J Anesth (2005) 19:302–308
DOI 10.1007/s00540-005-0336-y

Journal of
Anesthesia

Review article

Drugs to facilitate recovery of neuromuscular blockade and muscle strength

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Abstract
Several drugs that quicken recovery from neuromuscular blockade caused by vecuronium in anesthetized patients are reviewed. Ulinastatin, a protease inhibitor, is thought to promote the release of acetylcholine at the neuromuscular junction and increases hepatic blood flow and urine volume. For this reason, ulinastatin quickens recovery from neuromuscular blockade in anesthetized patients receiving vecuronium. Additionally, pretreatment with ulinastatin avoids prolongation of vecuronium-induced neuromuscular blockade in patients with hepatic cirrhosis. Gabexate mesilate is also a protease inhibitor. During a continuous infusion of gabexate mesilate, recovery from neuromuscular blockade was quickened. Amino acid-enriched solution supplies energy to the skeletal muscles and causes an increase in muscle strength. An infusion of amino acid-enriched solution hastens recovery from neuromuscular blockade in anesthetized patients. When amino acids supply energy to the skeletal muscles, they simultaneously produce heat in the skeletal muscles. This thermal generation may be closely related to fast recovery from neuromuscular blockade. Amino acid-enriched solution makes recovery from neuromuscular blockade quick and avoids hypothermia during general anesthesia. Milrinone, a phosphodiesterase III inhibitor, is supposed to increase the release of acetylcholine at the neuromuscular junction and make the neuromuscular junction sensitive to acetylcholine. Therefore, recovery from neuromuscular blockade is hastened. Nicorandil enhances membrane K^+ conductance in skeletal muscle and increases contraction of the skeletal muscle. Thus, nicorandil quickens recovery from neuromuscular blockade.

Key words Vecuronium · Protease inhibitor · Amino acid · Phosphodiesterase III inhibitor · Potassium channel agonist

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Received: June 30, 2004 / Accepted: May 11, 2005

Introduction

More than a decade ago many calcium channel blockers were reported to enhance the action of nondepolarizing neuromuscular relaxants [1–3]. Calcium channel blockers inhibit the release of acetylcholine at the neuromuscular junction and enhance the degree of neuromuscular blockade [1–3]. In anesthetized patients receiving calcium channel blockers, the duration of neuromuscular blockade is prolonged. On the other hand, we have recently documented that several drugs hasten recovery from neuromuscular blockade caused by vecuronium. This article reviews these drugs.

Protease inhibitor

Ulinastatin

Ulinastatin, a protease inhibitor, is often given to patients with acute pancreatitis or acute circulatory insufficiency [4–6]. Protease inhibitors are thought to promote the release of acetylcholine at the neuromuscular junction [7,8]. Thus, by the possible mechanism of protease inhibitor homologues, they enhance muscle contraction in response to motor nerve stimulation [7]. For this reason, patients receiving ulinastatin would become resistant to neuromuscular relaxant. Furthermore, it has been reported that ulinastatin increases hepatic blood flow and urine volume [8–11]. Vecuronium is eliminated mainly in the liver and partially in the kidney [12–15]. Therefore, administration of ulinastain results in an increase in hepatic and renal clearance of vecuronium.

In our previous study [8], ulinastatin 5000 U/kg and normal saline were given, respectively, in the ulinastatin and control groups just before administration of vecuronium 0.1 $mg \cdot kg^{-1}$. The patients were anesthetized with nitrous oxide 66%, oxygen 33%, isoflurane 0.5%, and fentanyl. The depth of neuromuscular blockade was

monitored mechanically using a force displacement transducer. The ulnar nerve was stimulated via surface electrodes, and the corresponding adduction of the thumb was quantified using the force displacement transducer. Before administration of vecuronium, twitch heights of T1, T2, T3, and T4—the first, second, third, and fourth responses in a train-of-four (TOF)—were measured, and the control twitch height (twitch height of T1) was recorded for all patients. After administration of vecuronium, the posttetanic count (PTC) was measured every 5 min in the two groups. Also, the T1/control and the TOF ratio (T4/T1) were evaluated every 10 min. Recovery of the PTC, T1/control, and TOF ratio were compared between the two groups. PTC, T1/control, and TOF ratio were significantly higher in the ulinastatin group than in the control group (Fig. 1). Recovery from neuromuscular blockade was measured for 120 min in the previous study [8]. However, the ulinastatin-induced effect on the recovery from neuromuscular blockade lasted for only 70 min. This result would be related to the fact that the plasma half-life of ulinastatin is as short as 33 min in humans [16].

