CASE REPORTS

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Human Plasma Cholinesterase for Antagonism of Prolonged Mivacurium-induced Neuromuscular Blockade

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MIVACURIUM, because of its rapid hydrolysis by plasma cholinesterase, has a considerably shorter duration of action than any other currently used nondepolarizing agent.[1] The *in vitro* rate of hydrolysis of mivacurium by plasma cholinesterase was found to be approximately 70% of that of succinylcholine.[2] Prolonged neuromuscular blockade from mivacurium has been reported in patients with plasma cholinesterase deficiency.[3–6] However, no reports exist documenting the use of purified human plasma cholinesterase to antagonize the unanticipated prolonged neuromuscular blockade after mivacurium. In this report, we describe the management of prolonged mivacurium-induced neuromuscular using intravenous plasma cholinesterase.

Case Report

A 23-yr-old woman, ASA physical status 1, scheduled for osteotomy and fusion of the proximal interphalangeal joint of the second toe of the left leg was selected for an institutionally approved study assessing the neuromuscular effects of mivacurium. The patient was 164 cm tall and weighed 80 kg, and physical examination revealed no abnormal physical findings. There was no known history of significant illness in the family, and neither the patient nor anyone in her immediate family had received anesthesia. There was no personal or family history of abnormal response to medications. Results of preoperative routine biochemistry (including liver function tests) and hematology investigations were normal.

Preoperatively, she received 2 mg lorazepam orally. Anesthesia was induced with 5 $mg \cdot kg^{-1}$ thiopental and 2 $\mu g \cdot kg^{-1}$ fentanyl and was maintained with 70% N_2O and 0.4–0.8% inspired isoflurane in oxygen. The concentrations of the isoflurane, nitrous oxide, oxygen, and carbon dioxide were measured continuously by a multiple-gas analyzer (Capnomac, Datex, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal partial pressure of carbon dioxide 35–40 mmHg). Electrocardiogram, pulse oximetry, and arterial blood pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5 ± 0.5°C. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer International). Preload tension on the thumb was maintained at 300 g throughout the procedure.

After stabilization of control responses, 0.15 $mg \cdot kg^{-1}$ mivacurium was administered over 10 s. The first measurable effect (lag time) and complete neuromuscular block (onset time) developed in 24 and 50 s, respectively. Tracheal intubation was carried out 115 s after mivacurium administration, and the conditions were excellent. The patient was kept anesthetized, and monitoring of the neuromuscular block was continued.

No signs of recovery were observed in the neuromuscular function at the usual expected time of about 15 min. The surgery lasted for 112 min, but there was still no measurable degree of recovery, nor was there any evidence of posttetanic response. Serum Cholinesterase P Behring (Behringwerke, Marburg, Germany), equivalent to the plasma cholinesterase activity of 200 ml of adult human plasma, was given. Serum Cholinesterase P Behring is a concentrate of highly purified enzyme. The contents of one vial are equivalent in activity to 500 ml of fresh normal human plasma. After 350 s (5.8 min), no response was detected to peripheral nerve stimulation, and a second dose of Serum Cholinesterase P Behring equivalent to the plasma cholinesterase activity of 125 ml of adult human plasma was administered. After 18.3 min from the administration of the second dose of serum cholinesterase, the response to peripheral nerve stimulation was still absent, and a third dose equivalent to the plasma cholinesterase activity of 175 ml of adult human plasma was administered. At this time, the total dose of Serum Cholinesterase P Behring administered to the patient was equivalent to the plasma cholinesterase activity of 500 ml of adult human plasma. The first sign of recovery of the first twitch (T1) of the TOF was observed 125 s (2.08 min)

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later, and reached 10% of the control tension 600 s (10 min) after the administration of the third dose of Serum Cholinesterase P Behring. Because the rate of recovery was slow, 0.05 mg · kg^{-1} neostigmine with 0.015 mg · kg^{-1} atropine was administered at this time (T1 = 10% of control tension) to hasten the recovery. The T1 recovered to 25%, 50%, and 75% in 150 s (1.75 min), 290 s (4.8 min) and 400 s (6.7 min), respectively, and to a maximum of 100% in 550 s (9.2 min), after neostigmine administration.

