, Belgium) and written informed consent, 29 healthy male volunteers were enrolled in this double-blind study. Because this was a phase I study, the sample size was based on practical considerations, not on statistical power calculations. Only healthy young subjects (aged 18–40 yr) with normal body weight (body mass index, 20–29 kg/m$^2$; weight, 60–90 kg) were included. Subjects with clinically significant abnormal 12-lead electrocardiographic data or laboratory results were excluded from participation.

In part 2, subjects were excluded if they had a history of difficult intubation, if they had a Mallampati score of III or IV, or if there was any suspected allergy to narcotics, muscle relaxants, or other medication used during general anesthesia. A (family) history of malignant hyperthermia led automatically to exclusion.

**Table 1. Number of Subjects Treated in Each Dose Group in Part 1 of the Study**

| | Period | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Org 25969 dose group, mg/kg | 0.1 | 0.2 | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 |
| No. of subjects receiving active | 4 | 4 | 4 | 6 | 6 | 5 | 2 |
| No. of subjects receiving placebo | 2 | 2 | 2 | 3 | 3 | 3 | 2 |
| Total subjects in group | 6 | 6 | 6 | 9 | 9 | 8 | 4 |

### *Treatment*

**Part 1.** In part 1, 19 subjects were randomized to receive a single dose of Org 25969 on two occasions, placebo on one occasion, or both (table 1). Subjects remained supine, under constant surveillance, in the nursing room until 2 h postdose. The first 6 subjects were all treated in three separate periods, during each of which the subject was randomly allocated to receive placebo in one period and Org 25969 during the other two periods at increasing doses of 0.1, 0.2, or 0.5 mg/kg. The next 9 subjects were also treated for three periods each (except for 1 subject who discontinued the study prematurely and received only one active dose and placebo) and were randomized to placebo in one period and Org 25969 at increasing doses of 1.0, 2.0, or 4.0 mg/kg. When, during part 2 of the study, it seemed that the plateau of the dose–response relation was not yet fully defined, the study was amended, and an additional 4 subjects were dosed in part 1 for a single period each. Two of these subjects were randomly allocated to receive placebo, and the other 2 subjects were randomly allocated to 8.0 mg/kg Org 25969.

**Part 2.** In this pilot efficacy study, 10 subjects were each anesthetized twice during two separate periods and received either placebo first or a single dose of Org 25969 first in a crossover manner. First, subjects received a saline infusion of 2 l/24 h, starting at least 6 h before anesthesia. As premedication, all subjects received 0.25 mg atropine and 1.25 mg lorazepam 1 h before induction. Before induction, the subjects were connected to routine monitoring equipment (*i.e.*, noninvasive blood pressure, electrocardiogram, Bispectral Index, oxygen saturation, and end-tidal carbon dioxide). The subjects were preoxygenated with 100% oxygen for 5 min.

Anesthesia was induced and maintained using propofol target-controlled infusion and remifentanil. A urinary catheter and an intraarterial line were inserted, and predose urinary and arterial samples were taken at baseline for safety, laboratory, and pharmacokinetic assessments

**Table 2. Number of Subjects Treated in Dose Groups in Part 2 of the Study**

| | Periods | | | | | |
|---|---|---|---|---|---|---|
| | 1 and 2 | 3 and 4 | 5 and 6 | 7 and 8 | 9 and 10 | 11 and 12 |
| Org 25969 dose group, mg/kg | 0.1 | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 |
| No. of subjects (each received both active and placebo) | 1 | 1 | 2 | 2 | 2 | 2 |

before the administration of rocuronium. The neuromuscular function of the adductor pollicis was monitored by acceleromyography using the TOF-Watch-SX® accelero-myograph (NV Organon, Oss, The Netherlands). After calibration of the TOF-Watch-SX®, the ulnar nerve at the wrist was stimulated through pediatric surface electrodes with TOF supramaximal stimulation with a pulse width of 200 $\mu$s at a frequency of 2 Hz, repeated every 15 s. Data were collected by a laptop computer connected to the TOF-Watch-SX®.

