RENAL FAILURE AND POSTOPERATIVE RESPIRATORY FAILURE: RECURARIZATION?

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SUMMARY

The occurrence of acute postoperative respiratory failure in three patients with renal failure is presented. The most likely cause was the return of muscle paralysis after the apparent antagonism of tubocurarine by neostigmine (recurarization). In addition to reducing the dose of tubocurarine, the authors recommend that pyridostigmine be used as an antagonist instead of neostigmine because the former has a longer duration of action.

Previous observations suggest that the duration of action of gallamine, but not tubocurarine (dtc), is prolonged markedly in the absence of renal function (Churchill-Davidson, Way and de Jong, 1967). However, dtc is eliminated primarily by renal excretion (Cohen, Brewer and Smith, 1967), and computer simulations predict that patients with impaired renal function will sustain prolonged neuromuscular blockade from dtc (Gibaldi, Levy and Hayton, 1972). We report three examples of patients who became “recurarized” after dtc had apparently been antagonized adequately.

Case 1

A 38-year-old, 65-kg male underwent surgery for removal of a rejected kidney transplant at the University of California Hospitals. His arterial pressure was 180/110 mm Hg. His haemoglobin concentration was 5.8 g%, serum creatinine concentration 5.4 mg% and albumin concentration 4.0 g%. Serum sodium, potassium, chloride and bicarbonate concentrations were 131, 4.6, 101 and 21 m-equiv/litre, respectively. The patient was receiving, by mouth per day, azathioprine 300 mg, prednisone 120 mg, Lugol’s solution, ten drops, and alpha methyldopa 300 mg. The patient received diazepam 10 mg, and atropine 0.4 mg, i.m. 50 min before coming to the operating room. After the administration of dtc 3 mg i.v. anaesthesia was induced with thiopentone, 250 mg, and suxamethonium 80 mg was used to facilitate intubation of the trachea. Anaesthesia was maintained with 1.0% inspired concentration of halothane and 60% nitrous oxide in oxygen. Neuromuscular blockade was induced with dtc, 21 mg i.v. Additional dtc was administered as indicated by “tightness” of the abdominal musculature. A total of 54 mg of dtc was administered. The subcutaneous tissue of the surgical wound was irrigated with bacitracin and neomycin which then were suctioned promptly from the wound. The neuromuscular blockade was antagonized by i.v. neostigmine 2.5 mg, and atropine 1.0 mg. Although specific measurements were not performed, ventilation and hand grip strength for 5 sec appeared adequate. The trachea was extubated. At no time, either during or following operation, was the systolic arterial pressure less than 120 mm Hg. After approximately 60 min in the recovery room, the patient complained of dyspnoea. The vital capacity was 0.6 litre. Stimulation of the ulnar nerve showed post-tetanic facilitation and an inability to sustain contraction in response to a tetanic stimulus of 50 Hz for 5 sec. Fifteen minutes after i.v. administration of neostigmine 2.0 mg, and atropine 0.8 mg, the vital capacity was 1.8 litre. Post-tetanic facilitation disappeared and contraction was sustained in response to tetanic stimuli. The patient experienced no subsequent ventilatory difficulties after operation.

Case 2

A 54-year-old, 53-kg male with end-stage renal disease secondary to chronic glomerulonephritis was admitted, for renal transplantation, to the University of California Hospitals. He had not exhibited systemic hypertension since beginning chronic haemodialysis 30 months before surgery. His arterial pressure was 140/80 mm Hg with atrial fibrillation at
a conducted rate of 90 beats/min. He was taking orally both digoxin 0.125 mg/day and diazepam 5 mg as needed. The haematocrit was 33% and the serum creatinine concentration was 18.5 mg%. Serum sodium, chloride, potassium and bicarbonate concentrations were 138, 95, 4.5 and 28 m-equiv/litre, respectively.