Ulinastatin pretreatment in patients with hepatic cirrhosis

As noted above, vecuronium is eliminated mainly in the liver. Upton et al. [11] reported that more than 40% of the vecuronium dose was recovered in the bile in rats. Bencini et al. [12] showed that in cats after administration of vecuronium 70% of the dose of vecuronium was recovered: 40% in the bile, 15% in the liver, and 15% in the kidney. The duration of neuromuscular blockade produced by vecuronium is substantially prolonged in patients with hepatic cirrhosis [13]. Lebrault et al. [13] demonstrated a 44% increase in the elimination half-life of vecuronium and a 100% increase in the duration of the recovery rate of neuromuscular blockade in patients with liver cirrhosis receiving vecuronium when compared with those measured in healthy patients.

We studied the effect of ulinastatin given prior to the administration of vecuronium in anesthetized patients with hepatic cirrhosis [9]. We found that times from vecuronium to the return of T1, T2, T3, or T4, those for the T1/control to return to 0.10, 0.25, 0.50, or 0.75, recovery index (time to recovery of T1/control from 0.25 to 0.75), and those for TOF ratio to return to 0.70 were significantly delayed in the cirrhosis group compared to the cirrhosis/ulinastatin (5000 U·kg^{-1}) and control groups; and all of them in the cirrhosis/ulinastatin group were, interestingly, almost equal to those in the control group (Table 1). This study clearly indicates that after pre-treatment of ulinastatin, the speed of recovery from vecuronium-induced neuromuscular blockade in patients with liver cirrhosis becomes similar to that seen in healthy patients. To avoid prolongation of the neuromuscular blockade caused by vecuronium in patients with hepatic cirrhosis, the pre-treatment of ulinastatin may be of clinical benefit.