After induction of anesthesia, each subject received an intubating dose of 0.6 mg/kg rocuronium at both periods. A laryngeal mask was inserted, or tracheal intubation was performed. At 3 min after the start of rocuronium administration, subjects received a single intravenous bolus injection of Org 25969 (0.1–8.0 mg/kg) in one treatment period and placebo in the other treatment period, in randomized order. Thereafter, neuromuscular monitoring was continued until recovery from anesthesia. To monitor the possible occurrence of recurarization, maintenance of anesthesia was continued for a minimum of 90 min after Org 25969 or placebo administration and at least until neuromuscular recovery to a TOF ratio of 0.9. Treatment in part 2 was given according to the dose groups shown in table 2. Doses in part 2 were adjusted as a result of findings on efficacy and safety in previous doses given in part 1 but did not exceed the highest well-tolerated dose observed in part 1 of the investigation. At doses of 1 mg/kg and above, the number of subjects at each dose in part 2 was increased from one to two, once clinically relevant efficacy was observed.

All subjects were randomly allocated to receive Org 25969 or placebo during one to three treatment periods, depending on which part of the study they participated in. In each treatment period, subjects remained in the clinical unit for an overnight stay, from the day before receiving the dose of investigational product until the day after. A follow-up visit was performed between the 7th and 10th day after the last treatment period. The minimum washout period between any two periods was 3 days. After each period, an interim safety report was made, including the results of all safety assessments during that period. Based on the results of the interim safety reports, a decision was made for continuation to each higher dose level.

*Safety Assessments*

The physician involved with safety assessments was blinded to the treatments. Physical examinations were performed at 24 h postdose and during the follow-up visit. To assess the occurrence of adverse events, each subject's well-being was assessed predose; at 5, 15, and 60 min postdose; at 3, 6, 12, and 24 h postdose; and during the follow-up visit. In part 2 of the study, assessment of adverse events was started after recovery of the subject from anesthesia. The maximum intensity of any adverse event was classified by the investigator into one of three categories: mild (no interference with normal function), moderate (no significant interference with normal function), or severe (significant interference with normal function). Local intolerance at the site of injection was assessed predose and at 5 min, 30 min, 1 h, 12 h, and 24 h postdose. Supine blood pressure, heart rate, oxygen saturation, and 12-lead electrocardiograms were assessed predose; at 2, 10, 30, 60, and 120 min postdose; and during the follow-up visit. Telemetric recording was performed from 10 min predose until 2 h postdose. Blood samples for hematology and clinical chemistry were taken predose and 20 min, 8 h, and 24 h postdose and during the follow-up visit. Clinical chemistry included standard clinical chemistry as well as haptoglobin to detect possible hemolysis. Urine samples for urinalysis and sediment were taken predose, from urine collection intervals of 4–8 h and 16–24 h, and during the follow-up visit. Urinalysis included standard urinalysis as well as analysis of *N*-acetyl-$\beta$-D-glucosaminidase to detect possible damage to proximal tubule epithelium.

*Pharmacokinetic Assessments*

In part 1 of the study, venous blood samples for determination of Org 25969 plasma concentrations were taken predose and at 2, 3, 4, 6, 8, 10, 15, 25, 40, 60, 90, 120, 180, 240, 360, and 480 min after administration of Org 25969. In part 2 of the study, arterial samples were drawn for assessment of rocuronium and Org 25969 plasma concentrations before administration of rocuronium; at 1, 1.5, 2, and 3 min after administration of rocuronium; and at 1, 1.5, 2, 3, 4, 6, 8, 10, 15, 25, and 40 min after Org 25969 administration, followed by venous samples until 480 min postdose. In volunteers receiving placebo, blood samples were drawn at the same scheduled times as volunteers receiving Org 25969. Urine was collected, to assess the urinary excretion of Org 25969 and rocuronium, in collection intervals up to 24 h after

**Table 3. Volunteer Characteristics**

| | Part 1 (n = 19) | Part 2 (n = 10) | Total (n = 29) |
|---|---|---|---|
| Age, yr | 29.5 (6.1) | 32.4 (5.3) | 30.5 (5.9) |
| Weight, kg | 77.0 (7.2) | 76.6 (4.2) | 76.8 (6.2) |
| Height, cm | 180.2 (5.7) | 177.3 (5.4) | 179.2 (5.7) |

Data are presented as mean (SD).

dosing. Determination of Org 25969 and rocuronium concentrations in plasma and urine were performed by NV Organon using validated liquid chromatographic–mass spectrometric assay methods. The lower limits of quantification were 0.1 and 100 $\mu$g/ml for Org 25969 in plasma and in urine, respectively, and 0.1 and 50 ng/ml for rocuronium in plasma and urine, respectively. The analyses were conducted in compliance with the Good Laboratory Practice principles of the Organisation of Economic Cooperation and Development. The assay methods did not discriminate between the Org 25969–rocuronium complex and free Org 25969 and rocuronium. Thus, concentrations and pharmacokinetic parameters pertain to total plasma and urine Org 25969 and rocuronium, because the free and bound concentrations of Org 25969 cannot be measured separately.

