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CLINICAL REPORT

Possible augmentation of neuromuscular blockade by propofol during recovery from rocuronium

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Abstract Propofol is a widely used drug in anesthesia practice, and its pharmacological characteristics are well known. However, propofol is not known for neuromuscular effects. As part of clinical neuromuscular monitoring, the neuromuscular responses to train-of-four (TOF) stimulation were monitored and recorded. We observed, in two cases of balanced anesthesia maintained by desflurane and fentanyl, that administration of a small dose of propofol during almost complete recovery from rocuronium in two patients resulted in marked decreases of both T1 (first twitch response of the TOF) and the TOF ratio. This neuromuscular block dissipated in both patients without any subsequent neuromuscular effects. These two observations provide visual confirmation of the possible impact of propofol on recovery from a rocuronium neuromuscular blockade.

Keywords Neuromuscular blockade · Rocuronium · Propofol · Drug interaction · Train-of-four

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Introduction

The augmentation of neuromuscular blocking drugs (NMBDs) by volatile anesthetics has been well defined [1]. In contrast, interactions with intravenous drugs have been less precise and more diverse in their responses [2, 3]. We describe two cases of unanticipated propofol-induced augmentation of NMB during recovery from a single intravenous 0.3 mg/kg dose of rocuronium.

NMB was documented by train-of-four (TOF) monitoring in response to stimulation of the ulnar nerve. After the normal neuromuscular function had recovered to about 80% of normal T1 twitch tension and TOF ratio, a small bolus dose of propofol was given to augment depth of anesthesia. The NMB immediately intensified. Subsequently, NMB dissipated within 20–30 min. At the end of the surgical procedures, in one patient recovery from NMB was spontaneous. Neostigmine was used to reverse the block in the other patient. Both patients were tracheally extubated uneventfully. We concluded that the use of propofol can substantially intensify a rocuronium neuromuscular blockade.

Case reports

Case 1

A healthy 30 year-old woman (166 cm, 50 kg) was scheduled for an elective mandibular osteotomy to correct a previous traumatic mandibular fracture. She denied any allergies or neuromuscular problems and was not receiving other medications. All her previous anesthetic experiences had been uneventful. The family history was negative for anesthetic-related complications. Her airway appeared normal, despite

the mandibular asymmetry. In addition to the standard anesthetic monitors, the TOF-Watch SX neuromuscular monitor was attached to the forearm of the patient; this monitor included two electrodes, a temperature sensor, and an accelometric sensor that quantifies and records the strength of contraction of the adductor pollicis muscle.

After midazolam 2 mg IV had been given preoperatively, anesthesia was induced by the IV administration of propofol 120 mg and fentanyl 100 μg. When the patient was unresponsive, neuromuscular monitoring was initiated. The TOF-Watch SX was calibrated over 2 min, and all readings were recorded in a connected portable computer. A train-of-four (TOF) stimulus of 50–60 mA was delivered every 15 s. Additional propofol 50 mg IV and fentanyl 50 mcg IV were given with no change in T1 or the TOF ratio. Immediately thereafter, rocuronium 15 mg IV (0.3 mg/kg) was given. The response to TOF stimulation disappeared 3 min after rocuronium administration. Endotracheal intubation was easily accomplished.

Ventilation was controlled sufficiently to maintain an end-tidal CO_2 between 32 and 38 mmHg. Anesthesia was maintained with inhaled 6–8% desflurane and oxygen/air mix. Fentanyl 50 μg was also given in incremental IV doses throughout the procedure. Twenty-two minutes after administration of rocuronium, responses to peripheral nerve stimulation started to appear (T1 of 14%). Eighteen minutes later, T1 and the TOF ratio were 80% of control and 82%, respectively. No clinical signs of light anesthesia such as tachycardia, hypertension, or sweating were evident. Shortly thereafter, in response to an announced painful stimulus (sawing and grinding on the denuded mandibular bone), fentanyl 50 μg IV and propofol 50 mg IV were given. No other changes were made at that time. Five minutes later, the T1 and TOF ratio decreased to 54% and 48%, respectively, of normal baseline (Fig. 1). A technical reason for the decreased TOF was ruled out by independent providers (anesthesia technician, anesthesia attending), including the possibility of injecting remaining rocuronium from the IV tubing. Twenty minutes later, the T1 and TOF ratio returned to 74% and 79%, respectively, and after another 12 min to 100%, which was sustained. The procedure lasted 4 h more and was uneventful. After discontinuation of desflurane, the trachea was extubated.

