Reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients

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Editor’s key points

- The efficacy of sugammadex in older patients has not been defined.
- Reversal of profound rocuronium block (PTC 2) was compared in older and younger patients.
- Full recovery was achieved with sugammadex in all patients but was slower in the older ones.
- Age-related cardiovascular changes are a possible explanation.

Background. This study compared the reversibility of rocuronium-induced profound neuromuscular block with sugammadex in younger and older patients.

Methods. Fifteen younger (20–50 yr) and 15 older (≥70 yr) patients were sequentially enrolled in this study. After induction of anaesthesia and laryngeal mask insertion, contraction of the adductor pollicis muscle in response to ulnar nerve stimulation was quantified using acceleromyography during 1.0–1.5% end-tidal sevoflurane and remifentanil anaesthesia. All patients initially received rocuronium 1 mg kg⁻¹, followed by 0.02 mg kg⁻¹ when a post-tetanic count (PTC) of 1 or 2 was observed. After completion of surgery, at reappearance of 1–2 PTC, the time required for a single bolus dose of 4 mg kg⁻¹ sugammadex to produce recovery to a train-of-four (TOF) ratio of 0.9 was recorded.

Results. There were no differences in the total dose of rocuronium administered between the younger [mean (sd): 93.4 (17.5) mg] and the older [97.5 (32.2) mg] groups. In all patients, adequate recovery of the TOF ratio to 0.9 was achieved after administration of sugammadex, although it was significantly slower in the older [3.6 (0.7) min, P<0.0001] than in the younger group [1.3 (0.3) min]. There were no clinical events attributable to recurarization.

Conclusions. Sugammadex can adequately restore neuromuscular function in older patients, although a longer time is required to recover from profound rocuronium-induced neuromuscular block than in younger patients.

Keywords: age factors; monitoring, neuromuscular function; neuromuscular block, antagonism; neuromuscular block, rocuronium; sugammadex

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Traditionally, anticholinesterases have been used to antagonize residual non-depolarizing neuromuscular block. However, they have limited efficacy in adequately reversing profound neuromuscular block induced by neuromuscular blocking agents with an intermediate duration of action.¹⁻⁵ For example, the time from administration of rocuronium 0.45 mg kg⁻¹ to recovery of the train-of-four (TOF) ratio to 0.9 could not be significantly shortened by the maximum dose of neostigmine 0.07 mg kg⁻¹ given 5 min after rocuronium (mean value: 42.1 min) in adult patients when compared with the time for spontaneous recovery (54.3 min).³ It is therefore recommended that antagonism with neostigmine should be delayed until at least the second twitch of the TOF response is detectable to completely restore neuromuscular function.⁵ Even in these circumstances, it takes up to 10 min to achieve the full effect of anticholinesterases.⁷ In comparison, sugammadex, a modified gamma cyclodextrin, is a selective relaxant binding agent specifically designed to encapsulate rocuronium,⁸ which can, therefore, promptly restore neuromuscular function regardless of any levels of neuromuscular block as the dose is increased.⁹⁻¹¹ If the marked reductions in recovery time are replicated in routine clinical practice, sugammadex contributes to save time and has the potential to be cost-effective compared with neostigmine.¹² Chemically encapsulating the rocuronium molecule with sugammadex results in a rapid decrease in plasma concentration of free rocuronium and induces rocuronium molecules to extensively diffuse from the neuromuscular junction into plasma along the concentration gradient of free rocuronium.¹³ Therefore, in older patients with a low cardiac output¹⁴ and regional blood flow,¹⁵ a slower increase in the plasma concentration of sugammadex and a slower facilitated recovery by sugammadex would be expected, when compared with younger adults. However, the age-related change in the efficacy of sugammadex has not been completely investigated. The only study¹⁶ carried out in elderly patients showed a slower recovery from the time of reappearance of the second twitch in the TOF to a TOF ratio of 0.9 following sugammadex 2 mg kg⁻¹ with increasing patient age. The average time of 3.6 min required
to attain a TOF ratio of 0.9 in patients aged ≥75 yr is significantly longer when compared with the 2.3 min in younger adults aged 18–64 yr. The efficacy of sugammadex in the reversal of deep neuromuscular block in the elderly has not been examined. Therefore, the aim of this study was to compare the reversibility of profound rocuronium-induced neuromuscular block, quantified by a mode of the post-tetanic counts (PTCs), with sugammadex between younger and older patients.