The slope ($\beta$) of the terminal log-linear phase of the concentration-*versus*-time curve was determined by linear regression. The data were fitted to the following function: $\log_e C = \log_e C_{interc} + \beta t_I$, in which $C_{interc}$ is the intercept with the concentration axis at zero time. The terminal elimination rate constant ($\lambda_z$) was defined as $-\beta$, from which the terminal elimination half-life was calculated as $\log_e 2/\lambda_z$. The area under the concentration-*versus*-time curve (AUC) from zero to the last time point with a measurable concentration ($AUC_{0-tlast}$) was calculated by means of the linear trapezoidal rule. The AUC from zero to infinity ($AUC_{0-\infty}$) was calculated as $AUC_{0-\infty} = AUC_{0-tlast} + C_{tlast}/\lambda_z$, where $C_{tlast}$ was the fitted concentration at time $t_{last}$ using the regression line from which $\lambda_z$ was calculated. The mean residence time was calculated from the area-under-the-moment curve (AUMC) divided by $AUC_{0-\infty}$, where AUMC was calculated from the product of concentration and time ($C_i \cdot t_i$) using the linear trapezoidal rule plus $(C_{tlast} \cdot t_{last}/\lambda_z) + (C_{tlast}/\lambda_z^2)$. The plasma clearance was calculated as CL = dose/$AUC_{0-\infty}$. The volume of distribution during the terminal phase was calculated by $V_z = CL/-\beta$.

## Results

In total, 29 subjects were randomly assigned in part 1 (19 subjects) and part 2 (10 subjects) of the study. All subjects were white men, and their characteristics are shown in table 3.

### *Safety*

All 29 subjects completed the study without any serious adverse events, and no deaths were reported. One subject in part 1 discontinued the study after the second treatment period. This was because of an unrelated cardiac adverse event, *i.e.*, a Wolff-Parkinson-White syndrome, which was also observed after administration of placebo.

In five subjects, a total of nine adverse events were reported, which were judged by the investigator as possibly related to the administration of Org 25969 (table 4).

In part 1, one subject simultaneously experienced a taste perversion, a sensation of a changed temperature, coughing, and an abnormal smell (parosmia) within 15 min after a dose of 4.0 mg/kg Org 25969. These events lasted for 2 min, except for the coughing, which lasted for 25 min. A subject receiving a dose of 0.1 mg/kg Org 25969 experienced taste perversion within 7 min, which lasted for 43 min. Another subject in part 1 experienced both dry mouth and paresthesia after a dose of 8.0 mg/kg Org 25969. The dry mouth was experienced approximately 1 h after administration and lasted for 2.5 h, whereas paresthesia started the day after Org 25969 administration and lasted for almost 7 days. In part 2, two subjects experienced dry mouth, one 6 h after a dose of 4.0 mg/kg Org 25969 and another subject almost 3 h after a dose of 8.0 mg/kg Org 25969. These events lasted for 1 h 50 min and 3 h 18 min, respectively. One subject experienced muscular contractions (fasciculations at the right thigh) for a 12-h period. They were judged to be possibly related to the study drug but occurred 12 h after administration of placebo.

All of the drug-related adverse events were mild in intensity, except the paresthesia. No adverse events re-

**Table 4. Adverse Events Judged as Possibly Related to Administration of Org 25969**

| Adverse Event | No. of Subjects | Org 25969 Dose Group, mg/kg | Intensity |
|---|---|---|---|
| Part 1 | | | |
| Taste perversion | 2 | 0.1 and 4.0 | Mild |
| Feeling of changed temperature | 1 | 4.0 | Mild |
| Coughing | 1 | 4.0 | Mild |
| Abnormal smell (parosmia) | 1 | 4.0 | Mild |
| Dry mouth | 1 | 8.0 | Mild |
| Paresthesia | 1 | 8.0 | Moderate |
| Part 2 | | | |
| Dry mouth | 2 | 4.0 and 8.0 | Mild |

**Table 5. Postdose QTc Prolongations**

| Subject | Org 25969 Dose Group | Part of Study | Baseline QTc, ms | Prolonged QTc,ms | Postdose Time Point of QTc Prolongation, min |
|---|---|---|---|---|---|
| 14 | Placebo | 1 | 430 | 451 | 2 |
| 14 | 4.0 mg/kg | 1 | 424 | 461 | 30 |
| 16 | Placebo | 2 | 390 | 432 | 20 |
| 17 | 0.5 mg/kg | 2 | 380 | 452 | 10 |
| 18 | Placebo | 2 | 389 | 456 | 120 |
| 20 | Placebo | 2 | 409 | 464 | 120 |
| 218 | 1.0 mg/kg | 2 | 430 | 452 | 2 |
| 218 | Placebo | 2 | 435 | 453 | 30 |

QTc = QT correction.

quired any treatment, and all subjects recovered from them. The paresthesia was of a moderate intensity and occurred in the forearm at the site of insertion of the intravenous cannula.