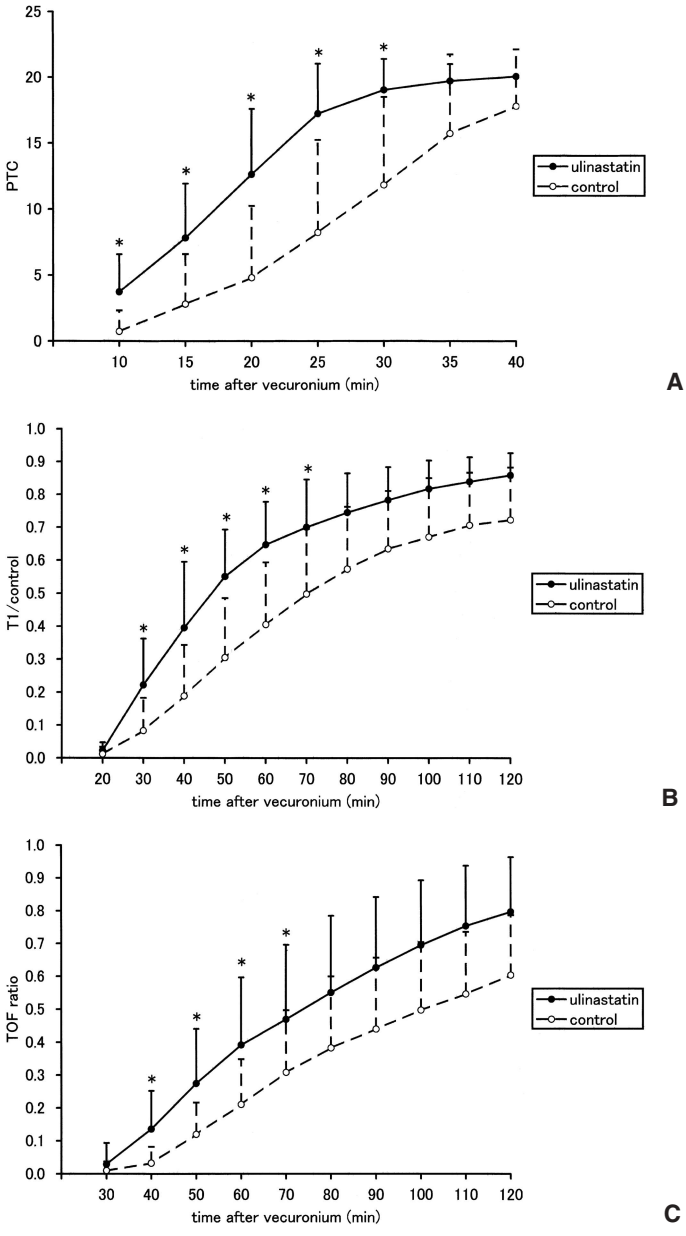

Fig. 1. Recovery of the post-tetanic count (*PTC*) (**A**), T1/control (**B**), and train-of-four (*TOF*) ratio (**C**) in the ulinastatin (●) and control (○) groups. Values are means ± SD. *$P < 0.05$ between the groups. (From [8], with permission.)

Gabexate mesilate

Gabexate mesilate, a protease inhibitor, is commonly administered for the treatment of acute pancreatitis [17]

Table 1. Times from administration of vecuronium to the return of twitch height values, recovery of the T1/control, recovery index and recovery of the TOF ratio: cirrhosis/ulinastatin vs. cirrhosis vs. controls

Group	Cirrhosis/ulinastatin	Cirrhosis	Control
Returns			
To T1 (min)	26.5 ± 8.8[a]	35.2 ± 8.1	26.7 ± 7.6[a]
To T2 (min)	39.0 ± 10.8[a]	48.5 ± 9.5	36.9 ± 9.1[a]
To T3 (min)	46.6 ± 11.1[a]	57.0 ± 11.6	43.1 ± 10.5[a]
To T4 (min)	49.3 ± 11.5[a]	61.0 ± 13.8	45.9 ± 11.0[a]
Recovery			
T1/control to 0.10 (min)	36.5 ± 11.8[a]	49.2 ± 12.5	34.5 ± 9.2[a]
T1/control to 0.25 (min)	49.3 ± 13.6[a]	65.0 ± 23.2	45.0 ± 10.1[a]
T1/control to 0.50 (min)	67.9 ± 21.7[a]	98.5 ± 41.9	63.4 ± 18.2[a]
T1/control to 0.75 (min)	93.7 ± 26.2[a]	143.7 ± 59.7	86.3 ± 28.0[a]
Recovery index (min)	44.3 ± 16.1[a]	77.4 ± 42.0	42.7 ± 21.1[a]
Recovery of TOF ratio to 0.70 (min)	112.1 ± 22.2[a]	160.2 ± 47.8	110.9 ± 32.1[a]

TOF, train-of-four
Values are the mean ± SD
[a] Times from administration of vecuronium 0.1 mg·kg^{-1} to the returns of T1, T2, T3, or T4; times to the recoveries of T1/control 0.10%, 0.25%, 0.50%, or 0.75%; recovery index (time to recovery of T1/control from 0.25 to 0.75); and times to the recoveries of TOF ratios to 0.70 in the cirrhosis/ulinastatin and control groups were significantly shorter than in the cirrhosis group ($P < 0.05$)

and disseminated intravascular coagulation syndrome [18]. In the same way as ulinastatin, gabexate mesilate is thought to release acetylcholine at the neuromuscular junction [7,8]. It has been also shown that gabexate mesilate reduces ischemia/reperfusion-induced hepatic injury and prevents the ischemia/reperfusion-induced decrease in bile flow in rats [19]. This hepatoprotective effect against ischemia/reperfusion injury has been also reported in humans [20]. Moreover, gabexate mesilate inhibits a decrease in hepatic microcirculation in rats with acute pancreatitis [21]. If gabexate mesilate increases hepatic blood flow and bile flow, elimination of vecuronium would be accelerated. We previously investigated the recovery from neuromuscular blockade caused by vecuronoium during continuous infusion of gabexate mesilate in anesthetized patients.