The patient received pethidine 100 mg, and hyoscine 0.3 mg i.m. approximately 1 hr before surgery. After the i.v. administration of dtc 3 mg, anaesthesia was induced with thiopentone 175 mg, and suxamethonium 80 mg was given to facilitate tracheal intubation. During the 5 hr 15 min of anaesthesia the patient was given 70% nitrous oxide in oxygen plus thiopentone 400 mg, pethidine 300 mg and dtc 48 mg; the dose of dtc was based on clinical evaluation of “tightness” of the abdominal musculature. At the end of the surgical procedure, the neuromuscular blockade was antagonized with neostigmine 5.5 mg and atropine 2.1 mg. Ventilation appeared sufficient to allow its spontaneous continuation and extubation of the trachea. No antibiotics were used for irrigation of the surgical wound. On arrival in the recovery room, the patient was awake and responded to verbal commands. With supplementary oxygen delivered from nasal cannulae, $P_{aO_2}$ was 110 mm Hg, $P_{aCO_2}$ was 47 mm Hg and pH was 7.23 units. Ninety minutes after the neostigmine was administered, the patient appeared to be weaker and restless and apnoea developed. The trachea was intubated, and ventilation was controlled. When a tetanic stimulus of 30 Hz was applied to the ulnar nerve for 5 sec, he was unable to sustain adduction of the thumb. After the i.v. administration of neostigmine 2.5 mg and atropine 1.2 mg, adduction of the thumb was sustained and spontaneous ventilation was initiated. Controlled ventilation was continued. Ten hours later the patient’s vital capacity was 2.0 litre and the urinary output was 100–150 ml/hr. His trachea was extubated with no further ventilatory problems. Twenty-four hours later his serum creatinine concentration was 21.8 mg%.

**Case 3**

A 44-year-old male with end-stage renal failure secondary to chronic glomerulonephritis was admitted, for nephrectomy and renal transplantation, to the Massachusetts General Hospital. He had been maintained previously on haemodialysis. In addition to renal failure, he had hypertension (arterial pressure 220/110–120 mm Hg) which was treated with hydralazine 250 mg, alpha methyldopa 300 mg, and chlorothiazide 1000 mg, given orally each day. The haematocrit was 19%, the serum creatinine concentration was 6.3 mg%, and the serum sodium, chloride, potassium and bicarbonate concentrations were 128, 96, 3.9 and 23 m-equiv/litre, respectively. He was dialysed immediately before surgery.

Diazepam 10 mg and atropine 0.5 mg were given i.m. approximately 1 hr before surgery. After the i.v. administration of dtc 3 mg, anaesthesia was induced with thiopentone 300 mg; suxamethonium 120 mg was used to facilitate intubation of the trachea. Anaesthesia was maintained with nitrous oxide 67% in oxygen, droperidol 5 mg, morphine 14 mg and tubocurarine 48 mg. The magnitude of the neuromuscular blockade was monitored with a peripheral nerve stimulator. A twitch was observed during all but the 1st hr of anaesthesia. At the end of the surgical procedure, the neuromuscular blockade was antagonized with neostigmine 5 mg and atropine 2 mg, i.v. A peripheral nerve stimulator was not used to evaluate antagonism of the block. Naloxone, 0.2 mg, was also given i.v. When the patient could empty a 3-litre bag with a single inhalation, complete antagonism of the neuromuscular blockade was assumed and his trachea was extubated. Twenty minutes after arriving in the recovery room, the patient complained of dyspnoea and appeared to have muscular weakness although no confirming tests were performed. Despite being awake and alert, his trachea was re-intubated easily without additional muscle relaxants. After 12 hr of controlled ventilation, the patient’s tidal volume was 0.5 litre, vital capacity 1.0 litre and inspiratory force $-50$ cm H$_2$O. His trachea was extubated, and he incurred no further ventilatory difficulty. In the period immediately after operation, renal function appeared to be adequate as indicated by a urinary output of 200–500 ml/hr.

**DISCUSSION**

The respiratory difficulties experienced after surgery by these patients might have several possible causes. We believe the most likely cause was recurrence of paralysis. However, the first patient received a large dose of dtc (54 mg) and his subcutaneous tissues were irrigated with neomycin, an antibiotic which enhances the neuromuscular blocking properties of dtc (Pittinger and Adamson, 1972). Perhaps the initial dose of neostigmine was inadequate, but specific testing of neuromuscular function, such as use of a peripheral nerve stimulator, was not performed. The low circulation to subcutaneous tissues and immediate suction of the applied solution probably limited the
amount of neomycin absorbed. In the third case, the effect of naloxone may have decreased, resulting in the return of narcotic depression. However, the fact that the patient was awake and alert, but weak, implicates relaxant- rather than narcotic-induced weakness.

