Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block

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Background. Org 25969 is a cyclodextrin compound designed to reverse a rocuronium-induced neuromuscular block. The aim of this study was to explore the efficacy, dose–response relation and safety of Org 25969 for reversal of a prolonged rocuronium-induced neuromuscular block.

Methods. Thirty anaesthetized adult patients received rocuronium 0.6 mg kg\(^{-1}\) as an initial dose followed by increments to maintain a deep block at a level of <10 PTCs (post-tetanic counts) recorded every 6 min. Neuromuscular monitoring was carried out using accelerometry, in a train-of-four (TOF) mode using TOF-Watch\(^{10}\)SX. At recovery of T₂, following at least 2 h of neuromuscular block, patients received their randomly assigned dose of 0.5, 1.0, 2.0, 4.0 or 6.0 mg kg\(^{-1}\) of Org 25969. Anaesthesia and neuromuscular monitoring were continued for a minimum period of 30 min after Org 25969 administration. The main end-point of the study was the time to achieve a sustained recovery of TOF ratio to 0.9. Patients were followed up for 7 days after anaesthesia.

Results. The results showed a dose-related decrease in the average time taken to attain a TOF ratio of 0.9 from 6:49 (min:s) with the 0.5 mg kg\(^{-1}\) dose to 1:22 with the 4.0 mg kg\(^{-1}\) dose. Weighted non-linear regression analysis showed the fastest achievable time to TOF ratio of 0.9 to be 1:35. Org 25969 produced no major adverse effects.

Conclusion. Org 25969 effectively reversed a deep and prolonged neuromuscular block induced by rocuronium. The effective reversal dose appears to be 2–4 mg kg\(^{-1}\).

Keywords: antagonists, Org 25969 (sugammadex); cyclodextrins; neuromuscular blocking agents, rocuronium

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Adequate reversal of neuromuscular block is an important consideration in anaesthesia.¹ Reversal may occur spontaneously as the neuromuscular blocking agents (NMBAs) diffuse away from the neuromuscular junction (NMJ) and are metabolized and/or eliminated, or it may be hastened with the use of acetylcholinesterase inhibitors such as neostigmine or edrophonium. These agents act by inhibiting the enzyme acetylcholinesterase thus facilitating an increase in the amount of acetylcholine to facilitate neuromuscular transmission. Acetylcholinesterase inhibitors, however, have some problems with their use. These agents antagonize the block slowly, or inadequately, if administered when the block is relatively dense, when reversal of block is attempted soon after the administration of the NMBAs or in the presence of potent volatile anaesthetics.²–⁴ In addition, acetylcholinesterase inhibitors have effects associated with stimulation of the muscarinic receptors resulting in bradycardia, arrhythmias, increased secretions and contraction of smooth muscle.

Cyclodextrins are cyclic oligosaccharide carbohydrates, a class of compounds first discovered in the nineteenth century as crystalline by-products of starch degradation.
by bacteria. They have a ring structure that has been of interest to chemists due to having a hydrophilic surface which allows cyclodextrins to dissolve in water, as well as the ability to complex hydrophobic molecules within the central core. The most common are designated α, β and γ containing 6, 7 and 8 glucose units respectively. Within medicine there is interest in the use of cyclodextrins as solubilizing agents for highly insoluble drugs. They are also used to improve the pharmacokinetic and pharmacodynamic properties of drugs delivered via the nasal, transdermal and rectal routes for a variety of drugs, including benzodiazepines, NSAIDs and opioids, with the advantage of causing less local irritation. Finally cyclodextrins have been used to provide controlled drug release formulations to enable delayed or prolonged drug release.

Org 25969 (Figure 1) is a modified γ-cyclodextrin which acts by rapidly encapsulating a steroidal NMBA such as rocuronium and forming a stable complex which prevents the pharmacological action of the NMBA at the NMJ. This provides a completely novel mechanism for reversal of neuromuscular block which is independent of acetylcholinesterase inhibition and does not require the co-administration of anticholinergic agents. Recent studies have shown that Org 25969 is effective in reversing blockade induced by single intubating doses of rocuronium in both healthy volunteers and surgical patients.

The efficacy of Org 25969 for antagonism of longer lasting blockade is, however, not known. This randomized, dose-finding, two centre, safety assessor-blinded, phase two study investigated the safety and efficacy of Org 25969 given at the reappearance of T2 [second response in the train-of-four (TOF) stimulation, after prolonged neuromuscular block (>2 h) with rocuronium].

