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Reversal of Intense Mivacurium Block with Human Plasma Cholinesterase in Patients with Atypical Plasma Cholinesterase

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THE short-acting nondepolarizing neuromuscular blocking agent mivacurium undergoes hydrolysis by plasma cholinesterase (pChe).[1] Patients with genetically abnormal pChe may show a prolonged neuromuscular block after mivacurium,[2–5] and patients homozygous for the atypical pChe gene show a prolonged response to mivacurium even at doses as low as about ED_{10} (0.03 mg/kg).[2] In these patients, a normal dose of mivacurium (0.15–0.20 mg/kg) causes a prolonged and intense neuromuscular block that cannot be antagonized readily with ordinary doses of neostigmine.[3–5] We speculated that injection of human pChe during the period of intense block might antagonize the block, as is the case when the intense block is caused by succinylcholine.[6] This report deals with the results obtained in two patients given human pChe during intense block after mivacurium, the one patient being heterozygous for the atypical and the silent genes, the other one homozygous for the atypical gene.

Case Reports

Neuromuscular monitoring was carried out because the patients were included in a phase 3 study assessing the clinical effect of mivacurium in phenotypically abnormal patients. The patients had warning cards previously issued from the Danish Cholinesterase Research Unit,[7] and the genotypes of the patients were known in advance. When the patients were scheduled for elective surgery, the Danish Cholinesterase Research Unit was informed. The study was approved by the local Ethics Committee, and informed consent was obtained from both patients.

The patients were premedicated with 0.2 mg kg^{-1} diazepam orally. Immediately before induction of anesthesia, a blood sample was taken to measure the dibucaine number and the pChe activity using benzylcholine as a substrate.[8] Anesthesia was induced with 3–5 mg/kg thiopental, 2–4 μg/kg fentanyl, and 0.07–0.10 mg/kg droperidol and maintained, also during recovery of the neuromuscular block, with 66% N_2O in oxygen and supplementary doses of fentanyl. Ventilation was adjusted to maintain normocapnia. During surgery, the central and peripheral skin temperatures were measured and kept greater than 36°C and 32°C, respectively. Monitoring consisted of electrocardiogram, noninvasive blood pressure, end-tidal carbon dioxide concentration, and pulse oximetry.

After induction of anesthesia, the mechanical twitch of the adductor pollicis muscle was recorded using a Myograph 2000 (Biometer, Odense, Denmark). Supramaximal train-of-four (TOF) ulnar nerve stimulation was administered every 12 s. When the response to TOF was stable, after 5–10 min, mivacurium was given.

In both cases, 270 mg (6 ampules) of purified human pChe (Beringwerke, Germany) were administered. This amount of human pChe is known to increase pChe activity to a value within the reference values (660–1620 U/l) for genotypically normal patients.[8] The purified human pChe is derived from donor plasma that is hepatitis B surfactant antigen-negative and anti-HIV-1-negative. It is pasteurized at 60°C to inactivate DNA viruses. The risk of the treatment with human purified pChe is considered comparable to the administration of human albumin.

Case 1

A 46-yr-old, 64 kg woman, ASA physical status 1, was admitted to the hospital for elective resection of an intercostal neurinoma. The patient, who received oral contraceptive pills, was known to be heterozygous for the atypical and the silent genes (table 1).

After induction of anesthesia, 0.1 mg/kg mivacurium was injected, and tracheal intubation was performed. The twitch response was abolished in 1.9 min. The period of no response to TOF was quantitated using the posttetanic count method (PTC),[9] and a PTC of 1 could not be detected until 123 min after the administration of mivacurium. Surgery was completed, and the neuromuscular block (PTC level of 1) was antagonized with 270 mg of purified human pChe 144 min after the administration of mivacurium. A blood sample was

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Table 1. Biochemical Characteristics of the Two Patients

Patient No.	Genotype	Plasma Cholinesterase Activity (U/l)		Dibucaine (number)	Fluoride (number)	Urea (number)
		Preoperatively	10 min after 270 mg Plasma Cholinesterase			
1	AS	106	973	21	21	92
2	AA	448	735	19	28	93
Reference values	AS	134–469		11–28	16–29	86–100
	AA	169–709		13–28	15–28	86–100
	UU	660–1,620		79–86	55–65	41–52