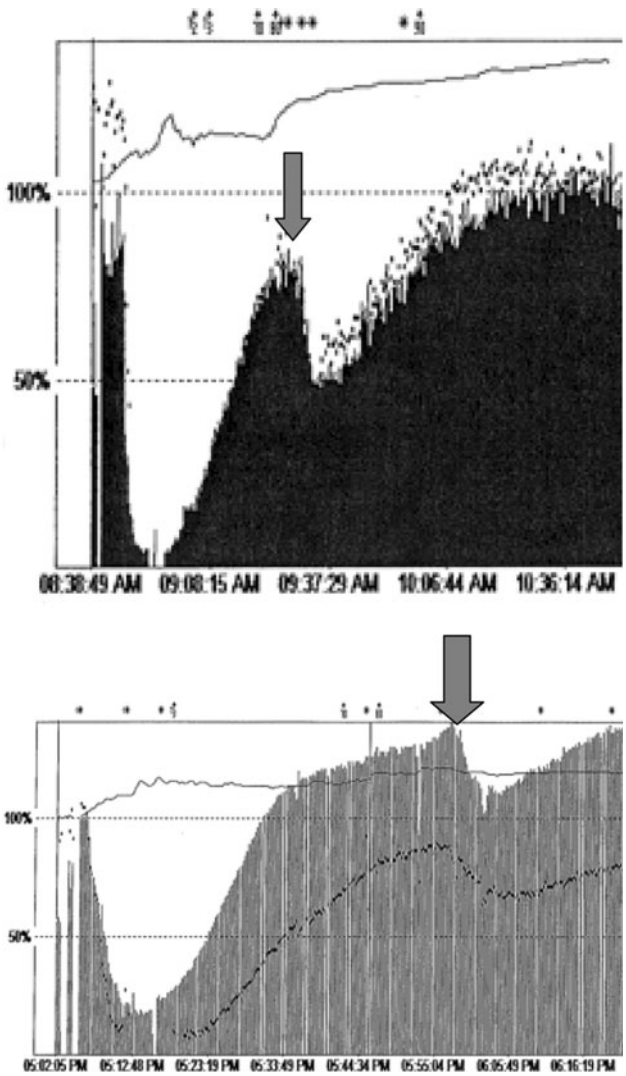

Fig. 1 Depression of train-of-four (TOF) ratio from propofol. *Gray arrows* indicate administration of propofol bolus. *x* axis, time; *y* axis, magnitude of TOF. In the first case, rocuronium 15 mg IV (0.3 mg/kg) was given at 0845. Via a separate printout, we had recorded percent change in the first twitch of the TOF (T1) and the TOF ratio. By 0849, T1 and TOF ratio were 6% of control and 0%, respectively. At 0925, T1 and TOF ratio had recovered to 80% and 82%, respectively, at which time fentanyl 50 μg followed by propofol 50 mg IV was given, which resulted in a partial enhancement of neuromuscular blockade. T1 and TOF ratio decreased to 54% and 48% of normal in 5 min. Twenty minutes later (0950), T1 and TOF ratio recovered to 74% and 79% of normal. In the second case, rocuronium 14 mg IV (0.3 mg/kg) was given at 1705. Fentanyl 25 μg IV was given at 1747. At 1755, recovery from rocuronium was 136% of control (T1) and the TOF ratio was 88%; propofol 20 mg IV was then given, which resulted in a partial restoration of neuromuscular blockade. At 1812, the T1 and TOF ratio were 125% of control and 73%, respectively. At 1822, the T1 and TOF ratio were 135% of control and 82%, respectively. Note time scales

Case 2

A 22-year-old woman (149 cm, 46 kg) was scheduled for functional endoscopic sinus surgery to remove nasal and frontal sinus polyps. This patient had well-controlled insulin-dependent diabetes mellitus. Furthermore, she previously had Hirschsprung's disease, which was surgically treated when she was 1 year old. Although she had mild decreases in vital capacity and forced expiratory volume in 1 s (both in the 90% ranges of expected), she had not been hospitalized except for an elective admission for high-dose antibiotic therapy. She denied any allergies. Her

medication on the day of surgery included azithromycin 500 mg orally (three times per week for sinusitis relapse prophylaxis), and other medications for symptom control of cystic fibrosis, such as mucolytic substances and enzyme substitution. Her insulin treatment was subcutaneous Humalog NPH (9 units a.m., 4 units p.m.), and subsequent doses were adjusted using a sliding scale. There were no known neuromuscular abnormalities. This patient had previous anesthetics for colon resection, takedown of a colostomy, and repeated nasal polyp resections. All anesthetics had been tolerated well, and the family history was negative for anesthesia-related complications. The airway was normal.