In patients in the gabexate mesilate group, immediately after administration of vecuronium 0.1 mg·kg^{-1}, a continuous infusion of gabexate mesilate was started at a rate of 1.5 mg·kg^{-1}·h^{-1}. Times to the recovery of the T1/control to 0.25 or 0.50, and recovery of the T1/control or TOF ratio at the adductor pollicis muscle were compared between the two groups. Time to the recovery of the T1/control to 0.25 or 0.50 were significantly shorter in the gabexate mesilate group than in the control group. The T1/control and TOF ratios in the gabexate mesilate group were significantly higher than in the control group 40–80 min and 40–120 min after administration of vecuronium, respectively.

It is likely that gabexate mesilate increases hepatic blood flow. Therefore, hepatic elimination of vecuronium may be promoted during administration of gabexate mesilate, resulting in accelerated recovery from vecuronium-induced neuromuscular blockade.

In a previous study [22], recovery from neuromuscular blockade was evaluated during continuous administration of gabexate mesilate. It was shown that the half-life of gabexate mesilate in plasma is as short as 55 s in humans [23]. If the infusion of gabexate mesilate is stopped, the gabexate mesilate-induced effect on the recovery from neuromuscular blockade would quickly become trivial.

Amino acid-enriched solution

Amino acid-enriched solution supplies energy to skeletal muscles [24–26]. Branched-chain amino acid (i.e., valine, leucine, isoleucine) are readily available energy substrates [24]. We suggest that an infusion of amino acid-enriched solution may strengthen the contraction of the skeletal muscles and hasten recovery from neuromuscular blockade during general anesthesia.

We previously studied recovery from vecuronium (0.1 mg·kg^{-1})-induced neuromuscular blockade during continuous intravenous infusion of a mixture of 18 amino acids (Amiparen; Otsuka Pharmaceutical, Tokyo, Japan) at a rate of 166 kJ·h^{-1} [27]. Recovery of PTC, T1/control, and TOF ratio were compared between the groups. PTC, T1/control, and TOF ratio in patients receiving amino acid-enriched solution were significantly higher than in the control patients 25–35, 40–120, and 50–120 min after vecuronium, respectively (Fig. 2). These results are based on the fact that amino acid-enriched solution can supply energy to the skeletal muscles. Our study showed that the amino acid-enriched solution-induced effect on recovery