The maximum TOF ratio attained was 0.41 in 700 s (11.7 min). At this time, a second dose of 0.025 mg · kg^{-1} neostigmine with 0.007 mg · kg^{-1} atropine was administered. The recovery of TOF ratio was slow and reached a maximum of 0.43 750 s (12.5 min) later. It was decided then to administer a fourth dose Serum Cholinesterase P Behring equivalent to the plasma cholinesterase activity of 250 ml of adult human plasma. It took another 250 s (4.2 min) for the TOF ratio to recover to 0.5. Recovery of the TOF ratio to 0.70 and 0.75 occurred 22.5 and 27.1 min, respectively, after the administration of the fourth dose of Serum Cholinesterase P Behring. Anesthesia then was discontinued, endotracheal tube was removed, and the patient was able to sustain a head-lift for 10 s and cough effectively. The total elapsed time from the first dose of plasma cholinesterase until a TOF ratio of 0.75 was reached was 85.3 min, and the course of recovery is illustrated in figure 1. The patient was observed in the recovery room over the next hour and later was discharged to the ward. She had an uneventful recovery and was discharged home after 2 days.

Three blood samples were taken from an antecubital vein in the contralateral arm to be used for intravenous fluid administration for determination of plasma cholinesterase activity and dibucaine number. The first sample was taken before the first administration of Serum Cholinesterase P Behring, the second sample was taken when the T1 started to appear (approximately 2.5 min after the third dose of Serum Cholinesterase P Behring), and third sample was taken immediately after the administration of the fourth dose of Serum Cholinesterase P Behring. The reported levels of plasma cholinesterase activity at the aforementioned times were, 750, 670, and 1,120 U · l^{-1}, respectively (reference range for adults is 4,700–14,400 U · l^{-1}). The dibucaine number of the first sample was zero. These data suggest

