Extended neuromuscular blockade with mivacurium following pancuronium

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Summary
A 21-year-old female weighing 55 kg was anaesthetized for facial reconstruction. After an initial bolus of pancuronium 5 mg and top-up doses of 2 mg at 135 min and 1 mg at 290 min and 335 min, no further relaxant was given for 130 min at which time neuromuscular transmission appeared fully recovered with a full train-of-four twitches and a sustained response to 50 Hz stimulation of the posterior tibial nerve. Subsequently, a single dose of mivacurium 8 mg (2 X ED95) produced extended paralysis with no response to train-of-four stimulation for 85 min. The prolonged effect of mivacurium may have been because of inhibition of plasma cholinesterase by pancuronium. The serum cholinesterase activity 12 h after surgery was 0.38 units mL⁻¹ (normal range 0.65–1.0 units mL⁻¹). There was no evidence of atypical cholinesterase.

Keywords: neuromuscular relaxants, pancuronium, mivacurium, interaction.

Introduction
Mivacurium is a recently introduced short-acting, non-depolarizing skeletal muscle relaxant which is broken down by plasma cholinesterase. A case is described in which administration of mivacurium to a patient who had already received pancuronium led to prolonged paralysis.

Case report
A 21-year-old Japanese female weighing 55 kg received extensive facial injuries in a road traffic accident and underwent facial reconstruction 12 h later. She had previously been in good health and had never undergone surgery. Anaesthesia was induced with thiamylal 300 mg and maintained with isoflurane in oxygen and nitrous oxide (FIO₂ 0.33–0.47) delivered via a circle system with fresh gas flow of 31 min⁻¹ and an isoflurane vapouriser setting of 1-3%. Fentanyl 500 μg and morphine 4 mg were given during surgery which lasted 490 min. Estimated blood loss was under 500 mL and a total of 4 litres of crystalloid and colloid were infused.

Suxamethonium 100 mg was given at induction followed by pancuronium 5 mg. Neuromuscular function was not tested between the suxamethonium and the first dose of pancuronium. Subsequent doses of pancuronium were 2 mg at 135 min and 1 mg at 290 min and 335 min. At 465 min, 130 min after the last dose of pancuronium, surgery was almost complete with only some delicate suturing around the eye remaining. Stimulation of the posterior tibial nerve gave a full train-of-four twitches and a sustained response to 50 Hz stimulation. In order to ensure no movement of a patient who was by now very lightly anaesthetized, a single dose of mivacurium 8 mg (2 X ED95) was given. Subsequently, neuromuscular function failed to return and the patient was ventilated with 50% nitrous oxide in oxygen. Oesophageal temperature was 36.6°C at this time. Intravenous (i.v.) cefuroxime 1.5 g had been given after induction of anaesthesia, no other antibiotics were given. After 85 min, a single twitch could be seen in response to train-of-four stimulation.
and full reversal of paralysis was achieved with neostigmine 2.5 mg and atropine 1.0 mg.

Because of the prolonged period of paralysis after mivacurium, the patient was thought to have an atypical plasma cholinesterase [1,2]. In a blood sample taken 12 h after the end of surgery, the serum cholinesterase activity was 0.382 units mL\(^{-1}\), normal range 0.65–1.01. Units of activity are micromoles of benzoylcholine hydrolyzed min\(^{-1}\) mL\(^{-1}\). Inhibition characteristics with dibucaine and fluoride were normal. Sequencing of her DNA revealed no abnormality in three regions in which mutations have previously been reported in Japanese subjects. Subsequently, a follow-up blood sample taken 8 days post-operatively had a serum cholinesterase activity of 0.761 units mL\(^{-1}\), within the normal range.

**Discussion**

This patient experienced a prolongation of the effects of mivacurium after having apparently recovered fully from pancuronium. In patients heterozygous for atypical cholinesterase, recovery from mivacurium 200 µg kg\(^{-1}\) to 90% of control twitch tension was prolonged from 33 to 43 min [3]. The very prolonged block of 85 min to a single twitch observed in this patient suggests that either plasma cholinesterase activity must have been much lower at the end of surgery than it was 12 h later, or there must have been another explanation. Although peripheral nerve stimulation prior to mivacurium administration suggested normal neuromuscular transmission in this patient, many receptors at the neuromuscular junction would still have been occupied by pancuronium. Brandon and colleagues [4] found that pre-treatment with pancuronium 15 µg kg\(^{-1}\) before mivacurium 200 µg kg\(^{-1}\) extended the time to 75% recovery of the train-of-four from 16.5 min to 35.3 min. Mivacurium has been reported to show synergism with atracurium and vecuronium [5], and it is possible that there may also be synergism with pancuronium. Pancuronium is known to inhibit human plasma cholinesterase in vitro and in vivo [6] and this inhibition may have decreased the rate of mivacurium hydrolysis and consequently prolonged its effect. A single patient with end-stage renal failure was reported to have experienced prolonged paralysis after mivacurium, possibly as a result of diminished synthesis of a normal cholinesterase [7]. The patient reported here also had a normal cholinesterase. The activity, temporarily diminished, may have been because of enzyme inhibition or haemodilution; however, the volumes of blood lost and fluid infused do not seem sufficient for haemodilution to have been a major factor. The extended effect of mivacurium in this patient may have been caused by the combined effects of an interaction with residual pancuronium and a low plasma cholinesterase activity.

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**References**