For comparison, reference values from the Danish Cholinesterase Research Unit are given.[8] AS = heterozygous for the atypical and the silent gene; AA = homozygous for the atypical gene; UU = homozygous for the usual (normal) gene.

taken to measure the pChe activity 10 min after the administration of purified enzyme, which caused an increase in pChe activity to 973 U/l (table 1). Reappearance of the first response to TOF (T_1) was seen in 11 min (fig. 1). Further recovery was slow, and the time to a TOF ratio of 0.75 was about 50 min. The patient then was able to maintain head lift for 5 s and was transferred to the recovery room.

Case 2

A 43-yr-old, 81-kg man, ASA physical status 2 and homozygous for the atypical gene, was scheduled for elective vitrectomy of the right eye because of proliferative retinopathy. The medical history revealed hypertension, insulin-dependent diabetes mellitus, and a medication of nifedipine and captopril. Blood pressure was 155/80 mmHg with this medication. Biochemical tests showed a serum creatinine of 0.330 mmol/l (normal range 0.060–0.130). After induction of anesthesia, increments of mivacurium were administered as part of a dose-response study. A total dose of 0.03 mg/kg was injected, which caused disappearance of the twitch response. Recovery was slow, and a PTC of 4 was detected 145 min after the injection of mivacurium. At this time, 270 mg of purified human pChe was administered, and reappearance of T_1 was seen in 10 min (fig. 1). At this time, pChe was measured to be 735 U/l (table 1). Five minutes later, when the T1 had recovered to 20%, 2.5 mg neostigmine, preceded by 1 mg atropine, was injected. The time to a TOF ratio of 0.75 was 9.5 min. At this time, the patient was able to maintain head lift for 5 s and was transferred to the recovery room.

