Clinical Reports

Prolonged neuromuscular blockade with atracurium

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During general anaesthesia with oxygen, nitrous oxide and enflurane, a 29-year-old woman received a total of 105 mg ($1.78 \text{ mg} \cdot \text{kg}^{-1}$) of atracurium over a 2.5 hour period. The neuromuscular blockade could not be completely reversed with neostigmine and mechanical ventilatory support was necessary for three hours postoperatively. The patient received succinylcholine without unusual sequelae before and after this episode. This is the first report of a patient who exhibited prolonged weakness after receiving atracurium.

Atracurium is a competitive neuromuscular blocking agent. Laboratory and clinical studies indicate that it is rapidly metabolized and lacks cumulative effects. A 29-year-old woman exhibited prolonged neuromuscular weakness after receiving atracurium. This report questions the claims that atracurium has no cumulative effects, that there is 95 per cent recovery from blockade within 60 minutes after injection, and that reversal is readily attained within eight to ten minutes.

Case Report

A 29-year-old woman presented for exploratory

laparotomy because of a haemorrhagic endometrioma. Her medical history was significant for mitral valve prolapse, allergies to penicillin and cephaxelin, and infertility. Her daily medications were danazol (a synthetic androgen) 200 mg four times daily and vitamins. She had undergone diagnostic laparoscopy for infertility twelve days earlier. General anaesthesia had been used and included the following intravenous medications: d-tubocurarine 3 mg, thiopentone 300 mg, succinylcholine 100 mg ($1.7 \text{ mg} \cdot \text{kg}^{-1}$) to facilitate tracheal intubation, and a succinylcholine infusion 150 mg ($2.54 \text{ mg} \cdot \text{kg}^{-1}$) to achieve neuromuscular blockade. Neuromuscular blockade had been monitored by assessing contractions of the adductor pollicis in response to stimulation of the ulnar nerve. Satisfactory recovery of the neuromuscular junction had been evident after the initial succinylcholine bolus and after the infusion was discontinued. Endometriosis was diagnosed and the patient was discharged the same day.

She was re-admitted nine days later because of fever, diarrhoea and postural dizziness. The admitting diagnoses were gastroenteritis and bleeding endometrioma. She was treated with bed rest and intravenous hydration. Her haematocrit had decreased by nine per cent since the laparoscopy. Surgery was deemed necessary to obtain haemostasis and to establish a diagnosis. The preoperative physical examination was normal except for a click murmur and abdominal tenderness. The patient weighed 59.1 kg. Laboratory data were: haematocrit, 32 per cent; serum potassium, $3.8 \text{ mEq} \cdot \text{L}^{-1}$; blood urea nitrogen, $10 \text{ mg} \cdot \text{dL}^{-1}$; and blood glucose $80 \text{ mg} \cdot \text{dL}^{-1}$. The patient had received gentamycin 60 mg IV and vancomycin 250 mg IV 1 hour and 45 minutes prior to induction of anaesthesia.

In the operating room the patient was given

Key words

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meperidine 100 mg and d-tubocurarine 3 mg IV, and oxygen by mask for three minutes. General anaesthesia was induced using thiopentone 300 mg. The trachea was intubated after the administration of succinylcholine 100 mg ($1.7 \text{ mg} \cdot \text{kg}^{-1}$). Recovery from succinylcholine was evident within ten minutes when the patient exhibited vigorous expiratory efforts. Stimulation of the facial and ulnar nerves revealed 1:1 train of four ratio and sustained tetanus (100 Hz). Atracurium 25 mg ($0.42 \text{ mg} \cdot \text{kg}^{-1}$) was given IV followed by loss of the twitch response within five minutes. Anaesthesia was maintained with oxygen, nitrous oxide and enflurane (0–1 per cent). Twenty-five minutes later the surgeons complained of poor abdominal muscle relaxation. Thiopentone 100 mg and atracurium 20 mg ($0.34 \text{ mg} \cdot \text{kg}^{-1}$) were given IV. At approximately 35-minute intervals the patient received three additional doses of atracurium 30 mg IV. Prior to each injection the response to train-of-four and tetanic stimulation had reverted to normal, suggesting recovery from neuromuscular block.

Surgery was completed 2.5 hours after atracurium was first given and 30 minutes after the last dose of atracurium. Cauterization of endometrial implants, uterine suspension and a right ovarian cystectomy had been performed. Train-of-four response showed fade and the response to tetanic stimulation was not sustained. Enflurane had been off for more than one hour and the patient had not received antibiotics intraoperatively. Neostigmine 4.0 mg and glycopyrrolate 1.0 mg were given. Nine minutes later a 1:1 train-of-four response and sustained tetanus were noted. Nitrous oxide was discontinued and the patient was given O_2 100 per cent. After three minutes she awoke promptly but was unable to maintain a hand grasp or keep her eyes open. Oral temperature was 35.5°C . While breathing spontaneously, her tidal volume and minute ventilation were 200 ml and 3 L respectively. She was calm and indicated that she felt weak and was short of breath. She remained weak and required mechanical ventilation. The patient received meperidine 50 mg IV, and was brought to the recovery room intubated. Three and one-half hours after the final dose of atracurium she was sufficiently strong to be extubated. She had an uneventful postoperative course and was discharged from the hospital six days later.