Eight cases of prolongation of the corrected QT interval of greater than 450 ms (using the Bazett correction) were observed in six subjects. Six of the eight cases were observed in part 2 (table 5). However, these prolongations were isolated (observed at a single time point during the 2-h period of cardiac monitoring after administration), and the majority (five of eight) were reported after placebo. The highest value of corrected QT observed was 464 ms, occurring 120 min after placebo.

There were no markedly abnormal vital signs after administration of Org 25969 alone (part 1). Any abnormal values for blood pressure or heart rate occurred during anesthesia (part 2 of the study). In general, there was a decrease in blood pressure during the first hour after induction of anesthesia, which was unaffected by Org 25969. A slight decrease in blood pressure and heart rate was observed after administration of both placebo and 8.0 mg/kg Org 25969.

*Pharmacokinetics*

**Part 1.** Org 25969 mean plasma concentration-*versus*-time curves for each dose are presented in figure 2. Org 25969 showed dose-linear pharmacokinetics over the dose range of 0.1–8.0 mg/kg, with a total plasma clearance of approximately 120 ml/min, a volume of distribution of approximately 18 l, and an elimination half-life of approximately 100 min (table 6). The mean percentage of the dose excreted in urine up to 24 h varied between 59% and 80%.

**Part 2.** When Org 25969 was administered 3 min after a single dose of rocuronium, its pharmacokinetics were similar to those observed in part 1, when it was given alone (table 7). Rocuronium plasma concentrations increased toward a plateau with increasing dose level of Org 25969, compared with administration of rocuronium plus placebo (fig. 3). The AUC of total rocuronium (free and in complex with Org 25969) after treatment with 0.6 mg/kg rocuronium followed by 0.1–8.0 mg/kg Org 25969 was higher compared with the AUC after administration of rocuronium followed by placebo (table 8). The plasma clearance decreased by a factor greater than 2 when administration of rocuronium was followed by an Org 25969 dose of 2.0 mg/kg or higher. The volume of distribution $V_z$ of rocuronium decreased from approximately 50 l in the absence of Org 25969 to approximately 15 l when 2.0–8.0 mg/kg Org 25969 was given 3 min after rocuronium. On average, 14% of the dose of rocuronium was recovered in urine within 24 h of administration of rocuronium followed by placebo. When rocuronium dosing was followed by administration of Org 25969, the percentage of the dose excreted in urine increased with increasing Org 25969 up to at least 39–68% at the highest dose level of 8.0 mg/kg Org 25969.

*Efficacy: Part 2*

Placebo-controlled administration of Org 25969 at doses ranging from 0.1 to 8.0 mg/kg, 3 min after rocuronium administration, allowed for investigation of the dose–response relation of Org 25969 as a reversal agent for rocuronium. The entire dose–effect relation curve was observed within the tested dose range. As shown in table 9, no NMB reversal effect was observed until the

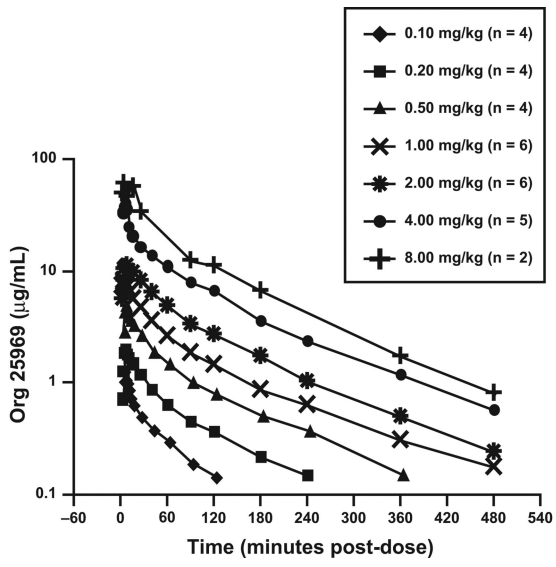


**Fig. 2. Org 25969 mean plasma concentration-*versus*-time curves in healthy volunteers receiving single doses of Org 25969 (0.1–8.0 mg/kg).**