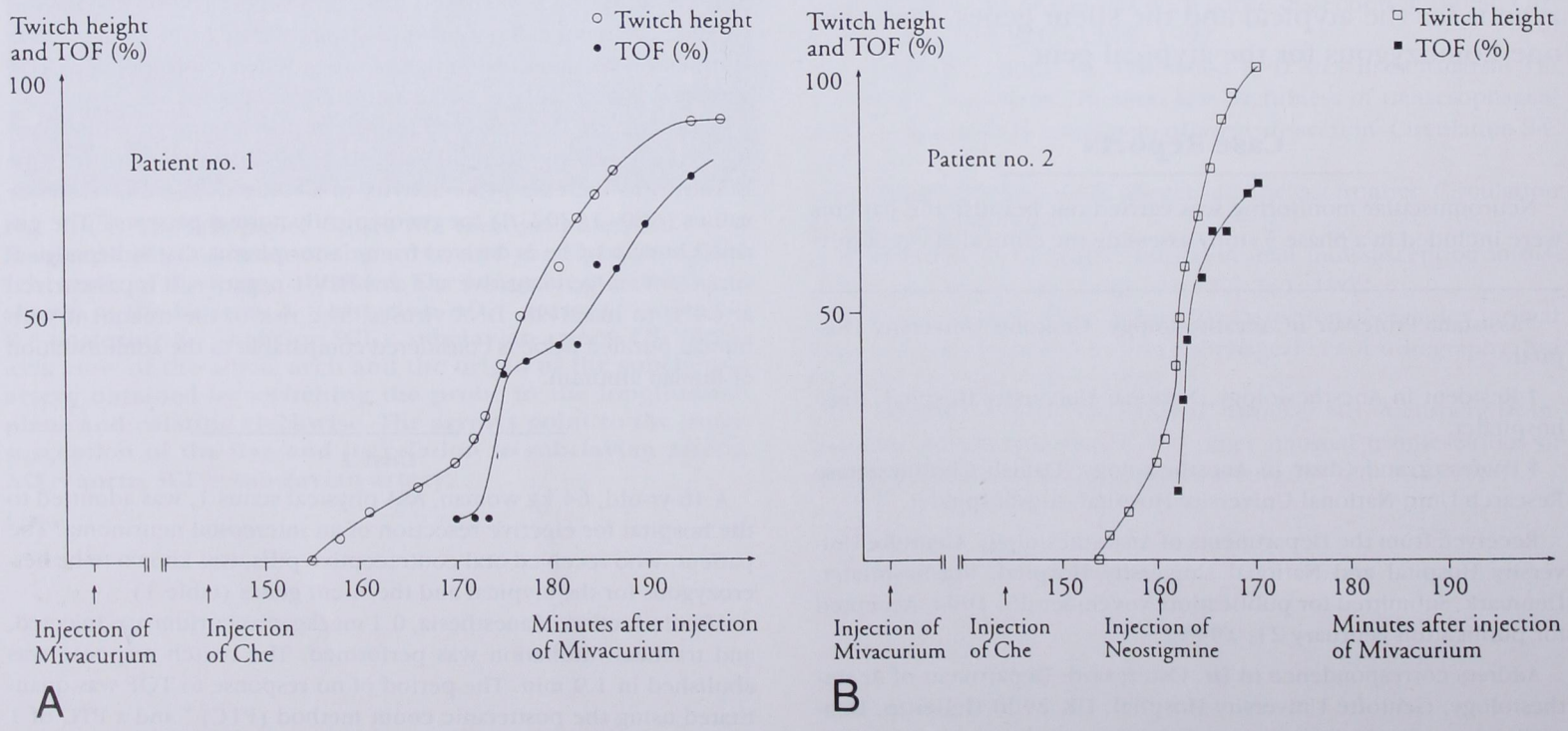

Fig. 1. Recovery of twitch height (open symbols) and train-of-four ratio (closed symbols) after mivacurium in two genotypically abnormal patients. Patient 1 received 270 mg of human plasma cholinesterase (pChe) 144 min after the injection of 0.1 mg kg^{-1} mivacurium. Patient 2 was given 270 mg of human pChe 145 min after mivacurium and 2.5 mg neostigmine 15 min later (at 160 min).

Discussion

Our findings indicate that it is possible in patients with atypical pChe to shorten the recovery time after mivacurium by injecting human pChe and that recovery is faster when the injection of pChe is followed by an injection of neostigmine.

In patient 1, who received 0.1 mg/kg mivacurium, the time to PTC 1 was 123 min. The slow spontaneous recovery was substantiated by an unchanged PTC response in the subsequent 21 min. These findings are in agreement with those of Petersen *et al.*[3] In our patient, injection of pChe 144 min after mivacurium at an intense level of block enhanced recovery, and T_1 reappeared in 11 min. This lag time from injection of pChe to reappearance of T_1 is in agreement with a period of no response to TOF of 10 min after 0.1 mg/kg mivacurium in patients with normal pChe activity.[1,2] After reappearance of T_1, 25%, 50%, and 90% T_1 recovery was reached after 16, 24, and 43 min, respectively, and recovery time (from 25% to 75% T_1) was 16 min. These reversal times are significantly shorter than the spontaneous recovery times reported by Østergaard *et al.*[2] and Goudsouzian *et al.*[4] in patients homozygous for the atypical gene or heterozygous for the atypical and the silent genes but also significantly longer than those reported in patients with normal pChe.[1,10] Thus, Østergaard *et al.*,[2] in five atypical homozygous patients, after only 0.03 mg/kg mivacurium, found spontaneous recovery times from the first appearance of T_1 to 25% and 50% T_1 ranging from 25 to 40 min and 50 to 60 min, respectively (fig 2). In an atypical adult patient given 0.18 mg/kg mivacurium, Goudsouzian *et al.*[4] found a time difference of 30 min between the appearance of the first and fourth responses to TOF (*i.e.*, about 25% T_1 recovery). In genotypically normal patients given 0.1 mg/kg mivacurium, we previously found a mean recovery time (from 25% to 75% T_1) of 7.5 min (range 3.5–14.0) and a mean time to 90% T_1 recovery of 25.6 min (range 14.5–35.6)[10]; *i.e.*, significantly shorter than the recovery data in the current patient.

In patient 2, who was given only 0.03 mg/kg mivacurium, the times to PTC 1 and 4 were 102 and 145 min, respectively. This is a slower recovery than found by Østergaard *et al.*[2] in five patients given the same dose of mivacurium. In those patients, the time to reappearance of T_1 varied between 28 and 128 min, with a median time of 38 min. The slower recovery in patient 2 might be due to this patient's physical status.