Patients and methods
Thirty adult patients were included at two centres (Belfast and Nottingham), following approval of the Research Ethics Committees and written informed consent from patients. All patients were aged 18 yr or above, of ASA grades I–III, and scheduled to undergo surgery anticipated to last at least 150 min. Most patients were undergoing orthopaedic or general surgery. Patients with a predicted difficult tracheal intubation, a neuromuscular disorder, hepatic or renal dysfunction, a history of malignant hyperpyrexia, suspected allergy to narcotics, NMBA, or other medication used during general anaesthesia, or those receiving medication known to interact with NMBA were excluded from the study.

Anaesthesia was induced and maintained with a target controlled infusion of propofol and supplemented with nitrous oxide and one or more out of fentanyl, alfentanil, remifentanil and morphine. No volatile anaesthetic agents were used. Heart rate (HR), blood pressure (BP), oxygen saturation and end-tidal carbon dioxide concentration were measured throughout the study. Skin temperature over the adductor pollicis muscle was maintained above 32°C by wrapping the arm in cotton wool and the use of warming blankets over the patients. Neuromuscular function was
monitored by stimulating the ulnar nerve at the wrist using supramaximal stimuli of 0.2 ms duration in a TOF mode using TOF-Watch\textsuperscript{®} SX (NV Organon, Oss, The Netherlands). Stabilization was performed by a 5 s 50 Hz tetanic stimulation followed by 2–5 min of repetitive TOF stimulation. Calibration was done using the CAL2 mode of the TOF-Watch SX. The same set up method was used at both the centres. Monitoring was carried out using the post-tetanic count (PTC) initiated manually every 6 min in the absence of T\textsubscript{1} (first response to TOF stimulation) to monitor more profound neuromuscular block. The TOF-Watch\textsuperscript{®} SX was calibrated after induction of anaesthesia, following which an intubating dose of 0.6 mg kg\textsuperscript{-1} of rocuronium was administered. Tracheal intubation was carried out at maximum block. Subsequent neuromuscular block was maintained to a depth of no responses to TOF and a PTC of <10 responses, using further boluses of rocuronium. The minimum time between administration of the intubating dose of rocuronium and administration of reversal, at reappearance of T\textsubscript{2} (second response in the TOF stimulation) after administration of the last dose of rocuronium, was 120 min.

The block was allowed to recover spontaneously after administration of the last dose of rocuronium until the appearance of T\textsubscript{2}. The patients were then given their randomly assigned dose of 0.5, 1.0, 2.0, 4.0 or 6.0 mg kg\textsuperscript{-1} of Org 25969 as a single bolus. Neuromuscular monitoring was continued for a minimum of 30 min after administration of Org 25969. HR and BP were recorded before and at 2, 10 and 30 min after the administration of Org 25969. Patients were visited at least 10 h later (most commonly the day after surgery) and assessed for any untoward effects. Adverse events and/or serious adverse events were recorded during the procedure, at the post-anaesthetic visit and at follow-up 7 days after the procedure for assessment of safety of Org 25969.

The primary efficacy variable was the time between the start of administration of Org 25969 and recovery of the TOF ratio to 0.9. Data from the per-protocol (PP) group were used to assess the efficacy. The PP group consisted of all subjects randomized to receive Org 25969, had at least one post-baseline efficacy measurement and had no major protocol violations. For subjects with a minor protocol violation, all affected data were excluded from the PP analysis. Weighted non-linear regression was used to explore the relationship between the dose of Org 25969 and the time to recover TOF ratio to 0.9.

**Results**

The demographics of the 30 patients (all subjects treated group) are summarized in Table 1. All 30 patients received Org 25969 and 28 completed the study. Major protocol violations were deemed to have occurred in three patients, these being loss of TOF-Watch recordings in one patient, and administration of Org 25969 in two patients before

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Org 25969 dose group (mg kg\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1 0 2 4 6</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>(30–70) (20–64) (30–76) (19–55) (22–75)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>78 (17) 80 (10) 80 (14) 86 (16) 87 (9)</td>
</tr>
<tr>
<td>Mean height (cm)*</td>
<td>173 (9) 157 (13) 162 (8) 176 (3) 174 (4)</td>
</tr>
<tr>
<td>ASA grade I</td>
<td>3 1 3 4 3</td>
</tr>
<tr>
<td>ASA grade II</td>
<td>3 3 2 2 2</td>
</tr>
<tr>
<td>ASA grade III</td>
<td>0 2 0 1 1</td>
</tr>
</tbody>
</table>

Data from the per-protocol (PP) group were used. *Data missing for one subject in each of the 0.5 and 6.0 mg kg\textsuperscript{-1} groups; data excluded for one subject because of a minor protocol violation.

