Short communications

Recovery of neuromuscular blockade caused by vecuronium is delayed in patients with hypertriglyceridemia

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Abstract
We investigated the effects of hypertriglyceridemia on the onset and recovery of neuromuscular blockade, induced by vecuronium, over the adductor pollicis muscle, electromyographically. Eighteen adult patients with hypertriglyceridemia (hypertriglyceridemia group) and 18 healthy patients with normal serum triglyceride (control group) were studied. The supramaximal stimulating current for train-of-four (TOF) in the hypertriglyceridemia group was significantly higher than that in the control group (45.7 ± 16.7 vs 31.5 ± 9.8 mA; mean $\pm$ SD; $P = 0.004$). The onset of vecuronium 0.1 mg·kg^{-1}-induced neuromuscular blockade in the hypertriglyceridemia group did not significantly differ from that in the control group (240 ± 60 vs 279 ± 88 s; $P = 0.132$). Times from vecuronium to the return of T1, T2, T3, and T4 in the hypertriglyceridemia group were significantly longer than those in the control group (31.4 ± 6.2 vs 25.5 ± 6.2 min for T1; $P = 0.008$). During recovery from neuromuscular blockade, T1/control did not differ between the two groups. However, the TOF ratios (T4/T1) in the hypertriglyceridemia group were significantly lower than those in the control group 80–120 min after vecuronium ($P < 0.05$). We conclude that, in patients with hypertriglycemidemia, a higher current is needed to elicit supramaximal response of the adductor pollicis muscle, and recovery from vecuronium-induced neuromuscular blockade is delayed.

Key words Vecuronium · Hypertriglyceridemia · Train-of-four

It has been reported that some patients with hypertriglyceridemia show signs of an asymptomatic motor and/or sensory and/or autonomic axonal polyneuropathy [1]. McManis et al. [2] showed neuropathy associated with hypercholesterolemia and hypertriglyceridemia. They noted that, in some patients with hypertriglyceridemia, compound muscle action potential amplitudes

were low [2]. We demonstrated previously that recovery of vecuronium-induced neuromuscular blockade was delayed in patients with hypercholesterolemia [3]. It has been postulated that hypertriglyceridemia, as well as hypercholesterolemia, causes neuropathy [3]. If motor nerve or skeletal muscle is impaired, the supramaximal stimulating current at which the maximal response of skeletal muscle contraction can be elicited becomes high, and the action of neuromuscular relaxants is exaggerated [4,5]. However, no previous study has investigated the monitoring of neuromuscular blockade in patients with hypertriglyceridemia.

After institutional ethics committee approval and written informed consent were obtained, 18 adult patients, American Society of Anesthesiologists (ASA) physical status I-II, who had hypertriglyceridemia (hypertriglyceridemia group), and 18 adult patients, ASA I-II, with normal plasma triglyceride (control group) were included in this study. For this study, hypertriglyceridemia was defined as plasma triglyceride more than 150 mg·dl^{-1}. This criterion was in accordance with that in previous reports [6]. In all patients in the two groups, the plasma triglyceride concentration was measured at least twice before the surgical procedure. Patients in whom the concentration was above normal limits each time were allocated to the hypertriglyceridemia group. Patients in whom the concentration was within normal limits in each examination were assigned to the control group. The plasma triglyceride concentration determined just prior to the surgical procedure was adopted as the true plasma triglyceride value in the patients studied. Patients with hypercholesterolemia, defined as a plasma total cholesterol of more than 220 mg·dl^{-1}, were excluded from this study. The patients were scheduled for elective surgery under general anesthesia. No patient in the hypertriglyceridemia group had known of their hypertriglyceridemia before hospitalization or had been treated for hypertriglyceridemia. No patient in either group had neuromuscular, hepatic,

renal, or cardiac disorders. Additionally, no patient had diabetes mellitus or was receiving any drugs known to affect the action of neuromuscular blocking drugs.

Premedication consisted of diazepam 5–10 mg, given orally 1 h before induction of anesthesia. After the patients arrived in the operating theater, two stimulating electrodes were positioned over the ulnar nerve at the wrist. Two recording electrodes were attached over the adductor pollicis muscle. Anesthesia was induced with propofol $1.5 \, mg \cdot kg^{-1}$ and fentanyl $2 \mu g \cdot kg^{-1}$. After loss of the eyelid reflex, train-of-four (TOF) stimuli were applied every 20 s, using an electrical nerve stimulator of a neuromuscular transmission module (M-NMT Module; GE Healthcare, Helsinki, Finland). Four single-twitch stimuli, consisting of 0.2-ms-duration square-waves were delivered at 2 Hz. The corresponding electromyographic amplitudes were quantified using the neuromuscular transmission module, and were displayed on an anesthetic monitoring system (Anaesthetic Monitoring System A/S3; Datex-Ohmeda, Helsinki, Finland). For each patient, the monitoring system searched automatically for the stimulus current needed to achieve the maximal response of the adductor pollicis muscle.