**Methods**

After approval of the protocol by the Hospital Ethics Committee on Human Rights in Research, 30 adult female patients consented to participate in this study. Patients were ASA physical status I–III, aged between 20 and 50 yr (younger) or ≥70 yr (older), and undergoing elective gynaecological surgery under general anaesthesia. None of the patients had neuromuscular, hepatic, or renal disorders, or were taking any drug known to interact with neuromuscular blocking agents. Patients whose BMI was ≥25 or <18.5 were excluded from the study. Premedication consisted of ranitidine 150 mg administered orally before going to bed on the day before surgery and on the morning of surgery. On arrival at the operating theatre, all patients were monitored with ECG, non-invasive arterial pressure, and pulse oximetry. Ringer’s solution (8–10 ml kg⁻¹ h⁻¹) was given i.v. in the right forearm. Patients were sequentially enrolled into the study groups on the basis of their age; each group comprised 15 patients. The neuromuscular block was monitored at the adductor pollicis muscle. General anaesthesia was induced with fentanyl 2–4 µg kg⁻¹ and propofol 2.5 mg kg⁻¹ i.v. while patients received 100% oxygen through an anaesthetic facemask. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anaesthesia was maintained with sevoflurane 1.0–2.2% with 3–5% Esmol. After loss of consciousness, a laryngeal mask was inserted without the aid of neuromuscular blocking agents. Anaesthesia was induced with propofol 2.0–2.5 mg kg⁻¹ i.v. and was maintained with fentanyl 0.2–0.3 µg kg⁻¹ min⁻¹ and nitrous oxide 50–60%. Skin temperature over the adductor pollicis muscle was recorded every 15 s throughout the experiment using a surface probe in the acceleromyograph and maintained at >36°C using a warming mattress blanket (Thermacare™ and Medi-Therm II™, Gaymer Industries, Inc., NY, USA) and warmed i.v. fluids. Skin temperature over the adductor pollicis muscle was recorded every 15 s throughout the experiment using a surface probe in the acceleromyograph and maintained at >36°C. After a stable depth of anaesthesia was obtained, the ulnar nerve at the wrist was stimulated supramaximally with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s. Contraction of the ipsilateral adductor pollicis muscle was measured using an acceleromyograph (TOF-Watch SX™, Organon Ltd, Dublin, Ireland). All data were collected on a computer and monitored throughout the study. After the control TOF, stimuli were administered for a minimum of 10 min to stabilize the TOF responses. Then, all patients received rocuronium 1 mg kg⁻¹ i.v. The ulnar nerve was repeatedly stimulated at a TOF mode at 2 Hz every 15 s. A PTC mode was initially applied 5 min after obtaining complete neuromuscular block and repeated every 6 min. Whenever 1 or 2 PTCs were observed, rocuronium 0.02 mg kg⁻¹ was given until the end of the surgical procedure. All patients received sugammadex 4 mg kg⁻¹ when a PTC of 1–2 was present after the last dose of rocuronium, and the time required for facilitated recovery to a TOF ratio of 0.9 was recorded. The TOF ratio of 0.9 normalized by the baseline TOF ratio was monitored. Sevoflurane and remifentanil were continued during recovery from neuromuscular block. Patients were monitored for postoperative respiratory events, such as respiratory distress and decrease in SpO₂, caused by recurarization, for 24 h after operation.

The sample size was calculated based on previous data on the averaged recovery time from profound rocuronium-induced neuromuscular block to a TOF ratio of 0.9, facilitated by sugammadex 4 mg kg⁻¹ in younger adult patients [1.7 (0.7) min]. We considered a 50% increase (2.55 min) in the recovery time to be clinically relevant. To obtain statistically significant results with α=0.05 and a power of 0.80 required 12 patients in each group. To compensate for any dropouts, we enrolled 15 patients in each group. Data are presented as mean (so) and (range). Statistical analysis was performed using the StatView™ software for Windows (SAS Institute, Cary, NC, USA). The unpaired Student’s t-test was used for comparing data between the two groups. A P-value of <0.05 was considered statistically significant.

**Results**

Data from all the 30 patients could be included in the analyses. The mean age in the younger patients was 38.4 (3.5) yr and 75.9 (6.1) for the older group (Table 1). The duration of anaesthesia was significantly longer in older [177.5 (45.7) min, P=0.0015] than in the younger patients [118.5 (32.8) min]. However, the total dose of rocuronium given did not differ between the older [97.5 (32.2) mg] and the younger groups [93.4 (17.5) mg]. In all the patients, sugammadex was given at a PTC of 1–2. The time for facilitated recovery to a TOF ratio of 0.9 was significantly longer in the older [3.6 (0.7) (2.4–4.5) s, P<0.0001] than in the younger adults group [1.3 (0.3) (0.8–2.0) s]. There were no clinical events attributable to recurarization with rocuronium after operation.

| Table 1 Patient characteristics. Data are presented as mean (so) (range). |
|-----------------|-----------------|-----------------|
| Monitoring muscle | Younger adult | Elderly |
| Age (yr) | 38.4 (3.5) (32–46) | 75.9 (6.1) (70–91) |
| Weight (kg) | 57.2 (4.0) | 55.9 (8.6) |
| Height (cm) | 164.0 (7.5) | 156.0 (10.0) |
Discussion

This study shows that the speed of facilitated recovery from profound rocuronium-induced neuromuscular block with sugammadex 4 mg kg \(^{-1}\) is age-related. The total recovery time to a TOF ratio of 0.9 in older patients is approximately three-fold longer than that in younger adults (3.6 vs 1.3 min). Although sugammadex is extremely useful to restore neuromuscular function even from profound rocuronium-induced neuromuscular block irrespective of age when compared with neostigmine, caution is recommended when using sugammadex, even with neuromuscular monitoring, especially in older patients.