**Table 6. Pharmacokinetic Parameters of Org 25969: Part 1**

| Parameter | Org 25969 Dose Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.1 mg/kg (n = 4) | 0.2 mg/kg (n = 4) | 0.5 mg/kg (n = 4) | 1 mg/kg (n = 6) | 2 mg/kg (n = 6) | 4 mg/kg (n = 5) | 8 mg/kg (n = 2) |
| $AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$ | 62.3 (17.0) | 149 (3.09) | 365 (4.44) | 647 (13.7) | 1100 (14.8) | 2627 (26.8) | 4837 (0.178) |
| CL, ml/min | 123 (9.33) | 99.2 (8.33) | 107 (12.7) | 119 (7.47) | 138 (14.9) | 118 (24.0) | 122 (2.64) |
| $V_z$, l | 11.7 (26.2) | 13.5 (7.95) | 16.7 (27.1) | 21.9 (10.7) | 20.9 (16.3) | 17.7 (30.8) | 17.2 (7.34) |
| $t_{1/2,\beta}$ , min | 65.8 (32.6) | 94.5 (12.0) | 108 (16.9) | 128 (12.2) | 105 (7.05) | 103 (9.46) | 97.9 (4.69) |
| MRT, min | 82.0 (29.1) | 112 (16.9) | 122 (6.07) | 133 (7.47) | 123 (11.5) | 119 (11.5) | 104 (13.7) |
| % of dose excreted in urine in 24 h | NC | NC | NC | 68.2* (11.5) | 58.8 (55.7) | 80.4 (13.1) | 73.5 (4.56) |

Data are presented as geometric means (geometric coefficient of variation).

* n = 5.

AUC = area under the curve; CL = plasma clearance; MRT = mean residence time; NC = not calculable; $t_{1/2,\beta}$ = terminal elimination half-life; $V_z$ = volume of distribution during the terminal phase.

dose level reached 1.0 mg/kg, and a plateau was reached between 4.0 and 8.0 mg/kg. In the subjects who received 8.0 mg/kg, the times from Org 25969 administration to recovery of a TOF ratio of 0.9 were 1.0 and 1.2 min. Figure 4 shows the TOF-Watch-SX® monitor traces of one of the subjects who received placebo on the first occasion and Org 25969 on the second occasion. It demonstrates graphically the large reduction in recovery time after treatment with Org 25969 as compared with placebo. No signs of recurarization were observed in the 90 min of TOF monitoring after treatment with Org 25969.

## Discussion

The study shows that Org 25969 was well tolerated when administered as single intravenous bolus at doses up to 8.0 mg/kg. Vital signs, laboratory safety tests, and 12-lead electrocardiograms showed a number of isolated out-of-normal-range values that were not dose dependent and were not considered to be clinically relevant by the investigator. However, in view of the small sample size in each dose group, the safety of Org 25969 must be confirmed in further studies. The only adverse event, which was of moderate intensity and was judged by the investigator as possibly related to the administration of Org 25969, was paresthesia in the forearm at the site of the insertion of an intravenous cannula. It was reported the day after administration and lasted for 7 days.

The observed plasma clearance of Org 25969 of approximately 120 ml/min is similar to the glomerular filtration rate in healthy humans. The lower limit of quantification of the urine assay (100 $\mu$g/ml) used in this study was not sufficiently low to enable quantification of the Org 25969 concentration in urine samples collected from subjects who received an Org 25969 dose of 0.5 mg/kg or less. After higher doses of 1.0–8.0 mg/kg, concentrations were above the lower limit of quantification only in the urine samples collected in the early postdose period up to 1, 2, 4, or 8 h. Consequently, the percentage of the Org 25969 dose excreted in urine could not be estimated for the lower doses, whereas the values reported for the higher doses (tables 6 and 7) are probably underestimates of the true percentage of the dose excreted in urine. Therefore, it could not be demonstrated unequivocally in this study that renal excretion is the only route of elimination of Org 25969 in humans, although in some individuals, as much as 90% of the dose was recovered in urine.