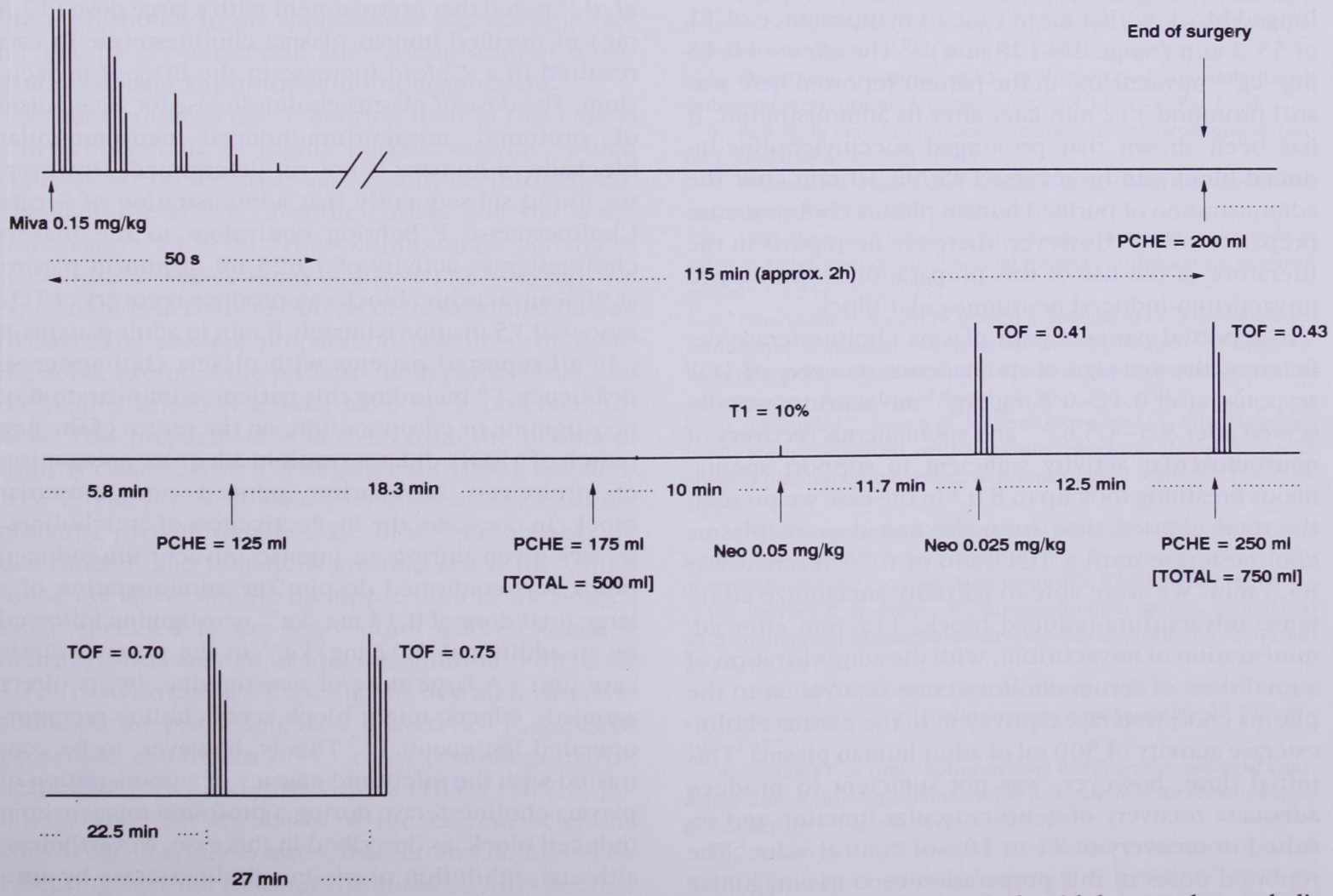

Fig. 1. The time course of antagonism of profound mivacurium-induced neuromuscular blockade with human plasma cholinesterase in the case described. The total elapsed time from the first dose of plasma cholinesterase until a train-of-four ratio (TOF) of 0.75 reached was 85.3 min. Miva = mivacurium; Neo = neostigmine; PCHE = human plasma cholinesterase (the corresponding doses are equivalent to plasma cholinesterase activity of fresh normal human plasma); T1 = first twitch of the TOF stimulation (percent of control); Total = total cumulative doses of PCHE.

that the patient is most probably heterozygous for the atypical and the silent gene ($E_1^a E_1^s$) or alternatively homozygous for the atypical cholinesterase gene ($E_1^a E_1^a$).[7,8]

Discussion

The duration of neuromuscular block after administration of mivacurium or succinylcholine is determined primarily by their rate of hydrolysis by plasma cholinesterase.[9–11] In patients with normal plasma cholinesterase phenotype, an inverse correlation was found between plasma cholinesterase activity and the duration of action of mivacurium.[9] Østergaard *et al.*[9] reported that, in patients heterozygous for the atypical gene, mivacurium-induced neuromuscular block was prolonged by approximately 50%. Further, they found that, in patients homozygous for the atypical plasma cholinesterase gene, a small dose of mivacurium (0.03 $mg \cdot kg^{-1}$, ED_{10} in normal patients) resulted in a prolonged block with a mean time to reappearance of T1 of 55.2 min (range 26–128 min).[10] The effect of 0.15 $mg \cdot kg^{-1}$ mivacurium in the patient reported here was still profound 112 min later after its administration. It has been shown that prolonged succinylcholine-induced block can be reversed within 10 min after the administration of purified human plasma cholinesterase preparation.[12–15] However, there are no reports in the literature of the use of this preparation in prolonged mivacurium-induced neuromuscular block.