Table 2 Summary of the times (mean (SD), median and range; min:s) from start of administration of Org 25969 to recovery of the TOF ratio to 0.9 by dose group (PP group). *Data missing for one subject in each of the 0.5 and 6.0 mg kg\textsuperscript{-1} groups; data excluded for one subject because of a minor protocol violation.

<table>
<thead>
<tr>
<th>Org 25969 dose group (mg kg\textsuperscript{-1})</th>
<th>0.5 1.0 2.0 4.0 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>4*</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6:49 (3:06) 2:43 (0:59) 1:46 (0:37) 1:22 (0:35) 2:37 (1:15)</td>
</tr>
<tr>
<td>Min–max</td>
<td>5:29 2:42 1:46 1:04 2:41</td>
</tr>
</tbody>
</table>

The mean time for recovery of the TOF ratio to 0.9 was 6 min 49 s in the group receiving the 0.5 mg kg\textsuperscript{-1} dose of Org 25969 and decreased to 1 min 22 s in the 4.0 mg kg\textsuperscript{-1} group, the time being 2 min 37 s in the 6.0 mg kg\textsuperscript{-1} group (Table 2).

Fitting the parameters of the exponential model to the recovery times for the PP group resulted in the following equation:

\[
	ext{Estimated time (min) to recovery of TOF ratio to 0.9} = 1.59 + 22.1e^{(-2.92 \times \text{dose})}.
\]

The estimated dose–response curve is shown in Figure 2. The curve adequately predicted the observed data (with a statistically significant dose–response effect) over the dose range 0.5–4.0 mg kg\textsuperscript{-1} although the recovery time was longer than expected for the 6.0 mg kg\textsuperscript{-1} group. The fastest achievable time to recover the TOF ratio to 0.9, irrespective of the dose, was estimated to be 1 min 35 s. A dose of
2–4 mg kg\(^{-1}\) of Org 25969 appeared to be an effective reversal dose.

There was no evidence of recurarization in any patient during the period of neuromuscular monitoring or during their stay in the postoperative recovery unit. In the two patients where Org 25969 was administered 68 and 7 s short of 120 min, the times to recovery of TOF ratio of 0.9 were 3 min 19 s following Org 25969 0.5 mg kg\(^{-1}\) and 1 min 13 s following Org 25969 6.0 mg kg\(^{-1}\) respectively.

The incidence of adverse events was low; 5 (17%) patients experienced events that were judged as possibly, probably or definitely related to Org 25969. These are listed in Table 3. Apart from nausea, these were single occurrences and were not dose-related. There were no deaths during this trial.

Atrial fibrillation and respiratory failure in one subject may possibly have been related to administration of Org 25969 although this is uncertain. This happened in a 65-yr-old hypertensive subject receiving bendroflumethiazide on the second postoperative day in the 0.5 mg kg\(^{-1}\) dose group. She had developed dehydration, her haemoglobin and serum potassium levels were 7.7 g dl\(^{-1}\) and 3.1 mmol l\(^{-1}\) respectively. The patient received blood and fluids and was administered digoxin and amiodarone and settled to a sinus rhythm within 2–3 days. Serious adverse events in two other patients (one developing a compartment syndrome and the other in whom cerebral oedema worsened) were not considered to be related to Org 25969 administration; once again, both made full recovery following appropriate treatment.

There were no major HR and BP changes following administration of Org 25969 and these did not differ between the various doses (Figures 3–5).

**Discussion**

Org 25969 was specifically developed to reverse the neuromuscular block produced by rocuronium. This study demonstrated that Org 25969 dose-dependently reversed a rocuronium neuromuscular block when given at the reappearance of T\(_2\) after being maintained at a profound level for 2 h or more. A dose–response relationship has previously also been observed for neostigmine,\(^{16,17}\) although the time course is different, being much faster for Org 25969.

The mean time to recover TOF to 0.9 decreased from 6 min 49 s in the group receiving 0.5 mg kg\(^{-1}\) Org

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**Table 3** Number of subjects with adverse events considered by the investigator to be possibly, probably or definitely related to treatment, by dose group (all subjects treated group)