After midazolam 2 mg IV had been given preoperatively, she was transferred into the operating room (OR) where standard anesthetic monitors and the TOF-Watch SX were applied. Anesthesia was induced by propofol 80 mg IV and fentanyl 50 μg IV. After induction of anesthesia, the TOF-Watch SX was calibrated, and rocuronium 14 mg (0.3 mg/kg) was given IV. One hundred fifty seconds after administration of rocuronium (TOF ratio $< 30\%$), the trachea was intubated uneventfully. Three minutes later, the TOF ratio decreased to less than 10% (Fig. 1, lower TOF tracing). Anesthesia was maintained with 6–8% inhaled desflurane and intermittent fentanyl 25–50 μg IV boluses.

Forty-two minutes after administration of rocuronium, both the T1 and TOF ratio had recovered to 80%. To augment depth of anesthesia, the clinical anesthesiologist gave propofol 20 mg IV. Six minutes later, both the T1 and TOF ratio decreased (see Fig. 1). In 15 min, the TOF ratio recovered to 70%. After an additional 10 min, recovery continued to 80%. Another 20 min later, the TOF ratio was 90%. As with the first case, technical problems and possible inadvertent injection of rocuronium were again ruled out. On finishing the procedure, neostigmine 5 mg IV and glycopyrrolate 1 mg IV were given, and the trachea was then extubated.

Both patients had an uneventful postoperative recovery and were discharged on the first postoperative day.

Discussion

Our first thought was that upon injection of the propofol, a small rocuronium dose that still remained in the IV tubing might have been subsequently flushed into the patient. However, this potential error did not occur because as a routine each substance had been flushed in with an appropriate bolus of saline.

Also, a technical defect or wrong use of the monitoring device had been ruled out in both cases.

Nondepolarizing NMBDs, such as rocuronium, can be enhanced by acidosis, hypocalcemia, hypermagnesemia, hypothermia, and concomitant medications, such as various antibiotics, steroids, beta-adrenergic receptor antagonists, calcium channel blockers, local anesthetics, and diuretics [2, 3]. Prolonged duration and augmentation of neuromuscular blockade with the combination of a NMBD and volatile anesthetics are well known. We demonstrate the first visualized recordings of a propofol-induced TOF augmentation of a nondepolarizing NMBD (Fig. 1). We had given several intermittent doses of fentanyl previously without any change in TOF; therefore, primary attention was given to propofol.

Propofol is used in routine clinical anesthesia because of its many desirable qualities including a rapid onset of action and a dose-dependent rapid and reliable recovery [4, 5]. However, propofol is not known to block postsynaptic receptors and to produce a neuromuscular blockade as documented by peripheral nerve stimulation [3, 6, 7]. When given in the presence of other anesthetics and rocuronium, propofol can augment neuromuscular blockade, as illustrated by the patients presented in this report. Perhaps propofol only produces its possible weak neuromuscular effects in the presence of other drugs such as volatile anesthetics and a partial NMB from a drug such as rocuronium [8]. Yet, propofol seems to be different than other intravenous anaesthetics. For example, propofol provides useful tracheal intubating conditions in the absence of NMBDs, presumably because of depressed laryngeal and pharyngeal reactivity [9]. Could a weak NMB be involved from propofol? [9].

Because of its pharmacodynamic profile, propofol is one of the preferred anesthetics to acutely treat light or inadequate anesthesia. Many of the medications and conditions that would enhance NMBDs can be retrospectively excluded in our two cases. In the second patient, who was a diabetic, the neuromuscular junction may be more sensitive to a drug such as propofol. However, the first patient had no such condition except for having received desflurane.

Whether the described augmentation of NMB by propofol is clinically important is speculative. A comparably small dose of rocuronium had been used; however, even with a TOF ratio of 70%, recovery from NMB cannot automatically be considered sufficient for airway protection and sufficient spontaneous ventilation [10]. These cases suggest that a formal randomized controlled trial (RCT) should investigate the possible reproducibility, dose dependence, drug interactions, and interindividual variations. In essence, these case reports have two major conclusions. First, routine monitoring of neuromuscular function will facilitate detection of unexpected augmentation of NMB. Second, propofol is one of the drugs that can

augment a neuromuscular blockade from rocuronium and possibly all nondepolarizing NMBDs.

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Conflict of interest None.

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