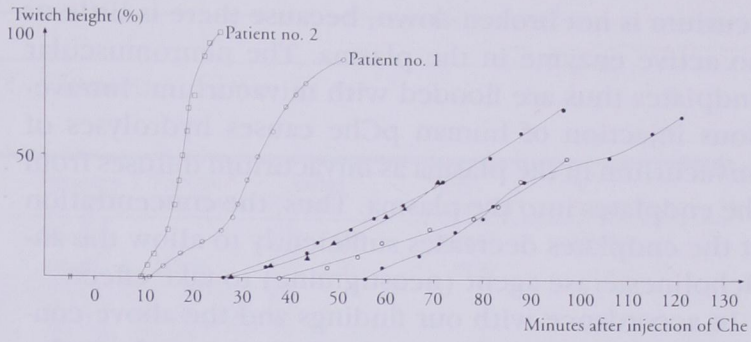

Fig. 2. Recovery of twitch height in two genotypically abnormal patients given 270 mg of human plasma cholinesterase (pChe) (patient 1) and 270 mg of human pChe plus 2.5 mg neostigmine (patient 2), respectively. For comparison, spontaneous recovery data of four other atypical homozygous patients are given.[2]

Homozygous atypical patients have no or very little active enzyme in plasma. Renal insufficiency in such a patient, therefore, may further increase the duration of action of mivacurium.[11] Also, in patient 2, injection of human pChe at an intense level of block enhanced recovery of neuromuscular function (figs. 1 and 2). After the injection, T_1 reappeared after 10 min, and 20% T_1 was reached in 15 min. Because the time to 90% T_1 was 43 min in the first patient given human pChe, we decided to administer neostigmine in patient number 2 to evaluate whether this could reduce recovery time. The injection of 2.5 mg neostigmine at 20% T_1 recovery resulted in a pronounced increase in recovery of T_1 and TOF ratio, the former reaching 90% in 7 min and the latter, 0.75 in 9.5 min. This reversal time is significantly shorter than the spontaneous recovery times reported in this type of patient[2,3] and shorter than the reversal times found by others after larger doses of neostigmine given during deep (one or two responses to TOF) or intense block (no response to TOF stimulation).[4,5]

One may ask why is it difficult to reverse deep or intense mivacurium-induced block with neostigmine in patients with atypical pChe,[4,5] whereas it is apparently easy to reverse it with a combination of human pChe and neostigmine? In genotypically normal patients with normal pChe activity, the mivacurium concentration in plasma decreases rapidly after the administration, because there is sufficient cholinesterase activity in the plasma to hydrolyze free mivacurium. In genotypically abnormal patients, especially those heterozygous for the atypical and the silent genes, homozygous for the atypical gene or the silent gene, miv-

acurium is not broken down, because there is little or no active enzyme in the plasma. The neuromuscular endplates thus are flooded with mivacurium. Intravenous injection of human pChe causes hydrolyses of mivacurium in the plasma as mivacurium diffuses from the endplates into the plasma. Thus, the concentration at the endplates decreases sufficiently to allow the anticholinesterase agent (neostigmine) to take effect.

In accordance with our findings and the above consideration is a study in cats by Bownes *et al.*,[12] who evaluated the effect of larger doses of purified human pChe in antagonizing mivacurium blockade. They found that, at about 10% T_1 recovery, antagonism of mivacurium by neostigmine or pChe was equally prompt. However, recovery from intense block (no response to 0.15 Hz twitch stimulation) was achieved with pChe and not with neostigmine. They conclude that, at profound levels of block, enzymatic reversal with pChe is more efficacious than is competitive antagonism. Hence, during profound block, reversal with neostigmine should not be attempted until evidence of pChe-induced antagonism is evident.

In conclusion, our results indicate that it is possible during intense block after mivacurium in patients with atypical pChe to accelerate recovery of neuromuscular function by an intravenous injection of purified human pChe. The results also indicate that the recovery after injection of pChe is prolonged compared to recovery in patients with normal pChe. However, when the injection of pChe is followed by an injection of a conventional dose of neostigmine, it may be possible to obtain a recovery time comparable to that of patients with normal pChe genotype and activity.

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