Reversal of rocuronium-induced neuromuscular block with sugammadex in heart failure patients: a prospective observational study

G. CAMMU (*), D. COART (*), K. DE GRAEVE (*) and R. BEELEN (**)
restore neuromuscular function in older patients following profound rocuronium-induced neuromuscular block, despite requiring a longer recovery time than in younger patients (8). These findings in older patients supported those of another study in which 2 mg/kg of sugammadex was given for the reversal of a moderate rocuronium-induced neuromuscular block (9). The present trial was designed to assess the hemodynamic stability and efficacy of 2 mg/kg of sugammadex in the reversal of rocuronium-induced neuromuscular block, specifically in patients with heart failure.

Methods

Patients

This was a single-centre study, conducted from January to March 2012. Twelve patients aged 18 years or older who were categorized as American Society of Anesthesiologists (ASA) class 3-4 and NYHA class 2-4 and who had an ejection fraction ≥ 25% were eligible for the study. They were scheduled to undergo elective surgery for cardiac resynchronization therapy, an automated ICD, or battery replacement of an ICD or biventricular pacemaker with general anesthesia. Patients were excluded from the study for the following reasons: they were expected to have a difficult intubation for anatomical reasons, or they had a neuromuscular disorder, a personal or family history of malignant hyperthermia, or a known allergy to medication used during general anesthesia. All subjects were required to give written informed consent before enrolment in the study. Ethical approval for this study (Ethical Committee N° 2011/073) was provided by the Ethical Committee of the Onze-Lieve-Vrouwe Ziekenhuis, Aalst, Belgium (Chairperson Dr A. Leloup) on 22 November 2011 (Belgian Registry N° B126201112363). Trial registration: ClinicalTrials.gov Identifier: NCT01509651.

Study Procedures

An IV cannula was inserted into the vein at the elbow. Routine monitoring included electrocardiography, pulse oximetry, invasive arterial pressure (left radial artery), and central venous pressure (right jugular vein). Anesthesia was induced and maintained with IV induction agents, IV opioids, inhaled anesthetics, and other agents according to each patient’s clinical needs. Central temperature was maintained above 36°C by forced-air warming. Neuromuscular function was monitored by acceleromyography of the adductor pollicis muscle using the TOF-Watch® SX acceleromyograph (Organon Ireland Ltd., a division of Merck and Co., Inc., Swords, Co., Dublin, Ireland). Preload to the thumb was applied by attaching a commercially available hand adapter (Organon). Neuromuscular transmission monitoring started after the induction of anesthesia (before rocuronium administration) and continued at least until recovery of the TOF ratio to 0.9 after the administration of sugammadex. Repetitive TOF stimulation was stable, calibration and supramaximal stimulation were assured by the in-built calibration function; namely, TOF-Watch® SX calibration was performed > 3 min after a 5-s, 50-Hz tetanic stimulation and was preceded by a 1-min repetitive TOF stimulation. After calibration, at least 2 min of repetitive TOF stimulation were required before the administration of rocuronium. In addition, peripheral body temperature was measured continuously by a thermistor at the thenar eminence of the palm and maintained at ≥ 32°C during neuromuscular transmission monitoring. Each patient received a single IV bolus rocuronium dose of 0.6 mg/kg, and after the T1 response ceased to be effected in the TOF stimulation mode, tracheal intubation was performed. Spontaneous recovery was allowed to progress until the re-appearance of the second twitch of the TOF response. Maintenance doses of 0.1 mg/kg of rocuronium were then permitted. Upon the reappearance of the second twitch at the end of surgery, patients received a single IV bolus dose of 2 mg/kg of sugammadex for reversal. If necessary, anesthesia was continued to allow the block to recover spontaneously after administration of (the last dose of) rocuronium until the appearance of T2.

Study End Points

The primary efficacy variable was the time from the start of sugammadex administration to recovery of the normalized TOF ratio to 0.9. The baseline TOF ratio (i.e., before the onset of the neuromuscular block) was used to normalize TOF ratios during recovery from the block (e.g., 0.9 × baseline TOF ratio resulted in a corrected TOF ratio of 0.9). Safety was assessed based on the incidence of perioperative adverse events, as well as by vital signs (heart rate and blood pressure) and
respiratory events (SpO₂ < 90% and/or signs of airway obstruction), prior to transfer to and discharge from the postanesthesia care unit (PACU). All data are presented as means, medians, standard deviations and/or ranges.