In reported patients with plasma cholinesterase deficiency, the first sign of spontaneous recovery of TOF response after 0.12–0.2 $mg \cdot kg^{-1}$ mivacurium was observed after 3.5–4.5 h,[3–5] and spontaneous recovery of neuromuscular activity sufficient to support spontaneous breathing took up to 8 h.[4] In the case we present, the total elapsed time from the first dose of plasma cholinesterase until a TOF ratio of 0.75 reached was 85.3 min. We were able to partially antagonize an intense mivacurium-induced block, 112 min after administration of mivacurium, with the administration of a total dose of serum cholinesterase equivalent to the plasma cholinesterase equivalent to the plasma cholinesterase activity of 500 ml of adult human plasma. This initial dose, however, was not sufficient to produce adequate recovery of neuromuscular function and resulted in recovery of T1 to 10% of control value. The reported doses of this preparation used to antagonize prolonged succinylcholine-induced block in adult patients with plasma cholinesterase deficiency were equivalent to the plasma cholinesterase activity of 1,000 ml of adult human plasma.[12,14] We noted in our case that adequate reversal of neuromuscular block after recovery of T1 to 10% of control tension could not be achieved by subsequent administration of neostigmine. However, administration of the fourth dose of serum cholinesterase equivalent to the plasma cholinesterase activity of 250 ml of adult human plasma after neostigmine resulted in adequate recovery of neuromuscular function (TOF 0.75). Therefore, it could be argued that, if larger doses of this preparation were administered earlier, it could have resulted in a faster recovery of neuromuscular activity in our patient. In fact, the manufacturer recommended a larger dose (equivalent to the plasma cholinesterase activity of 2,000 ml of adult human plasma) for treatment of succinylcholine apnea, if necessary. In addition, Bownes *et al.*[16] noted that pretreatment with a large dose (12.5 mg) of purified human plasma cholinesterase in cats resulted in a 27-fold increase in the ED_{50} of mivacurium. The dose of plasma cholinesterase for antagonism of profound mivacurium-induced neuromuscular blockade in humans is not yet determined. However, we found subsequently that administration of Serum Cholinesterase P Behring equivalent to the plasma cholinesterase activity of 1,625 ml of human plasma at 90% mivacurium block can produce recovery of TOF ratio to 0.75 in approximately 8 min in adult patients.#

In all reported patients with plasma cholinesterase deficiency,[3–6] including this patient, administration of neostigmine or edrophonium, on the return of the first twitch of a TOF, did not result in adequate antagonism of prolonged mivacurium-induced neuromuscular block. In one case, the ineffectiveness of anticholinesterases given during an intense mivacurium-induced block was confirmed despite the administration of a large total dose of 0.14 $mg \cdot kg^{-1}$ neostigmine followed by an additional 0.02 $mg \cdot kg^{-1}$ in the postanesthesia care unit.[4] A large dose of neostigmine, by its direct agonistic effects, might block acetylcholine receptor-operated ion channel.[17] This is, however, to be contrasted with the safety and efficacy of administration of plasma cholinesterase during a profound mivacurium-induced block, as described in this case. Nevertheless, although inhibition of plasma cholinesterase by anticholinesterase drugs can occur and would decrease plasma cholinesterase activity,[18] anticholinesterases proved to be effective in antagonizing mivacurium-induced neuromuscular block in normal patients[19] and

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in patients homozygous for the atypical plasma cholinesterase gene receiving smaller doses of mivacurium.[10]

It should be noted, however, that after the first three doses of plasma cholinesterase, the TOF response returned to a detectable response. At this point, antagonism with neostigmine was attempted. This resulted in a TOF ratio of 0.43. Tactile evaluation of TOF response at this time could have resulted in a dangerous situation, because it is unlikely to detect the presence of TOF fade. Viby-Mogensen *et al.*[20] reported that TOF fade went undetected and often was missed at values as low as 0.41 to 0.5, even by experienced observers.

Human plasma cholinesterase has a molecular weight of 342,000 and is a tetrameric glycoprotein rich in carbohydrate, containing four identical subunits, each having one active catalytic site.[21,22] The half-life of plasma cholinesterase administered to patients with enzyme deficiency is approximately 10–11 days[23,24]; this corresponds to the spontaneous regeneration rate for plasma cholinesterase after administration of organophosphate Diisopropylfluorophosphonate.