<table>
<thead>
<tr>
<th>Org 25969 dose group (mg kg(^{-1}))</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
<th>6.0</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rigors</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Agitation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Polyuria</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
25969 to 1 min 22 s in the 4.0 mg kg\(^{-1}\) group. Recovery occurred within 4 min with all doses of Org 25969 from 1.0 to 6.0 mg kg\(^{-1}\), and within 3 min at doses of 2.0–4.0 mg kg\(^{-1}\). The reversal was sustained without any evidence of recurarization. These recovery times and dose ranges are similar to those previously reported when Org 25969 was administered at reappearance of \(T_2\) after a single bolus dose of rocuronium.\(^{14}\) Thus, the effective dose of Org 25969, when given at the first signs of recovery, appears to be independent of whether neuromuscular block was produced by a single bolus dose or several maintenance doses of rocuronium.
Even though there is a progressive reduction in the average time taken to attain the TOF ratio of 0.9 (Table 2), the relationship shown in Figure 2 indicates the 2, 4 and 6 mg doses to lie on the plateau of the dose–response curve, giving these data points little statistical leverage. The doses selected for this study were based on the other studies conducted with Org 25969 following single doses of rocuronium. However, in retrospect, it might have been useful to include a placebo group or groups given different doses at the lower end of the dose range used rather than the group given the 6.0 mg kg\(^{-1}\) dose.

Preclinical studies and studies in human volunteers have demonstrated the ability of Org 25969 to reverse profound neuromuscular block induced by rocuronium.\(^{12,13,18,19}\) The results of an animal study, by Epemolu and colleagues,\(^{20}\) showed that Org 25969 reversed profound blockade within 10 min of administration of rocuronium with no muscarinic side-effects. Others have reported that Org 25969 produced rapid and efficacious reversal of rocuronium-induced profound neuromuscular block with no signs of postoperative residual curarization (PORC) or curarization in Rhesus monkeys.\(^{18}\) Because cyclodextrins are generally more water-soluble and biologically better tolerated than most small synthetic host molecules,\(^{7,21}\) they do not by themselves have any appreciable activity in the body as shown by the successful use of several cyclodextrins as pharmaceutical excipients to increase water solubility, stability or bioavailability of lipophilic drugs, as well as the absence of any significant drug-related side-effects in this and previous clinical studies.

We used acceleromyography (AMG) for monitoring neuromuscular block in the present study which may not be considered as gold standard by some. However, the use of monitoring based on the principle of AMG is now widespread. It has been the method of monitoring in the only published Phase I study\(^{22}\) and in all the Phase II studies with Org 25969 (currently published as abstracts only and exemplified in references 13–15). Although it has been recommended to use mechanomyography (MMG) in Phase I and II studies of new compounds,\(^{23}\) and while accepting that the values obtained with MMG and AMG may not be interchangeable, several workers have suggested that AMG can be used with confidence for neuromuscular monitoring provided a TOF ratio of 0.9 or more is used to denote adequate recovery.\(^{24–26}\) While some recent studies have suggested that a TOF ratio of 1.0 should be aimed for to denote adequate recovery using AMG monitoring,\(^{27}\) the general consensus is to attain a TOF ratio of 0.9 or more using this technique.\(^{24,28}\)

PORC and recurarization always remain a risk following the use of NMBAs even for those with an intermediate duration of action.\(^{29}\) Even intermediate acting nondepolarizing neuromuscular blocking drugs have a relatively prolonged effect and a slow offset, and are, therefore, not ideal for short procedures. Moreover, a rapid reversal of blockade is critical in emergency situations such as a ‘cannot intubate, cannot ventilate’ scenario. In addition, none of the available reversal agents, such as neostigmine or edrophonium, are capable of reliably reversing profound blockade.\(^{31,12}\) Side effects preclude the
use of higher doses of anticholinesterase agents. Consequently, there is a need for a reversal agent with greater efficacy and safety that would be fast acting, lead to complete recovery and be able to reverse profound blockade. Based on the studies in human volunteers and on early studies in patients given rocuronium, this may be feasible with Org 25969.13,15

There were minimal effects on HR and arterial pressure following Org 25969 administration. As the drug does not act via the nicotinic receptors or by influencing the liberation or metabolism of acetylcholinesterase, there are no muscarinic side-effects associated with its use. Such effects are responsible for the side-effects observed with the use of anticholinesterase agents requiring the concomitant use of anticholinergic drugs. The anticholinergic drugs, in particular atropine, may produce undesirable tachycardia and/or arrhythmias.30,31 The absence of cardiovascular and other muscarinic effects during the process of reversal will be of great advantage in patients with cardiovascular and respiratory disease. Org 25969 was well tolerated. Any side effects were transient and even those considered by the investigators to be probably related to Org 25969 administration, were transient and even those considered by the investigators to be probably related to Org 25969 administration, resolved with the patients making a full recovery. Other clinical studies with Org 25969 have generally confirmed this profile.

In conclusion, this study shows that Org 25969, at a dose of 2–4 mg kg⁻¹, is both safe and effective in reversing rocuronium-induced neuromuscular block, when given at reappearance of T₃ after profound blockade maintained with repeated rocuronium dosing. A dose–response effect is observed in the time to recover the TOF ratio to 0.9.

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