The pharmacokinetic data collected in the second part of this study support and illustrate the mechanism of action of complex formation. When rocuronium dosing

**Table 7. Pharmacokinetic Parameters of Org 25969: Part 2**

| Parameter | Org 25969 Dose Group | | | | | |
|---|---|---|---|---|---|---|
| | 0.1 mg/kg (n = 1)* | 0.5 mg/kg (n = 1)* | 1 mg/kg (n = 2)† | 2 mg/kg (n = 2)† | 4 mg/kg (n = 2)† | 8 mg/kg (n = 2)† |
| $AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$ | 99.2 | 377 | 985 (18.3) | 1,573 (3.33) | 3,494 (22.2) | 5,102 (2.39) |
| CL, ml/min | 78.6 | 95.7 | 74.7 (19.7) | 94.5 (11.8) | 84.8 (14.3) | 118 (2.16) |
| $V_z$, l | 9.64 | 14.2 | 12.7 (22.0) | 15.1 (5.35) | 14.6 (1.74) | 19.1 (9.21) |
| $t_{1/2,\beta}$, min | 85.1 | 103 | 118 (2.22) | 111 (6.45) | 119 (16.1) | 112 (7.04) |
| MRT, min | 101 | 132 | 143 (4.05) | 139 (3.51) | 137 (8.09) | 114 (0.0513) |
| % of dose excreted in urine in 24 h | 13.8 | NC | 31.5 (57.0) | 33.3 (5.43) | 50.4 (40.8) | 76.2 (24.8) |

* Data are presented as individual parameter. † Data are presented as geometric mean (geometric coefficient of variation).

AUC = area under the curve; CL = plasma clearance; MRT = mean residence time; NC = not calculable; $t_{1/2,\beta}$ = terminal elimination half-life; $V_z$ = volume of distribution during the terminal phase.

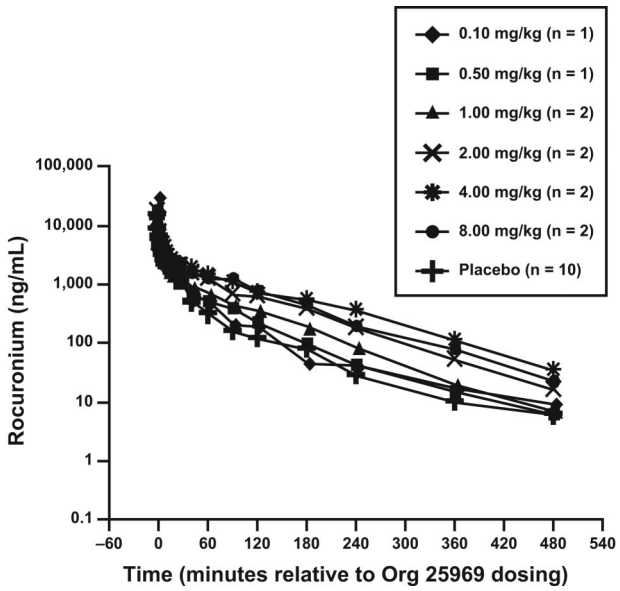


**Fig. 3. Rocuronium mean plasma concentrations increase with increasing dose level of Org 25969, compared with administration of rocuronium followed by placebo.**

was followed by administration of Org 25969, 3 min later, an increase in plasma concentrations of rocuronium was seen. After encapsulation by Org 25969, rocuronium is no longer free to distribute over the body as it usually does, but instead is confined to the space in which Org 25969 resides. As a result, the volume of distribution, $V_z$, of rocuronium decreases with increasing doses of Org 25969 until the $V_z$ of rocuronium approaches the $V_z$ of Org 25969 at the higher dose levels. Similarly, the plasma clearance of rocuronium assimilates into the plasma clearance of Org 25969 with increasing doses of Org 25969. Although both biliary and renal excretions contribute to the elimination of free rocuronium, these results suggest that the extrarenal route of elimination is unavailable to rocuronium captured by Org 25969, and consequently, rocuronium clearance decreases to a value approaching the glomerular filtration rate. The altered elimination of rocuronium is also demonstrated by the increase in urinary excretion. On average, 14% of the dose was recovered in urine within 24 h after administration of 0.6 mg/kg rocuronium followed by placebo. This is in accord with the 12–22% recovered in urine in previous studies investigating the pharmacokinetics of rocuronium.[14,15] When rocuronium dosing was followed by administration of Org 25969, the percentage of the rocuronium dose excreted in urine in 24 h increased with increasing Org 25969 up to at least 39% and 68% for the two subjects who received the highest dose of 8.0 mg/kg. Because of missing urine concentrations for both subjects for at least one of the urine collection intervals, these values are underestimates of the cumulative percentages of rocuronium excreted in urine. In summary, administration of Org 25969 leads to altered distribution and elimination of rocuronium as a result of complex formation.