Once the supramaximal current had been established, the electromyographic amplitude of T1 was considered to be the control value. The control value was again determined 10 min after starting TOF stimuli, which were applied every 20 s, as recommended previously [7,8]. During the stabilization of neuromuscular monitoring, the lungs were ventilated using a facemask with oxygen $6 \, l \cdot min^{-1}$ and sevoflurane 2.0% of inspired concentration. If the bispectral index was above 60, a bolus dose of propofol $0.5 \, mg \cdot kg^{-1}$ was given. After the recording of the control value, vecuronium $0.1 \, mg \cdot kg^{-1}$ was administered intravenously and the trachea was intubated.

After vecuronium injection, TOF stimuli were continuously applied every 20 s. The onset of neuromuscular blockade (time from vecuronium to the disappearance of the TOF response) was compared between the groups. Also, times from vecuronium to the return of T1, T2, T3, and T4 (the first, second, third, and fourth response of the TOF) were compared between the groups. After vecuronium, T1/control was compared every 10 min between the groups. Similarly, the TOF ratio was compared every 10 min between the groups.

Anesthesia was maintained with nitrous oxide 66% in oxygen and sevoflurane 1.7% end-tidal concentration. A bolus dose of fentanyl $2 \mu g \cdot kg^{-1}$ was administered intravenously before skin incision. Whenever the level of anesthesia was thought to be inadequate, a supplemental bolus of fentanyl $2 \mu g \cdot kg^{-1}$ was administered. Ventilation was controlled to maintain normocapnia ($P_{ET_{CO_2}}$, 32–37 mmHg). The rectal and surface skin temperatures over the adductor pollicis muscle were measured.

Patient characteristics were compared between the groups using the χ^2 test or unpaired t-test. The supramaximal stimulating currents, times to the onset of neuromuscular blockade, and times to the return of T1, T2, T3, or T4 were compared between the groups using unpaired t-tests. Comparison of T1/control or the TOF ratio during recovery from neuromuscular blockade between groups was done using analysis of variance (ANOVA) and the unpaired t-test with Bonferroni's adjustment. All values for results are expressed as numbers or means ± SD (range). A P value of less than 0.05 was considered statistically significant.

Patient characteristics were comparable in the two groups (Table 1). As shown in Table 1, plasma triglyceride was significantly higher in the hypertriglyceridemia group than in the control group ($P < 0.001$). Plasma total cholesterol did not significantly differ between the hypertriglyceridemia group and the control group ($P = 0.280$). The supramaximal stimulating current in the hypertriglyceridemia group was significantly higher than that in the control group (45.7 ± 16.7 vs 31.5 ± 9.8 mA; $P = 0.004$). The onset of neuromuscular blockade in the hypertriglyceridemia group was similar to that in the control group (240 ± 60 vs 279 ± 88 s; $P = 0.132$). Time from vecuronium to return of T1 in

Table 1. Patient characteristics in the two groups

	Hypertriglyceridemia ($n = 18$)	Control ($n = 18$)	P value
Sex (male/female)	6/12	8/10	0.480
Age (years)	61 ± 13	54 ± 9	0.084
Height (cm)	161 ± 9	159 ± 6	0.458
Weight (kg)	60 ± 9	55 ± 7	0.060
Triglyceride ($mg \cdot dl^{-1}$)	202 ± 51 (154–335)	131 ± 7 (120–140)	<0.001
Total cholesterol ($mg \cdot dl^{-1}$)	189 ± 20 (143–219)	181 ± 23 (142–217)	0.280