Study Assessments

After the bolus injection of 0.6 mg/kg of rocuronium, the onset time to maximum twitch depression was recorded. The time to spontaneous return of T2 was also noted. Vital signs were recorded while the patients were under anesthesia and at 2, 5, 10, and 30 min after the administration of sugammadex. Continuous cardiac and respiratory monitoring was performed throughout anesthesia and postoperatively in accordance with routine practice. Core body temperature was measured intraoperatively in the distal esophagus. Oxygen saturation was monitored for the duration of each patient’s stay in the PACU. Evidence of recurrence of a neuromuscular blockade was sought by clinical assessment, the evaluation of any respiratory problems, or a significant decrease in the TOF ratio to less than 0.8 in patients still under anesthesia. PACU nurses caring for the patients documented the following events during the first 30 min of PACU admission: symptoms of muscle weakness, the number of patients with episodes of hypoxemia (SpO₂ < 90%), the lowest SpO₂ observed, the requirement for either tactile or verbal stimulation to maintain an SpO₂ greater than 90%, and any clinical evidence of airway obstruction requiring any airway maneuver (e.g., a head-tilt, chin-lift, or jaw-thrust maneuver, placement of a nasal or oral airway, or re-intubation). All collected data were stored on a PC.

RESULTS

Table 1 shows the patients’ baseline characteristics. Four patients had associated pulmonary disease, while 3 had a smoking history. After the intraoperative bolus injection of rocuronium 0.6 mg/kg was administered, the onset time to maximum twitch depression was 1.97 ± 0.54 min. The time to spontaneous return of T2 was 52.1 ± 12.4 min. Four patients required maintenance doses of rocuronium in all 12 patients, sugammadex was administered at T2, and adequate recovery of the corrected TOF ratio to 0.9 was achieved. The time for recovery to a normalized TOF ratio of 0.9 was 2.78 ± 0.67 min after the start of sugammadex administration (Table 2). The duration of anesthesia was 71.6 ± 12.8 min.

Blood pressure remained relatively stable in all patients for up to 10 min after the administration of sugammadex and then increased by the time of the 30 min assessment. Heart rate was relatively stable up to 10 min after the administration of sugammadex. At 30 min after sugammadex administration, the heart rate was higher (Table 3). Upon arrival in the PACU, the body temperature was 36.4 ± 0.3 °C. Three patients had episodes of SpO₂ < 90% in the PACU; the lowest SpO₂ in the PACU was 93.8 ± 7.6% (range: 78-100). Stimulation was required to maintain the SpO₂ > 90% during the PACU stay in 3 patients, and 3 patients required an airway maneuver. No patients exhibited symptoms of muscle weakness in the PACU. No patient was reintubated. The PACU length of stay was 183 ± 53 min. There were no sugammadex-related adverse events reported, and there were no reports of neuromuscular block reoccurrence. One patient developed a pacemaker-mediated tachycardia postoperatively, which was resolved by reprogramming the device.

DISCUSSION

To our knowledge, this is the first study to assess the efficacy and safety of 2 mg/kg of
is frequently observed, which may lead to increased dosing regimen, tachycardia rather than bradycardia older patients (13). Moreover, depending on the also associated with adverse effects, typically in acetylcholinesterase inhibitors, these agents are concentration increases the risk of cardiac dysrhythmias (12). While the co-administration of anticholinergic agents can reduce the adverse effects of acetylcholinesterase inhibitors, these agents are also associated with adverse effects, typically in older patients (13). Moreover, depending on the dosing regimen, tachycardia rather than bradycardia is frequently observed, which may lead to increased myocardial oxygen consumption and ischemia (12). A decreased clearance and decreased initial distribution volume of neostigmine contribute to its prolonged duration of action in older people (14). This may be a potential advantage, as the duration of most non-depolarizing neuromuscular blocking agents is also prolonged in older adults. However, in patients with a reduced clearance of neostigmine, it may precipitate bradycardia or an atrioventricular block, especially when combined with shorter-acting atropine.