In these first experiments with Org 25969 in human volunteers, the acceleromyography technique was chosen to ensure comparability with future clinical studies on Org 25969, and the main purpose was to demonstrate the efficacy of Org 25969. Furthermore, mechanomyographic and electromyographic monitors are no longer being manufactured and are, therefore, unavailable for routine clinical use. Previous authors have shown that acceleromyography can be used with confidence in the clinical setting[16] and that there is a good correlation between measurements from acceleromyography, mechanomyography, and electromyography, although the different techniques cannot be used interchangeably.[17] Finally, because the slope of the recovery curve from muscle relaxation with Org 25969 is very steep (fig. 4), the differences between the various techniques are a matter of seconds rather than minutes.

The data presented here support the view that Org 25969 is capable of rapidly and safely reversing rocuronium-induced NMB in human beings. In the two subjects given 8 mg/kg Org 25969 during profound NMB, at 3 min after the administration of 0.6 mg/kg rocuronium, the TOF ratio returned to 0.9 at approximately 1 min after Org 25969 administration. No signs of recurariza-

**Table 8. Effect of Org 25969 on the Pharmacokinetic Parameters of Rocuronium: Part 2**

| | Org 25969 Dose Group | | | | | | |
|---|---|---|---|---|---|---|---|
| Parameter | 0.1 mg/kg (n = 1)* | 0.5 mg/kg (n = 1)* | 1 mg/kg (n = 2)† | 2 mg/kg (n = 2)† | 4 mg/kg (n = 2)† | 8 mg/kg (n = 2)† | Placebo (n = 10)† |
| $AUC_{0-\infty}$, $\mu g \cdot min \cdot ml^{-1}$ | 200 | 158 | 182 (9.46) | 302 (12.1) | 364 (25.4) | 331 (6.75) | 139 (20.9) |
| CL, ml/min | 234 | 272 | 249 (9.54) | 155 (2.13) | 121 (16.7) | 135 (4.26) | 327 (19.4) |
| $V_z$, l | 38.1 | 34.4 | 22.4 (17.3) | 15.1 (6.43) | 12.5 (3.23) | 15.4 (12.3) | 49.3 (24.7) |
| $t_{1/2,\beta}$, min | 113 | 87.5 | 62.3 (7.66) | 67.7 (4.29) | 71.6 (13.4) | 79.5 (16.6) | 104 (21.0) |
| MRT, min | 40.8 | 53.2 | 67.2 (15.2) | 77.6 (6.05) | 99.2 (0.840) | 88.7 (5.11) | 41.8 (16.1) |
| % of dose excreted in urine in 24 h | 18.9 | 21.5 | 24.7* 33.7* | 32.1* 34.1* | 44.0* 24.0*‡ | 39.2*‡ 68.4*‡ | 14.3 (34.0) |

* Data are presented as individual value. † Data are presented as geometric mean (geometric coefficient of variation). ‡ Underestimated value due to missing urine concentration data.

AUC = area under the curve; CL = plasma clearance; MRT = mean residence time; NC = not calculable; $t_{1/2,\beta}$ = terminal elimination half-life; $V_z$ = volume of distribution during the terminal phase.

**Table 9. Time between Administration of Org 25969 and a TOF Ratio of 0.9 in 10 Subjects Participating in Part 2**

| | Org 25969 Dose Group | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0.1 mg/kg | 0.5 mg/kg | 1.0 mg/kg | 1.0 mg/kg | 2.0 mg/kg | 2.0 mg/kg | 4.0 mg/kg | 4.0 mg/kg | 8.0 mg/kg | 8.0 mg/kg |
| Time to TOF ratio of 0.9 after placebo, min | * | 64 | 46 | 43 | 60 | 56 | 47 | 69 | 58† | 36 |
| Time to TOF ratio of 0.9 after Org 25969, min | 43 | 71 | 31 | 23 | 13 | 17 | 2.6 | 3.3 | 1.0† | 1.2 |

Org 25969 was given at 3 min after 0.6 mg/kg rocuronium bromide.

* This patient did not receive placebo. † Data from the patient whose train-of-four (TOF) tracings are shown in figure 4.

tion were observed in the 90 min after Org 25969 administration (fig. 4), even though the bound form of rocuronium takes longer to clear from the plasma. Further monitoring over extended periods is in progress to ensure that recurarization does not occur, although this is thought to be unlikely. A recovery to a TOF ratio of 0.9 within 2 min is remarkable because this speed of recovery is considerably faster than could be expected after administration of neostigmine during profound NMB. There was little indication of variability of recovery times between the two subjects after Org 25969, but further studies in more subjects must be performed to verify this issue. However, the mechanism of NMB reversal by Org 25969 (*i.e.*, physicochemical binding of rocuronium) supports the lack of important interindividual variability.