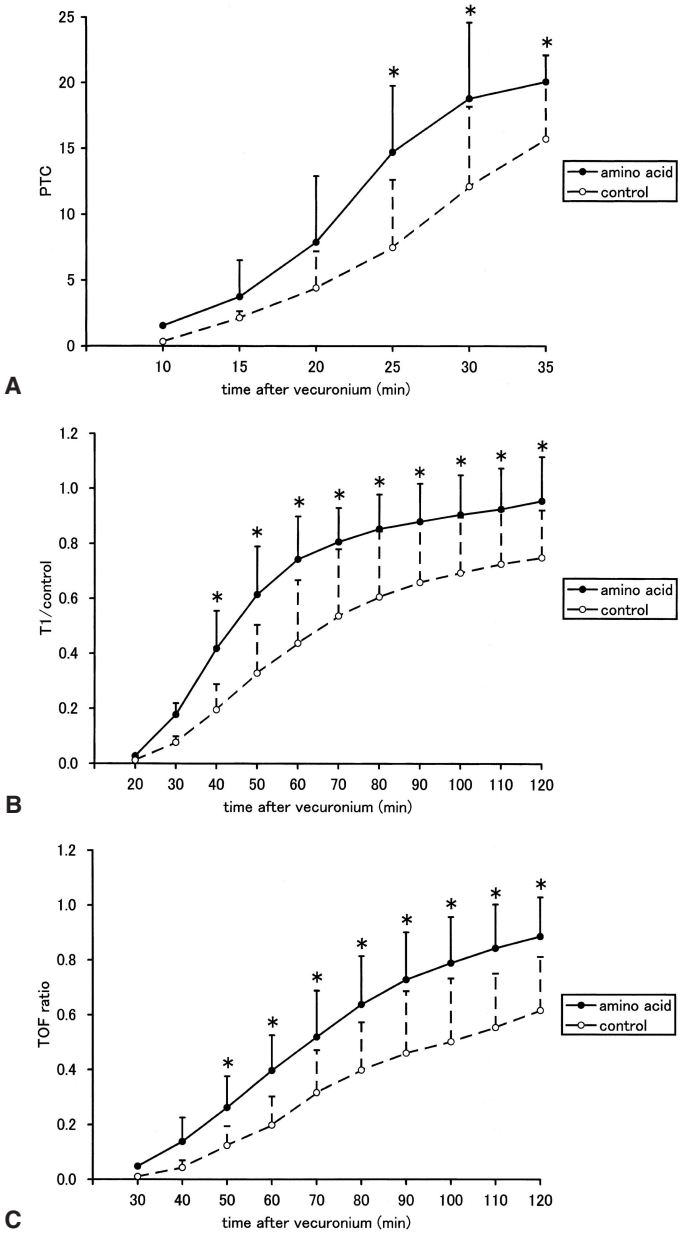

Fig. 2. Recovery of PTC (**A**), T1/control ratio (**B**), and TOF ratio (**C**) in the amino acid and control groups. Values are means ± SD. *$P < 0.05$ between the groups. No difference was observed between the two groups. (From [7], with permission.)

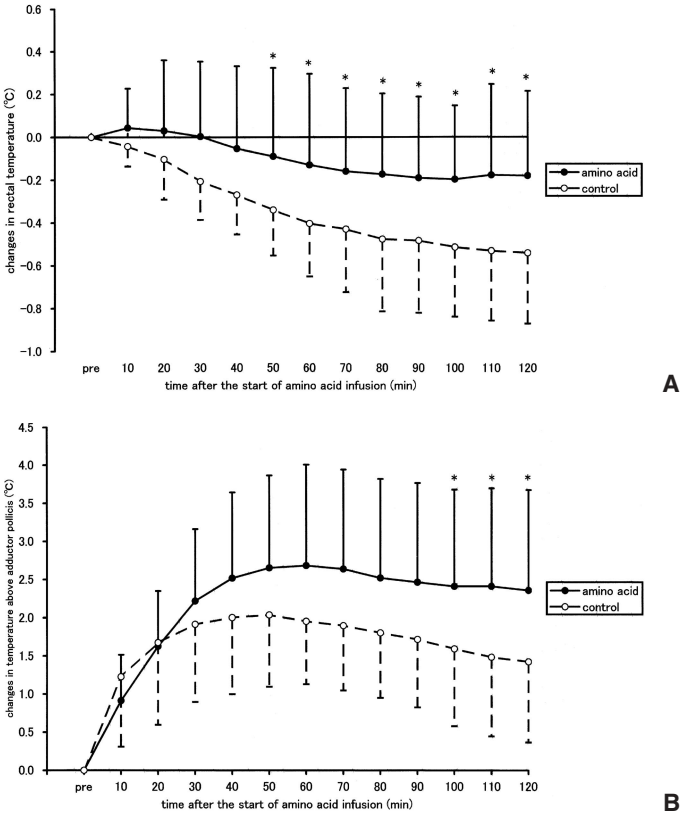

Fig. 3. Changes in rectal temperature (**A**) and temperature (**B**) over the adductor pollicis muscle from baseline measurements during anesthesia in patients in the amino acid and control groups. Values are means ± SD. *$P < 0.05$ between the groups. (From [7], with permission.)

from neuromuscular blockade had an extremely rapid onset.

