Clinical Reports

Anaphylactoid reaction to atracurium

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Atracurium is a new intermediate-acting muscle relaxant, relatively devoid of cardiovascular effect in the clinical dose range. Histamine release is reported in a dose-dependent fashion, but below the threshold for haemodynamic effect within the recommended dose limits. We report a case of an anaphylactoid reaction to a low dose (0.2 mg·kg^{-1}) of atracurium, and discuss the peculiar aspects of this case that predisposed the patient to this event.

Massive histamine release (anaphylactoid reaction) following administration of neuromuscular blocking agents has been reported.[1–8] The new muscle relaxant atracurium has been reported to produce clinically insignificant histamine release when given in the recommended dose range. We report a case of severe cardiovascular instability following intravenous administration of atracurium and discuss possible factors accentuating histamine release in this patient.

Case report

A 74-year-old man, 173 cm, 95 kg, with carcinoma of the prostate was scheduled for pelvic lymph node dissection with concomitant placement of I_{131} implants. His past medical history included hypertension and glaucoma, both adequately controlled. Medications included hydroclorothiazide, pilocarpine and timolol opthalmic drops. The timolol dose was one drop of a 0.5 per cent solution in each eye twice daily. Previous bilateral pulmonary decortication under general anaesthesia had been without complication. The patient denied any history of allergies.

The morning of surgery the patient was premedicated with 10 mg of diazepam PO, and given his morning doses of timolol and pilocarpine. Lumbar epidural anaesthesia was established using 15 ml two per cent mepivicaine with a resultant T_6 sensory level. A radial arterial catheter was placed.

In the operating room, the patient's initial blood pressure was 130/70 mmHg with a regular heart rate of 60 beats/min. Induction of anaesthesia was accomplished with 3 mg curare, 350 mg thiopentone, 100 mg succinylcholine, and 2 ml four per cent lidocaine by intratracheal instillation. Maintenance of anaesthesia was with isoflurane (0.25–0.5 per cent), N_2O/O_2 70–30 per cent, and two per cent mepivicaine via continuous epidural catheter. The patient was permitted to breathe spontaneously and normocarbia was verified by arterial blood gas analysis, pH 7.43, $PaCO_2$ 38, and PaO_2 203 (FiO_2 0.30).

Forty-five minutes following the initial epidural dose of mepivicaine, an additional 5 ml was administered. Fifteen minutes later the surgeons complained of abdominal muscle movement and inadequate relaxation. It was decided to control ventilation and establish neuromuscular blockade. Blood pressure was 110/70, heart rate 60. Atracurium 20 mg (0.2 mg·kg^{-1}) was administered by rapid intravenous infusion. Immediately following the infusion, hypotension was noted (70/40) followed shortly by bradycardia (40 beats/min). Facial and truncal flushing was noted. The patient was

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immediately placed in a head-down position and rapid infusion of crystalloid begun. Atropine 0.8 mg and ephedrine 10 mg were given intravenously. The initial response was appropriate: blood pressure 100/60, heart rate 60; however, there was rapid deterioration (80/50, heart rate 62). Phenylephrine (0.3 mg) was given in three divided doses with transient improvement of systolic blood pressure; however, further deterioration of haemodynamic variables occurred almost imediately. At this time, the patient's blood pressure failed to respond to ephedrine or phenylephrine and an anaphylactoid reaction was suspected.

Epinephrine (0.5 mg) was given intravenously. A prompt response was noted, with hypertension (200/100) and an increase in heart rate to 72 beats/min. Multifocal premature ventricular contractions were noted. Ischaemic changes were also observed, as evidenced by ST segment depression monitored by modified V_5 EKG lead. Lidocaine 100 mg was administered intravenously, followed by a continuous infusion ($1\ mg \cdot kg^{-1} \cdot min^{-1}$), with resolution of the ventricular irritability. Blood pressure was 98/60 and ST segment depression was still presennt. In order to maintain blood pressure, a phenylephrine infusion ($100\ \mu g \cdot min^{-1}$) was started. ST segments reverted to isoelectric.

Within 60 minutes of the incident, surgery was concluded. Despite full twitch response by nerve stimulator, atracurium was reversed with edrophonium $0.5\ mg \cdot kg^{-1}$ and atropine $7\ \mu g \cdot kg^{-1}$. The patient was extubated without complication. He was transferred to the intensive care unit for observation and to rule out myocardial infarction. Volume infusion in excess of $250\ ml \cdot hr^{-1}$ and phenlephrine at $40\ \mu g \cdot min^{-1}$ were required for the next 2–3 hours. After 48 hours cardiac isoenzymes remained negative and serial electrocardiograms showed no change from the preoperative trace. The remainder of the postoperative period was uneventful.

Four weeks after discharge from the hospital, the patient returned to the anaesthesia clinic for intradermal testing. Subcutaneous injections of normal saline 0.2 ml, atracurium 0.2 ml (1:1000 dilution), d-tubocurarine 0.2 ml (1:1000), metocurine 0.2 ml (1:1000) and pancuronium 0.2 ml (1:1000) were placed in the right forearm. A 42 mm flare was noted to atracurium, with a 24 mm flare noted to pancuronium and no response to the others. The patient was advised that safe use of these two agents could not be assured and that he should not receive these medications in the future.