The possibility of routine, rapid reversal of NMB will give anesthesiologists control over the level of NMB during the course of surgery. NMB may be provided until the end of the procedure, up to the last stitch, after which the NMB can be quickly reversed, avoiding residual block. Furthermore, the possibility of reversing profound NMB within a few minutes may be a valuable contribution to the therapeutic options available for the anesthesiologist facing a "cannot intubate, cannot ventilate" situation, which requires the immediate restoration of spontaneous ventilation.

## Conclusions

In the current study conducted in 29 healthy male subjects, Org 25969 was safe and well tolerated when administered as single intravenous bolus at doses up to 8.0 mg/kg, given either alone or 3 min after administration of a bolus dose of 0.6 mg/kg rocuronium. No signs of recurarization were observed after Org 25969. The chemical encapsulation mechanism of action of Org 25969 is a unique and highly novel approach to NMB

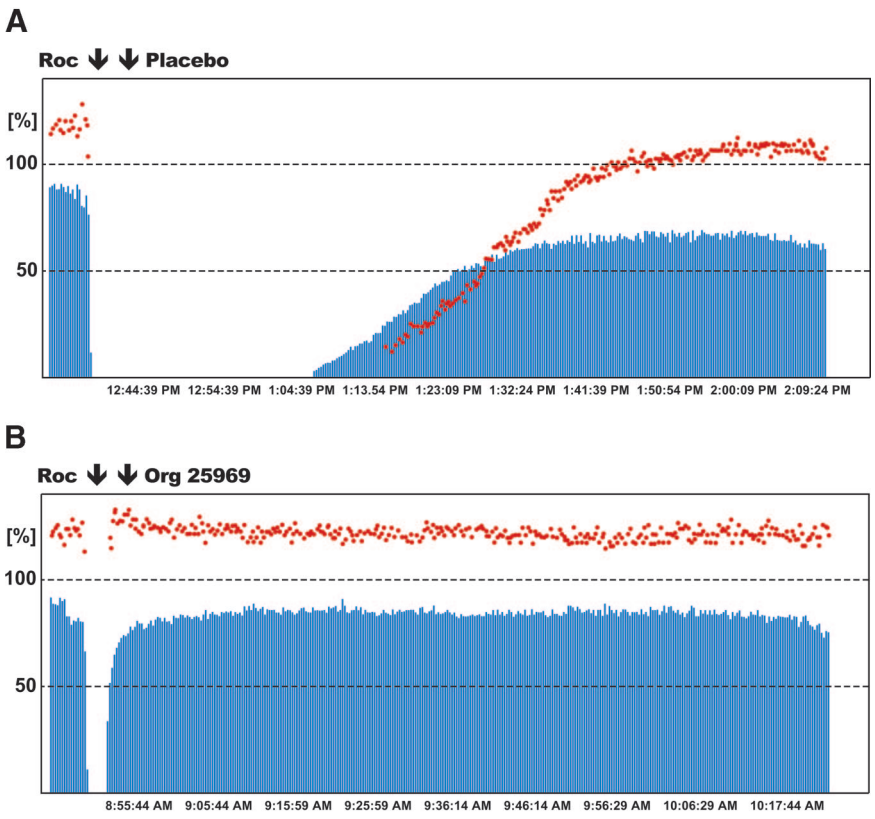


**Fig. 4. Train-of-four tracing from one volunteer who participated during part 2 of the study. The *blue line* represents the height of the twitch, and the *dashed red line* is the value of the train-of-four ratio. The volunteer received 0.6 mg/kg rocuronium (Roc) followed by placebo at 3 min (*A*) in one treatment period, followed by 8 mg/kg Org 25969 in another treatment period (*B*). No recurarization was observed in the 90 min during which the neuromuscular block was monitored.**

reversal. In the two subjects to whom 8.0 mg/kg was given, the time to recovery to a TOF ratio of 0.9 was reached after 1.0 and 1.2 min, respectively, whereas in two subjects given 4.0 mg/kg, a TOF ratio of 0.9 was reached in 2.6 and 3.3 min. The results indicate that rocuronium-induced NMB can be safely reversed with Org 25969. Therefore, Org 25969 may meet the criteria for an improved agent for the reversal of the action of rocuronium: a fast and reliable recovery from NMB, and favorable safety and tolerability profiles. Continued safety and efficacy for this promising agent will be confirmed in future clinical studies.

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