Cyclosporine-pancuronium interaction in a patient with a renal allograft

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A case is described of a 54-year-old 55 kg patient who presented for clipping of a middle cerebral aneurysm two years after a successful renal allograft. Immunosuppression was maintained with azathioprine 100 mg daily, cyclosporine 300 mg daily and prednisone 10 mg daily. The patient had chronic hypertension controlled with nifedipine 40 mg daily and furosemide 20 mg daily. The cyclosporine level taken on the morning of surgery was $166 \mu\text{g} \cdot \text{L}^{-1}$. Induction of anaesthesia consisted of fentanyl 350 μg , thiopentone 125 mg and pancuronium 5.5 mg. Anaesthesia was maintained with nitrous oxide 70 per cent in oxygen and isoflurane 0.5–1.5 per cent. No additional doses of pancuronium were given during the four hour surgical procedure. At the end of surgery, four twitches were present with train-of-four stimulation, but evidence of residual muscle paralysis was present. Residual neuromuscular blockade was reversed with atropine 1.2 mg and neostigmine 2.5 mg. Residual paralysis was present in the Recovery Room and edrophonium 10 mg was given prior to extubation. Clinical testing demonstrated adequate reversal of neuromuscular blockade. Twenty minutes following extubation, increasing respiratory distress was noted. There was clinical evidence of muscle paralysis. The patient was re-intubated. It is proposed that cyclosporine potentiated the pancuronium blockade producing prolonged neuromuscular relaxation resulting in residual paralysis following surgery. The potential interactions of cyclosporine and muscle relaxants deserve further study.

Key words

DRUG INTERACTIONS: pancuronium, cyclosporine;
COMPLICATIONS: respiratory failure, muscle paralysis.

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Cyclosporine is a new immunosuppressive agent that has done much to improve outcome in transplant surgery, decreasing the incidence of graft rejection and increasing graft survival.¹ Increasing numbers of patients who are receiving cyclosporine therapy following organ transplantation are presenting for anaesthesia. As well, protocols for organ transplantation often call for preoperative and intraoperative administration of cyclosporine.

The intravenous preparation of cyclosporine is dissolved in an ethanol-cremophor vehicle. Interactions between cremophor and muscle relaxants have been reported in man.² Interactions between both cremophor and cyclosporine and muscle relaxants have been reported in experimental animals.³

The following is a case report of a patient treated with cyclosporine who demonstrated prolonged muscle paralysis after administration of pancuronium during an operative procedure. Residual muscle paralysis persisted in the postoperative period after reversal of pancuronium blockade.

Case Report

A 54-year-old, 55 kg female was admitted to hospital with an incapacitating headache and was diagnosed as having a right posterior communicating artery aneurysm. Craniotomy for the purpose of aneurysm clipping was scheduled. The patient had received a renal allograft two years previously for dialysis-dependant chronic renal failure secondary to chronic glomerulonephritis. Immunosuppression was maintained with azathioprine 100 mg daily, cyclosporine 300 mg daily and prednisone 10 mg daily. Nifedipine 40 mg daily and furosemide 20 mg daily were prescribed for chronic hypertension. A smoking habit of one pack per day and thirty pack-years was noted.

Preoperative evaluation revealed an agitated and confused middle-aged female. The right pupil was 1–1.5 mm larger than the left and both pupils were light-reactive. The neurological examination was otherwise normal. Blood pressure was 170/96 and heart rate $84 \cdot \text{min}^{-1}$ and regular. The chest was clear on auscultation. Results of laboratory studies revealed a haemoglobin of $104 \text{ g} \cdot \text{L}^{-1}$. Platelet count and coagulation studies were normal. The

serum creatinine was $182 \mu\text{mol} \cdot \text{L}^{-1}$ ($n = 50\text{--}120 \mu\text{mol} \cdot \text{L}^{-1}$). All other laboratory studies were normal as were the electrocardiogram and chest x-ray. The patient was classified as a Hunt Grade III risk for surgical intervention.⁴

A cyclosporine infusion of $12 \text{ mg} \cdot \text{hr}^{-1}$ was started twelve hours before surgery and continued for 36 hours. The cyclosporine level taken on the morning of surgery was $166 \mu\text{g} \cdot \text{L}^{-1}$ (therapeutic range = $10\text{--}200 \mu\text{g} \cdot \text{L}^{-1}$). Hydrocortisone 100 mg was administered IM. No premedication was given.