Values are numbers or means ± SD (ranges). Sex, age, height, weight, and total cholesterol were similar in the two groups. The value for plasma triglyceride was significantly higher in the hypertriglyceridemia group than in the control group
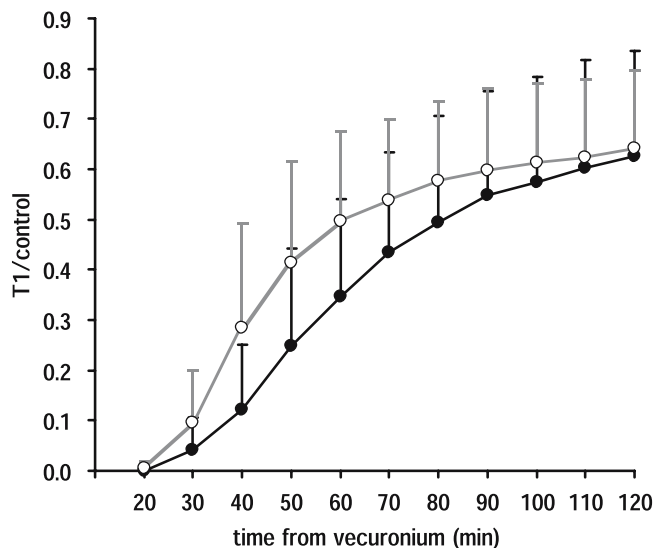
Fig. 1. Recoveries of T1/control after administration of vecuronium $0.1\,mg\cdot kg^{-1}$ in the hypertriglyceridemia (*closed circles*) and control (*open circles*) groups. Values are means ± SD
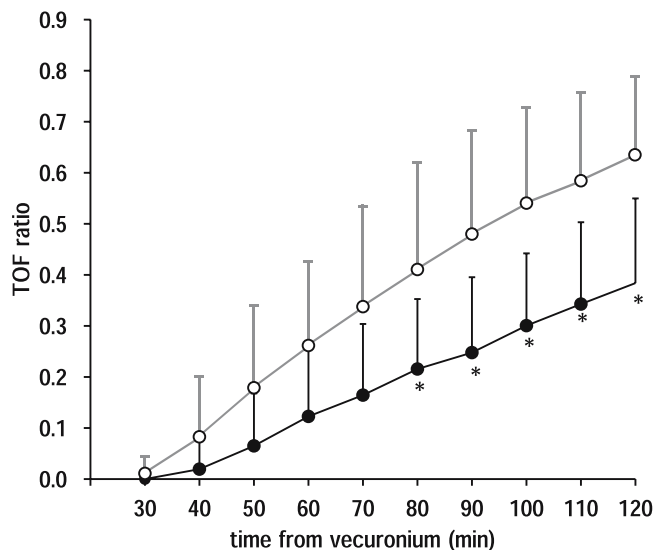
Fig. 2. Recoveries of train-of-four (*TOF*) ratio after administration of vecuronium $0.1\,mg\cdot kg^{-1}$ in the hypertriglyceridemia (*closed circles*) and control (*open circles*) groups. Values are means ± SD. *$P < 0.05$ between the two groups

the hypertriglyceridemia group was significantly longer than that in the control group ($31.4 ± 6.2$ vs $25.5 ± 6.2\,min$; $P = 0.008$). Also, times from vecuronium to return of T2, T3, and T4 in the hypertriglyceridemia group were significantly longer than those in the control group ($46.2 ± 12.2$ vs $34.1 ± 7.9\,min$; $P = 0.001$ for T2, $55.9 ± 16.5$ vs $40.5 ± 10.7\,min$; $P = 0.002$ for T3, and $58.4 ± 16.7$ vs $42.9 ± 11.4\,min$; $P = 0.003$ for T4). During recovery from neuromuscular blockade, T1/control did not significantly differ between the two groups (Fig. 1). However, the TOF ratios in the hypertriglyceridemia group were significantly lower than those in the control group 80–120 min after vecuronium ($P < 0.05$; Fig. 2). In no patient did the rectal temperature or peripheral temperature over the adductor pollicis muscle decrease to less than $35.5°C$ or $32.0°C$, respectively.

Drory et al. [1] described that some patients with hypertriglyceridemia showed signs of an asymptomatic motor and/or sensory and/or autonomic axonal polyneuropathy. In their study, nerve conduction velocities were abnormal in some hypertriglyceridemic patients [1]. McManis et al. [2] also reported that neuropathy was associated with hypertriglyceridemia. In their study, although no patient with hypertriglyceridemia had muscle weakness on manual strength testing, compound action potential amplitudes were low in one of six hypertriglyceridemic patients [2]. Moreover, they showed that needle electromyography revealed fibrillation potentials in foot muscles in hypertriglyceridemic patients [2]. Thus, motor nerve and skeletal muscle are thought to be damaged in hypertriglyceridemic patients.

It has been shown that if motor nerve or skeletal muscle is impaired, the supramaximal stimulating current at which the maximal response of skeletal muscle contraction can be elicited becomes high [4], and the action of neuromuscular relaxants is exaggerated [4,5]. In hypertriglyceridemic patients, probably because motor nerve and skeletal muscle are impaired [3], the supramaximal stimulating current becomes higher and recovery from neuromuscular blockade is delayed [3].

The return of T1, T2, T3, or T4, and T1/control indicates the degree of neuromuscular blockade at the postjunctional region of the neuromuscular junction, i.e., the muscle membrane [9]. In this study, the return of T1, T2, T3, or T4 was delayed, which suggested that the skeletal muscle could be damaged in hypertriglyceridemic patients. The TOF ratio represents the neuromuscular blocking effect in the prejunctional region, i.e., the nerve ending [9]. The present study showed that recovery of T1/control was not retarded, but that of the TOF ratio was delayed. Based on this, damage of the nerve ending may be more apparent than that of the skeletal muscle in hypertriglyceridemic patients.

As noted above, the delayed recovery of neuromuscular blockade in hypertriglyceridemic patients is thought to be due to damaged motor nerve and skeletal muscle. However, several previous studies have revealed that hypertriglyceridemia might cause liver dysfunction [10,11]. In patients with liver dysfunction, of course, the duration of action of vecuronium is prolonged [12,13]. The prolonged duration of vecuronium-induced neuromuscular blockade in hypertriglyceridemic patients may occur partially because of liver dysfunction.

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