The metabolic and respiratory acidosis in Case 2 may have interfered with neostigmine antagonism. However, we believe the acidosis was not severe enough to be important clinically (Miller et al., 1975). All three patients received diazepam. The ability of diazepam to enhance a non-depolarizing block is controversial (Feldman and Crawley, 1970; Dretchen, Ghoneim and Long, 1971). Excluding the above conditions, these cases suggest that a single administration of neostigmine will not provide permanent antagonism of the neuromuscular blockade in patients with a reduced rate of excretion of d-tubocurarine, such as occurs in renal failure.

We suggest that d-tubocurarine concentration at the neuromuscular junction had not decreased sufficiently by the time inhibition of acetylcholinesterase by neostigmine had decreased. The duration of the action of neostigmine is about 60 min and probably it is not altered by impaired renal function (Gibaldi, Levy and Hayton, 1972; Miller et al., 1974). The slow reduction in d-tubocurarine concentration at the neuromuscular junction may have been partly a result of the large doses of d-tubocurarine administered and of a reduced excretory rate. In any event, administration of additional neostigmine may be required 60 min after the first administration (Gibaldi, Levy and Hayton, 1972). The use of pancuronium instead of d-tubocurarine may cause the same problem because it, also, is primarily dependent on urinary excretion for its elimination (Agoston, Vermeer and Kersten, 1973; Miller, Stevens and Way, 1973). The ability of a newly transplanted kidney to excrete d-tubocurarine and pancuronium is unknown.

If renal failure retarded the excretion of d-tubocurarine and neostigmine to the same extent, the return of paralysis would be unlikely. Although both are metabolized by liver microsomes, elimination of neostigmine is not dependent on normal renal function, since it is eliminated rapidly and completely in animals with ligated renal pedicles (Burdfield and Calvey, 1973). In contrast, elimination of pyridostigmine from the circulation is extremely slow in the absence of intact renal function. This slower elimination rate is probably related to in vitro differences in hepatic metabolism (Burdfield and Calvey, 1973). Therefore, pyridostigmine may be preferred to neostigmine as an antagonist to non-depolarizing blockade in patients with renal failure (Miller, Stevens and Way, 1973).

Probably most important in preventing a return of paralysis is the use of smaller doses of d-tubocurarine (Gibaldi, Levy and Hayton, 1972). Less d-tubocurarine is required for neuromuscular blockade during isoflurane or halothane than during nitrous oxide–narcotic anaesthesia (Katz and Gissen, 1967; Miller et al., 1971). Cases 2 and 3 might have required less d-tubocurarine if a potent inhalation anaesthetic had been administered instead of nitrous oxide–narcotic and barbiturate anaesthesia. Although Case 1 received halothane, 54 mg of d-tubocurarine were given. Perhaps more precise monitoring, using a peripheral nerve stimulator, for example, would have indicated that less relaxant was required. Finally, perhaps a longer-lasting antagonism could be achieved with pyridostigmine instead of neostigmine (Burdfield and Calvey, 1973; Miller et al., 1973).

Note added in proof. Since this report was written, two other cases of recurarization in patients with renal failure have occurred. One patient received d-tubocurarine 55 mg and the other pancuronium 12 mg.

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REFERENCES


INSUFFISANCE RENALE ET INSUFFISANCE RESPIRATOIRE POSTOPERATOIRE: RECURARISATION?

RESUME
On expose dans cet article l'apparition d'insuffisance respiratoire postopératoire aiguë observée sur trois malades souffrant d'insuffisance rénale. La cause la plus plausible de cet état de choses est le retour de la paralysie musculaire après l'antagonisme apparent de la tubocurarine vis à vis de la néostigmine (recurarisation). Les auteurs recommandent qu'en plus d'une réduction de la dose de tubocurarine, on utilise la pyridostigmine comme antagoniste, au lieu de la néostigmine parce que le premier produit a une durée d'action plus longue.

INSUFICIENCIA RENAL E INSUFICIENCIA RESPIRATORIA POSTOPERATORIA: ¿RECURARIZACION?

SUMARIO
Se presenta el caso de insuficiencia respiratoria aguda postoperatoria en tres pacientes con insuficiencia renal. La causa más probable fue el retorno de parálisis muscular después del manifiesto antagonismo de la tubocuramina por la neostigmina (recurarización). Además de la reducción de la dosis de tubocuramina los autores recomiendan el uso de piridostigmina como antagonista en vez de la neostigmina ya que la primera tiene efectos de duración más largos.