Discussion

Atracurium is a new intermediate-acting, non-depolarizing muscle relaxant. Few adverse cardiovascular effects have been reported. Basta *et al.*[9–11] have demonstrated the histamine releasing potencies of several non-depolarizing muscle relaxants (Table).

Several investigators[7,12–17] have examined the cardiovascular effects of non-depolarizing muscle relaxants. Atracurium, when compared to other agents, has been shown to cause little or no change in heart rate, blood pressure, cardiac output or systemic vascular resistence. Local histamine-like responses over the venous distribution of an intravenous infusion of atracurium have been described.[18,19] Philbin *et al.*[13] noted a significant decrease in sytemic vascular resistence and blood pressure following the administration of atracurium with a concomitant increase in cardiac output. However, Hilgenberg *et al.*[14,17] did not demonstrate any change in mean arterial pressure, cardiac output or systemic vascular resistence with 0.2 or $0.4\ mg \cdot kg^{-1}$ of atracurium.

Life-threatening reactions to muscle relaxants appear to occur with a low incidence.[6] Cardiovascular instability with cutaneous vasodilation, low central venous pressure, and sinus tachycardia were the most common presentation, followed by bronchospasm, angioedema and pulmonary oedema.[21]

These clinical events are described as anaphylactoid because of their resemblance to the immediate, immune-mediated hypersensitivity reactions. The chief difference is the absence of prior exposure to prime the immunological system for an IgE, or less frequently IgG, reagin to adhere to mast cells and trigger degranulation. Degranulation results in histamine release with subsequent local and systemic response. In the anaphylactoid response, the histamine release occurs by a direct mast cell response to the injected substance, without reagin interface.

Severe reactions of this type to atracurium have been reported by Mercer ($0.8\ mg \cdot kg^{-1}$), Siler *et al.* ($0.6\ mg \cdot kg^{-1}$), and Lavery *et al.* ($1.0\ mg \cdot kg^{-1}$).[20,26,27] Severe hypotension, bronchospasm and truncal flushing were the presenting features, and were most likely histamine-mediated.

TABLE Doses of relaxants associated with serum histamine and cardiovascular changes

Drug	*Dose* $mg \cdot kg^{-1}$	*ED_{95} (multiple)*	*MAP fall*	*Histamine increase (multiples)*
d-Tubocurarine	0.5	1	yes	4
Metocurine	0.5	2	yes	1.9
Atracurium	0.6	3	yes	2
Vecuronium	0.2	3.5	no	0

Lavery *et al.* additionally reported a positive intradermal test to atracurium.[27] Moss *et al.*[12] demonstrated that histamine release caused a linear decline in blood pressure. Rapid atracurium infusion may also magnify the histamine release, with slow infusion and H_1 blockade by antihistamines attenuating this phenomenon.[22,23]

Our patient received a rapid infusion of a low dose ($0.2\,mg \cdot kg^{-1}$) of atracurium. The response was immediate hypotension, bradycardia and cutaneous vasodilation. The patient had a preoperative heart rate of 60 beats/min, suggesting beta-blockade from systemic absorption of opthalmic timolol. Beta antagonism has been shown to greatly increase histamine release by decreasing tissue levels of cyclic adenosine monophosphate (c-AMP).[24] Conversely, beta-antagonists, such as epinephrine, increase c-AMP and attenuate histamine release.[24] Cholinergics may decrease histamine release, or its activity on pulmonary receptors, independent of c-AMP.[25] The ST segment depression noted may have been augmented by the coronary vasoconstrictive property of H_1 stimulation by histamine. The huge fluid and alpha agonist support required can be attributed to capillary permeability with massive "third space" fluid requirements.

Finally, the intradermal testing was highly suggestive of histamine-mediation of this reaction; however, definitive serum electrophoresis for IgE or IgG was not available to support or dispute these equivocal tests.

In summary, this patient experienced, while under general/epidural anaesthesia, an adverse cardiovascular response to atracurium. The onset of the symptoms and the suggestive intradermal tests implicate atracurium as the offending agent. The patient was known to be hypertensive and may have had significant compromise of his cardiovascular system. This medical history, the treatment regimen for glaucoma (beta-antagonism) and the histamine releasing properties of atracurium would suggest this combination of clinical circumstances as one where atracurium should be used with caution, such as by slow infusion.

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Résumé

L'atracurium est un nouveau bloqueur neuromusculaire à action intermédiaire, relativement libre d'effet cardiovasculaire aux doses habituellement utilisées en clinique. Une libération d'histamine dose-dépendante est rapportée et ce, avec les doses habituellement recommandées pour éviter les effets hémodynamiques. On rapporte le cas d'une réaction anaphylactoïde après administration d'une petite dose (0.2 $mg \cdot kg^{-1}$) d'atracurium et on discute des aspects particuliers de ce cas pouvant disposer le patient au choc anaphylactoïde.