Nissen et al. [25] reported that, in particular, the leucine metabolite β-hydroxy-β-methylbutyrate caused a significant increase in muscle strength. They also suggested that the leucine metabolite β-hydroxy-β-methylbutyrate prevented or slowed muscle damage as well as partially preventing the increase in proteolysis associated with intense muscular work. Mourier and colleagues [24] showed that the combination of moderate energy restriction and branched-chain amino acid supplementation induced significant and preferential losses of visceral adipose tissue and allowed maintenance of a high level of performance. It has also been reported that the decrease in body temperature that occurs during general anesthesia can be attenuated by a continuous infusion of amino acid-enriched solution [28,29]. This thermal effect of amino acid-enriched solution is thought to be due to the supply of energy to skeletal muscle [28,29].

When amino acids supplies energy to the skeletal muscles, they produce heat simultaneously in the skeletal muscles [26,28,29]. As shown in Fig. 3, the rectal temperature and surface temperature over the adductor pollicis muscle were significantly higher in the patients receiving amino acid infusion than in the control patients 50–120 and 100–120 min after vecuronium in our previous study [27]. However, other studies [28,29] showed that the amino acid-induced heat production became significant only within 20 min during general anesthesia, which was comparable to the amino acid-induced hastening effect on neuromuscular blockade.

Thus, the thermal generation may be closely related to the fast recovery from neuromuscular blockade.

Phosphodiesterase III inhibitor (milrinone)

Milrinone, a phosphodiestrese III inhibitor, has an positive inotropic effect and is often administered to patients with heart failure [30]. Milrinone strengthens not only the contractility of the cardiac muscles but also that of the skeletal muscles. Fujii et al. [31] noted that milrinone enhanced the contractility of the fatigued diaphragm in the rats. It has also been reported that milrinone antagonizes the action of nondepolarizing neuromuscular relaxant in a rat phrenic nerve/hemidiaphragm preparation [32]. The effect of phosphodiestrese III inhibitor on the skeletal muscles is thought to be based on selective inhibition of subtype 1 adenosine receptors (A1 receptors) [33,34]. If the A1 receptors are blocked, the release of acetylcholine increases at the neuromuscular junction [35]. Additionally, milrinone is supposed to augment the sensitivity of the neuromuscular junction to acetylcholine [36].

We previously studied recovery from neuromuscular blockade caused by vecuronium in anesthetized patients during continuous infusion of milrinone [37]. In the previous study [37], 30 min before induction of anesthesia an initial loading dose of milrinone was given at a rate of $5\,\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min followed by a maintenance dose of milrinone at $0.5\,\mu g \cdot kg^{-1} \cdot min^{-1}$ in the milrinone group. These doses were in accordance with those used in the clinical settings [30]. It has been reported that 30 min after the beginning of the initial and maintenance doses the plasma concentration of milrinone was stabilized [38,39]. Normal saline was given continuously in the control group. In the two groups, the times from administration of vecuronium $0.1\,mg \cdot kg^{-1}$ to the return of T1, T2, T3, or T4, the times of recovery of the T1/control to 0.25, 0.50, or 0.75, and the times of recovery of the TOF ratio to 0.25, 0.50, or 0.75 were compared. As shown in Table 2, except for the time of recovery of the T1/control to 0.75 and that of TOF ratio to 0.75, recovery of neuromuscular blockade was significantly faster in the milrinone group than in the control group.

K_{ATP} channel agonist (Nicorandil)

Nicorandil, a K_{ATP} channel agonist is being investigated as an antiischemic drug that may produce cardioprotective effects and enhance functional recovery of the stunned myocardium [40–43]. It has been reported that characteristics of the interaction between K_{ATP} channel agonists and K_{ATP} channel agonists in skeletal muscle and in cardiac muscle are similar [44]. K_{ATP} channel agonists enhance the membrane K^+ conductance in the skeletal muscle and increase the contraction of the skeletal muscle [45–47]. However, Weselcouch et al. [45] noted that the mechanism by which the force of the skeletal muscle was enhanced was not clear. They suggested that the K_{ATP} channel agonist-induced effect on the skeletal muscle was related to direct action on the skeletal muscle or an increase in blood flow due to a vasodilating activity. It was also shown that the K_{ATP} channel agonist might be of therapeutic benefit in patients with muscle paralysis. Spuler et al. [46] reported that, in the absence of neuromuscular relaxant, K_{ATP}