Serum Cholinesterase P Behring used in this case is a dry concentrate of highly purified enzyme, which contains no preservative and should be refrigerated. The shelf-life is 2 yr, and the cost of one vial is approximately $300.00. The cholinesterase activity is standardized. The contents of one vial (27–83 mg) are equivalent in activity to 500 ml of fresh normal human plasma. The enzyme preparation produced by Behringwerke excludes the presence of hepatitis virus, and no anaphylactoid reactions have been observed till now. This preparation is derived from the plasma of healthy donors, which is negative for HBsAg and anti-HIV 1. The levels of alanine aminotransferase/serum glutamic pyruvic transaminase in the plasma also are determined, and donations are rejected if the values found are above double the upper limit of the normal range specified in the test. Serum Cholinesterase P Behring is heat-treated in aqueous solution at 60°C for 10 h (pasteurization). Experiments in which virus was added during processing have proved that this special procedure inactivates DNA viruses (cytomegalovirus, herpes simplex) and RNA viruses (HIV 1, HIV 2, poliomyelitis). On the basis of the current scientific knowledge, it is safe to assure that Serum Cholinesterase P Behring does not transmit HIV-induced AIDS because HIV 1 and HIV 2 are inactivated by the special production process.

This case represents the first reported use of plasma cholinesterase for antagonism of a profound mivacurium-induced neuromuscular block due to plasma cholinesterase deficiency. It illustrates that this complication can be managed successfully with the administration of purified human plasma cholinesterase preparation.

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Aortic Intussusception: A Rare Complication of Aortic Dissection

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AORTIC dissection is a separation of the layers of the media so as to create two lumens: a false lumen and a true lumen. We describe a patient having a potentially lethal, complication of aortic dissection—intimal intussusception—that was undiagnosed preoperatively by computed tomography with contrast but was seen perioperatively with transesophageal echocardiography (TEE). This information altered surgical management and may have prevented a serious neurologic sequela.

Case Report

A 66-yr-old man with a medical history of hypertension presented to the emergency room of his community hospital after a syncopal episode. Physical examination revealed a cold, pulseless left upper extremity. Angiography of the left upper extremity suggested occlusion of the left axillary artery secondary to a probable embolus. Computed tomography of the chest showed an ascending aortic aneurysm. Contrast enhancement revealed an "ill defined low density opacity within the posteromedial aortic arch of undetermined significance." He was taken emergently to the operating room for a thromboembolectomy of the left upper extremity. Because no embolus was found, the possibility of an aortic dissection was considered, and TEE was performed. It revealed "extensive aortic dissection" and "severe" aortic insufficiency. With a copy of the computed tomography, and a verbal report of the TEE, he was transferred to our institution for surgical treatment.

After tracheal intubation, a biplane TEE examination was performed. A transverse-plane, short-axis view through the ascending aorta revealed an intimal flap just distal to the aortic valve (fig. 1). Color-flow Doppler confirmed communication between the true and false lumen. In the longitudinal plane, the spiral nature of the dissection could be seen (fig. 2), and the distal portion of the flap disappeared from view. Subsequent evaluation of the aortic arch in the transverse plane revealed the intussusception of the torn intimal flap (fig. 3), and the proximity to the subclavian artery was seen in the longitudinal plane (fig. 4). Color-flow mapping revealed 3–4+ aortic insufficiency and 1+ mitral regurgitation, and a left pleural effusion was detected. There was no evidence of a pericardial effusion, and biventricular function was normal.

After median sternotomy and establishment of bypass *via* right atrium and left femoral artery, the aortic cross-clamp was applied to the distal ascending aorta, and the ascending aorta was transected. Inspection of the ascending aorta confirmed the absence of the dissection flap. To permit retrieval of the intussusception flap, the patient was cooled to a core temperature of 14°C, and a period of deep hypothermic circulatory arrest was instituted. At this time, the surgeons removed the aortic cross-clamp and inspected the aortic arch lumen. The distal portion of the torn intima and media was completely prolapsed into the junction of the distal aortic arch and the descending aorta. The prolapsed flap was resected to ensure perfusion of the

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