Our results show that, even in older patients, reversal with sugammadex does not have to be delayed until the second twitch of the TOF response or spontaneous respiration is detectable, as is required with neostigmine. This indicates that a profound depth of neuromuscular block can be maintained during anaesthesia right up to the end of the surgery. For some thoracic and abdominal surgery, PTC stimulation is used to maintain a sufficient depth of neuromuscular block. A PTC level of at least 5 is required to achieve total diaphragmatic paralysis in response to tracheal suction.\(^3\) So far, PTC stimulation has been clinically used to estimate the approximate interval to reappearance of the first twitch in response to TOF stimulation during intense neuromuscular block.\(^4\) However, the rapid reversal effects of sugammadex are changing the use of PTC for maintaining deep neuromuscular block during clinical anaesthesia. The present study could contribute to this by demonstrating the safety and effectiveness of reversing a deep rocuronium-induced neuromuscular block with sugammadex.

Our study does not elucidate why complete recovery from an intense rocuronium-induced neuromuscular block after administration of sugammadex is slower in older patients. However, the onset of action of sugammadex injected is likely to be dependent on cardiac output and muscle blood flow. Especially in females, cardiac output decreases modestly with an age-related decline in heart rate.\(^5\) Limb blood flow decreases progressively with advancing age, even in healthy men.\(^6\) This lower blood flow may be explained by age-related reduced vascular conductance, the loss of muscle volume, and decline in oxygen consumption. Age-associated arteriosclerosis also contributes to further decrease in peripheral perfusion. A lower regional blood flow would result in a slower increase in the plasma concentration of sugammadex and a slower decrease in the plasma concentration of free rocuronium. Hence, free rocuronium molecules cannot rapidly diffuse from the neuromuscular junction into the plasma. Therefore, it seems reasonable that an age-related reduction in cardiac output and muscle blood flow is a primary cause of the slower recovery of neuromuscular function after sugammadex.

Volatile anaesthetics cause marked peripheral vasodilation. If simultaneously, arterial pressure can be maintained and cardiac output can be increased, a greater blood flow to the peripheral tissues will be expected during inhalation anaesthesia. This was verified in younger patients. When receiving 0.8–1.2% isoflurane in combination with 66% nitrous oxide, muscle blood flow in the forearm progressively increased in patients 18–34 yr of age. In contrast, forearm blood flow in patients 60–79 yr of age significantly decreased when compared with baseline values during isoflurane anaesthesia.\(^7\) Although sevoflurane, as was used in our study, has quite similar cardiovascular actions to isoflurane, sevoflurane-induced reduction of left ventricular function, such as end-diastolic volume, ejection fraction, and cardiac output, is much greater in magnitude when compared with isoflurane.\(^8\) It can therefore be estimated that the peripheral blood flow might have typically decreased in the older patients in our study. These changes in blood flow to peripheral tissues produced by sevoflurane may have contributed to the age-related variation in the recovery with sugammadex from rocuronium-induced neuromuscular block.

We did not strictly fix the end-tidal concentration of sevoflurane to an age-adjusted minimum alveolar concentration (MAC) value and used a concentration of 1–1.5% according to routine clinical practice. This means that elderly patients may have received a greater MAC. Sevoflurane significantly enhances the effect of neuromuscular blocking agent\(^9\) and therefore, the efficacy of sugammadex may theoretically be diminished during sevoflurane anaesthesia. However, sugammadex has been shown to be equally effective for reversal of rocuronium-induced neuromuscular block during sevoflurane or propofol anaesthesia.\(^10\) It is therefore conceivable that sevoflurane does not pharmacodynamically inhibit chemical binding between rocuronium and sugammadex. In contrast, it remains possible that the difference in sevoflurane concentration between the two groups may affect the reduction in cardiac output and regional blood flow as mentioned above and consequently change actions of sugammadex in older patients. In addition, the longer duration of sevoflurane anaesthesia in the older patients may have contributed.

In conclusion, sugammadex can restore neuromuscular function in older patients. However, a longer time is required for recovery from profound rocuronium-induced neuromuscular block than in younger patients. Further studies are warranted to examine the effective dose of sugammadex required in older patients for more rapid reversal of neuromuscular block.

Conflict of interest

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