Discussion

Atracurium is one of a new series of competitive, non-depolarizing neuromuscular blocking agents. Basta *et al.*¹ described the clinical pharmacology of atracurium in a study of 70 patients in 1982. They reported a rapid, dose-related onset of action, an intermediate duration of action, minimal cardiovascular side effects, a lack of clinically significant cumulative effects, insignificant histamine release, and decomposition in plasma via Hoffman elimination.

Recovery from neuromuscular blockade with atracurium has been reported to be appreciably faster than recovery from gallamine, fazadinium, pancuronium, tubocurarine and dimethyl tubocurarine, with a lack of cumulative effects.^{2–4}

Metabolism of atracurium differs considerably from that of other competitive blockers. Most likely it involves two mechanisms; Hoffman elimination and enzymatic hydrolysis. Hoffman elimination is a non-enzymatic, pH dependent decomposition *in vivo*. Furthermore, atracurium may undergo non-specific ester hydrolysis even in patients with atypical plasma pseudocholinesterase. Therefore, its inactivation is likely to be independent of hepatic and renal function.⁵ In addition, metabolites from both pathways do not appear to have neuromuscular blocking effects.

Neuromuscular effects of atracurium are enhanced by halothane⁵ and isoflurane.⁴ Interactions between neuromuscular blocking agents and other drugs are common^{6–9} but beyond the scope of this discussion. Neomycin, streptomycin, gentamycin, kanamycin, paramomycin, viomycin, polymyxin A & B, tetracycline, lincomycin, local anaesthetics, magnesium, diuretics, clindamycin and colistin are known to prolong neuromuscular block. The patient had received vancomycin, a glycopeptide related to ristocetin and danocrine, a synthetic androgen, neither of which have been reported to enhance blockade. Patients with myasthenia gravis,^{10–12} Eaton-Lambert syndrome, myotonia¹³ and upper and lower motor neuron diseases¹⁴ are more sensitive to neuromuscular blocking agents.

Our patient had no evidence of neuromuscular disease or electrolyte disorder. She had received gentamycin preoperatively. The total dose of atracurium administered was 105 mg ($1.78 \text{ mg} \cdot \text{kg}^{-1}$) in a 2.5-hour period. The initial dose was 25 mg ($0.42 \text{ mg} \cdot \text{kg}^{-1}$) and each subsequent dose was

20 mg ($0.34 \text{ mg} \cdot \text{kg}^{-1}$). The three final doses were preceded by a full train-of-four response and a sustained tetanic response. Thus, although the maintenance dose of $0.34 \text{ mg} \cdot \text{kg}^{-1}$ seems high, this dose was required to achieve adequate surgical relaxation. Reversal with neostigmine and glycopyrrolate were required at the end of the procedure. Train-of-four and tetanic response reverted to normal; however, the patient remained weak. This finding could represent a cumulative effect.

During this anaesthetic and after general anaesthesia 12 days earlier the patient had recovered after succinylcholine administration. Gentamycin is known to potentiate the effects of competitive neuromuscular blockers; however, atracurium was administered only when the patient showed signs of recovery from blockade. Prolonged weakness in the presence of normal train-of-four, twitch height and tetanic contraction is difficult to explain; particularly so with atracurium, a short-acting drug that does not depend on hepatic or renal function for metabolism. The patient did not have hypothermia¹⁵ or an electrolyte imbalance^{16,17} which might explain weakness.

It is possible that even with a normal response to tetanic stimulation at 100 Hz, up to 33 per cent of receptors are occupied by atracurium.¹⁸ It is conceivable that such a residual blockade could explain some of the weakness. In addition, the patient had received diazepam 5 mg IV for sedation. Diazepam is a centrally acting muscle relaxant and could theoretically potentiate the effects of other muscle relaxants. Although it is difficult to explain why our patient had prolonged weakness, one can speculate that repeated doses (five doses) of atracurium may result in weakness due to presynaptic, postsynaptic or centrally mediated actions. This appears to be the first report of persistent weakness when atracurium was used for muscle relaxation.

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Résumé

Lors de l'anesthésie générale avec oxygène, protoxide d'azote et enflurane, une femme âgée de 29 ans a reçu une dose totale de 105 mg ($1.78 \text{ mg} \cdot \text{kg}^{-1}$) d'atracurium pour une période de 2.5 heures. Le blocage neuro-musculaire ne pouvait être renversé avec la neostigmine et la ventilation mécanique était nécessaire pour une période de trois heures post-opératoire. La patiente a reçu de la succinylcholine sans aucune séquelle avant et après cette épisode. Ceci est le premier rapport sur une patiente ayant démontré une faiblesse prolongée après avoir reçu l'atracurium.