Table 2. Times from administration of vecuronium to the return of twitch height values, recovery of the T1/control, and the TOF ratio: milrinone vs. controls

Group	Milrinone	Control	*P*
Returns			
To T1 (min)	18.5 ± 6.5	23.9 ± 7.3	0.041
To T2 (min)	25.9 ± 7.3	32.1 ± 8.2	0.039
To T3 (min)	30.4 ± 8.2	37.3 ± 9.4	0.040
To T4 (min)	32.4 ± 8.5	39.7 ± 9.8	0.037
Recovery of T1/control			
To 0.25 (min)	32.3 ± 7.1	40.9 ± 10.8	0.015
To 0.50 (min)	42.9 ± 11.5	54.9 ± 16.9	0.032
To 0.75 (min)	74.8 ± 35.6	81.8 ± 39.3	0.061
Recovery of TOF ratio			
To 0.25 (min)	45.5 ± 11.0	57.0 ± 12.3	0.012
To 0.50 (min)	62.3 ± 16.0	77.4 ± 20.5	0.033
To 0.75 (min)	83.5 ± 25.7	101.1 ± 25.4	0.070

Values are the mean ± SD
Time to the returns of T1, T2, T3, or T4, and time to the recovery of T1/control to 0.25 or 0.50, and time to the recovery of TOF ratio to 0.25 or 0.50 in the milrinone group were significantly shorter than in the control group ($P < 0.05$)

channel agonist enhanced muscular response rapidly in patients who had the following diseases: myotonic dystrophy, chondrodystrophic myotonia, hypokalemic periodic paralysis, recessive generalized myotonia, amyotrophic lateral sclerosis, and myositis and in patients without neurological diseases.

We studied the effect of nicorandil on the recovery from neuromuscular blockade after administration of vecuronium in anesthetized patients [48]. Before induction of anesthesia, a bolus dose of nicorandil $0.1\,mg \cdot kg^{-1}$ was administered followed by a continuous infusion at a rate of $1\,\mu g \cdot kg^{-1} \cdot min^{-1}$. Recovery of PTC, the T1/control, or the TOF ratio were measured mechanically during infusion of nicorandil and were compared with those evaluated in control patients receiving normal saline. Also, PTC did not significantly differ between groups. However, the T1/control and TOF ratios in the nicorandil group were significantly higher than in the control group 80–120 min and 100–120 min after administration of vecuronium, respectively.

Thus, it is suggested that the onset of the nicorandil-induced effect on neuromuscular blockade may be slow. However, it was demonstrated that cromakalim, a K_{ATP} channel agonist, induced an effect on healthy human skeletal muscle that had a rapid onset [49]. In the previous study, membrane K^+ conductance was enhanced only a few minutes after administration of cromakalim. Therefore, the nicorandil-induced effect on the recovery from neuromuscular blockade would have a slow onset in anesthetized patients. On the other hand, when the degree of neuromuscular blockade is intense, nicorandil presumably cannot open the blocked K_{ATP} channel. As the level of neuromuscular blockade weakens, the K_{ATP} channel may open and K^+ conductance is enhanced [48]. For this reason, the nicorandil-induced effect on neuromuscular blockade might have been significant, as the degree of neuromuscular blockade subsided in our study.

It has been reported that PTC and the TOF ratio represent the degree of neuromuscular blockade at the prejunctional region of the neuromuscular junction, and the T1/control is related to the depth of neuromuscular blockade in the postjunctional region [1]. As noted above, nicorandil speeds not only recovery of the T1/control but also that of the TOF ratio. Therefore, nicorandil is thought to act at both regions of the neuromuscular junction, resulting in fast recovery from the neuromuscular blockade caused by vecuronium. Similarly, gabexate mesilate and milrinone hasten the recovery of the T1/control and TOF ratios. Ulinastatin and amino acid-enriched solution hasten the recovery of PTC and the T1/control and TOF ratios. Drugs to facilitate recovery from neuromuscular blockade described in this article may act at the pre- and postjunctional regions of the neuromuscular junction.

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