Our results show that, in heart failure patients, it takes longer for these patients than healthy, younger patients to recover from a moderate rocuronium-induced neuromuscular block after the administration of 2 mg/kg of sugammadex (6, 15). The median recovery times in the referenced studies were 1.3 and 1.2 min, respectively. Moreover, there was a pronounced inter-individual variability in the reversal time in our study. Suzuki and colleagues had previously reported that 4 mg/kg of sugammadex administered at a post-tetanic count of 1-2 could reverse profound rocuronium-induced neuromuscular block within 3.6 min in elderly patients (8). Recently, the same authors showed the total recovery time from moderate rocuronium-induced neuromuscular block with 2 mg/kg of sugammadex in elderly patients to be approximately 3 min (16). A full recovery is therefore likely to be obtained irrespective of the depth of neuromuscular block when an appropriate dose of sugammadex is given, even in elderly patients. The reversal time in older patients was, however, significantly greater than that in younger adults (8). An inverse correlation between the speed of facilitated recovery with sugammadex from a rocuronium-induced neuromuscular block and cardiac output has been confirmed (16). The authors concluded that regulation of the delivery rate of sugammadex to the peripheral muscles by the cardiac output had a profound effect on the recovery to a TOF ratio of 0.9.

The hemodynamic profile of a 0.6 mg/kg bolus of rocuronium is acceptable for patients with cardiovascular disease (17). Despite this safety profile, rocuronium exhibits an increased onset time in elderly patients, possibly as the result of a less dynamic circulation in elderly people and, thus, an increased transfer time to the effector site. An increased onset time in elderly patients has been demonstrated for pancuronium, vecuronium, rocuronium, mivacurium, and cisatracurium (18). Furthermore, rocuronium has an increased duration of action in elderly patients as the result of decreased elimination of the drug (3, 18, 19). The decreases in total body water and liver mass that normally accompany aging are likely explanations

<table>
<thead>
<tr>
<th>Time point</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
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<tr>
<td>2 min</td>
<td>-0.3 ± 7.7</td>
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<td>5 min</td>
<td>5.5 ± 12.9</td>
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<td>10 min</td>
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<td>30 min</td>
<td>33 ± 19.5</td>
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<td>Diastolic BP (mmHg)</td>
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<tr>
<td>2 min</td>
<td>1.1 ± 6.0</td>
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<tr>
<td>5 min</td>
<td>3.4 ± 7.9</td>
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<tr>
<td>10 min</td>
<td>-0.5 ± 12.7</td>
</tr>
<tr>
<td>30 min</td>
<td>6.6 ± 19.5</td>
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<tr>
<td>Heart rate (beats/min)</td>
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<tr>
<td>2 min</td>
<td>-0.7 ± 4.3</td>
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<tr>
<td>5 min</td>
<td>-1.3 ± 5.5</td>
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<tr>
<td>10 min</td>
<td>-1.5 ± 6.8</td>
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<tr>
<td>30 min</td>
<td>7.9 ± 10.4</td>
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Table 3
Mean changes of systolic and diastolic blood pressure and heart rate from baseline (i.e., immediately before sugammadex administration) to time points following sugammadex administration.

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for the pharmacokinetic changes found in the elderly. After the bolus injection of 0.6 mg/kg of rocuronium, we recorded an onset time to maximum twitch depression of 1.97 ± 0.54 min. The mean times to the onset of maximum block after the administration of 0.6 mg/kg of rocuronium were 1.0 and 1.1 min under anesthesia with desflurane and isoflurane, respectively, in adult ASA class 1-2 patients (20). In our study, the time to spontaneous return of T2 was 52.1 ± 12.4 min, while the time from administration of rocuronium to the reappearance of T2 was 40.6 ± 13.9 min in the Staals control group and 32.9 ± 9.2 min in the Plaud sugammadex group. 

In conclusion, sugammadex can adequately restore neuromuscular function in heart failure patients and its use is associated with hemodynamic stability. We confirmed that the reversal effect of sugammadex is markedly slower in patients with a lower cardiac output, as observed in cardiovascular failure.

Acknowledgements

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References