The patient arrived in the operating room agitated and confused, with a blood pressure of 180 mmHg systolic and a heart rate of $100 \cdot \text{min}^{-1}$. Two large bore intravenous infusions were started and a left radial artery catheter was inserted. Anaesthesia was induced with fentanyl 350 μg and thiopentone 125 mg. Neuromuscular relaxation was obtained with pancuronium 5.5 mg. The blood pressure was controlled with nitroglycerine 50 μg IV. Lidocaine 80 mg was administered IV to reduce laryngeal reflexes. The trachea was intubated. Anaesthesia was maintained with nitrous oxide 70 per cent in oxygen, and isoflurane 0.5–1.5 per cent. Fentanyl 50 μg was administered twice during the procedure. Mean arterial pressure was maintained at 80 mmHg systolic during the clipping of the aneurysm. Urine output was 950 ml intraoperatively.

Neuromuscular blockade was monitored with a handheld PIC (Professional Instruments Company peripheral nerve stimulator, Model NS-3A) twitch monitor. The patient was noted to have a single twitch in the train-of-four following intubation, but this was abolished in the first half-hour of surgery. The surgery lasted four hours and no additional doses of pancuronium were given. At the end of surgery, four twitches were present in train-of-four stimulation. Tetanus was poorly sustained and post-tetanic facilitation was present. Residual neuromuscular blockade was reversed with atropine 1.2 mg and neostigmine 2.5 mg. The patient was transferred to the Recovery Room intubated, because she was difficult to arouse. In the Recovery Room, edrophonium 10 mg was administered because of clinical evidence of residual paralysis characterized by incoordinate movements and poor grip strength. Signs of residual muscle paralysis improved over the next five minutes and the patient was extubated. She maintained headlift for greater than five seconds and manifested good grip strength bilaterally. Following extubation, she vocalized appropriately.

Twenty minutes after extubation, she was noted to be experiencing increasing respiratory distress and uncoordinated movement of the extremities. Blood pressure was 210 mmHg systolic, heart rate was $120 \cdot \text{min}^{-1}$ and respiratory rate was $36 \cdot \text{min}^{-1}$. Grip strength was poor and headlift was poorly maintained. Blood gases drawn prior

to intubation revealed pH 7.17, PaCO_2 63 mmHg, PaO_2 106 mmHg. The patient was reintubated and transferred to the Intensive Care Unit where she was extubated four hours later. She was discharged from hospital on the ninth postoperative day following an uneventful recovery.

Discussion

Pancuronium is a bisquaternary ammonium steroidal molecule with non-depolarizing muscle relaxant properties. Forty to fifty per cent of an injected dose of pancuronium is eliminated unchanged in the urine⁵ and up to 80 per cent is dependent on renal pathways for elimination.⁶ Plasma concentrations of pancuronium of $88 \text{ ng} \cdot \text{ml}^{-1} \pm 34 \text{ ng} \cdot \text{ml}^{-1}$ produce clinical evidence of neuromuscular blockade.⁷ Plasma pancuronium concentrations of $67 \text{ ng} \cdot \text{ml}^{-1} \pm 2 \text{ ng} \cdot \text{ml}^{-1}$ have been demonstrated four hours after administration in patients with normal renal function. The clearance of pancuronium has been found to be reduced significantly in patients with renal failure.⁵

Cyclosporine A was isolated in 1970. It was discovered to possess an inhibitory action in lymphocyte proliferation assays and was further noted to be predominately T-cell specific in its action. Cyclosporine is an eleven amino-acid cyclical polypeptide that is markedly hydrophobic. It is metabolized in the liver and excreted through feces, via bile. Ten per cent of metabolites undergo renal excretion and less than one per cent is excreted unchanged. *In vitro*, cyclosporine exhibits a preferential binding to T-lymphocytes. Inhibition of calcium entry into the cytosol, thus inhibiting calcium dependent membrane activity, is a proposed mechanism of action.⁸ Dose-dependent nephrotoxicity is an important factor limiting use of cyclosporine, although it is usually possible to continue therapy at a lower dose. The half life of cyclosporin in serum is 17–40 hours.⁸ The cyclosporine level in our patient was $166 \mu\text{g} \cdot \text{L}^{-1}$ on the day of surgery.

Cremophor is a nonionic, surface-active agent used as a vehicle for lipid-soluble hydrophobic compounds such as diazepam, propofol, alfentanil, as well as cyclosporine. Onset time for pancuronium blockade is decreased in patients induced with cremophor-containing anaesthetics.² This is not seen with alcuronium. Other muscle relaxants have not been studied. Cremophor may interfere with pancuronium association at non-specific intravascular binding sites, increasing effective concentration at the neuromuscular junction.

The interactions of both cyclosporine and cremophor with atracurium and vecuronium have been studied in the cat.⁹ Cyclosporine, in clinically relevant doses, potentiates a vecuronium-induced neuromuscular block. Cremophor potentiates the block to a lesser degree and for a shorter period than does cyclosporine but also to a significant degree. The interaction with atracurium is less pronounced.

The most potent interactions between both cremophor and cyclosporine and muscle relaxants have been seen with pancuronium and its analogue, vecuronium.⁹

Residual curarization is a common problem. It has been demonstrated, using train-of-four testing in postoperative patients, that 20 to 40 per cent of patients have evidence of clinically significant residual curarization on arrival in the recovery room. It is recommended that neuromuscular monitoring be utilized routinely intraoperatively and postoperatively to aid titration of muscle relaxants and their antagonists.¹⁰ If muscle paralysis is noted in the early postoperative period, residual curarization is likely. There are a number of factors that may potentiate residual curarization, thereby increasing its clinical significance. Included are respiratory acidosis, hypothermia, hypomagnesemia, hypocalcemia, residual anaesthetic effects and inherent neuromuscular disease. A large number of drugs have been shown to interact with the muscle relaxants.⁹ In our patient, adequate reversal was confirmed by the return of the train-of-four following antagonism of the residual blockade. Clinical criteria were satisfied prior to extubation that reversal was adequate. Twenty minutes later there was evidence of increasing muscle paralysis and respiratory insufficiency.

It is our hypothesis that interaction between cyclosporine, cremophor and pancuronium prolonged the expected duration of neuromuscular block in this patient. Although the effect of cyclosporine is predominantly T-cell specific and myelotoxicity is minimal, inhibition of calcium entry into the muscle cell may be the cause of potentiation of the neuromuscular blocking effect of pancuronium. The effect exerted on the kidney by cyclosporine which resulted in a moderate elevation of creatinine in this patient may have interfered with the excretion of pancuronium thus prolonging the neuromuscular blockade. The effect of cremophor which increases the effective concentration of pancuronium at the neuromuscular junction may have also contributed to the prolonged effect of pancuronium. The potential interactions of cyclosporine and muscle relaxants deserves further study. Considering the patient's elevated creatinine level and the possibility of a less pronounced cyclosporine-atracurium reaction, the preferred agent for muscle relaxation in this patient was atracurium.

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Résumé

On décrit le cas d'un patient qui s'est présenté pour clampage d'anévrisme de l'artère cérébrale moyenne deux ans après une greffe rénale. L'immunosuppression était maintenue avec l'azathioprine 100 mg par jour, cyclosporine 300 mg par jour et prednisone 10 mg par jour. Le patient présentait de l'hypertension chronique contrôlée avec la nifédipine 40 mg par jour et du furosémide 20 mg par jour. Le niveau de cyclosporine pris le matin de la chirurgie était de $166 \mu\text{g} \cdot \text{L}^{-1}$. L'induction de l'anesthésie comprenait du fentanyl 350 μg , thiopentone 125 mg et pancuronium 5.5 mg. L'anesthésie était maintenue avec du protoxyde d'azote 70 pour cent dans l'oxygène et de l'isoflurane 0.5 à 1.5 pour cent. Aucune dose additionnelle de pancuronium n'était donnée pendant les quatre heures de la procédure chirurgicale. A la fin de la chirurgie les quatre "twiches" étaient présents lors de la stimulation par "ondée-de-quatre" (train-of-four) mais aucune évidence de paralysie musculaire résiduelle n'était présente. Une blocage neuromusculaire résiduel était antagonisé avec de l'atropine 1.2 mg et de la néostigmine 2.5 mg. Une paralysie résiduelle était présente en salle de réveil et de l'édrophonium 10 mg était donné avant l'extubation. Les tests cliniques ont démontré un antagonisme adéquat du blocage neuromusculaire. Vingt minutes après l'extubation une détresse respiratoire croissante fut notée. Il y avait une évidence clinique de paralysie musculaire. Le patient fut réintubé. On propose que la cyclosporine potentialise le blocage neuromusculaire du pancuronium et prolonge la relaxation neuromusculaire provoquant une paralysie résiduelle après la chirurgie. L'interaction possible de la cyclosporine et des relaxants musculaires méritent d'autres études.