ADVERSE REACTIONS TO ATRACURIUM

Sir,—The recent report of a severe adverse reaction to atracurium [1] has prompted us to report two further severe reactions to this drug.

An obese 9-yr-old 45-kg boy was admitted to our hospital unconscious with a closed head injury and a fractured right elbow. A CT scan showed diffuse brain injuries and surgery was planned to insert a ventricular drain for intracranial pressure monitoring. The patient had no significant past medical history except for occasional “asthma attacks” which did not require admission to hospital. Anaesthesia comprised thiopentone 250 mg, suxamethonium 5 mg, alcuronium 20 mg, nitrous oxide and oxygen, and increments of fentanyl 50 µg. He was admitted to the ICU after operation for 4 days.

Surgery for internal fixation of the right elbow was planned 10 days after admission. No premedication was given. Anaesthesia was induced with thiopentone 250 mg, followed by atracurium 20 mg after flushing the i.v. cannula with normal saline. Tracheal intubation was undertaken without difficulty. However, attempts to ventilate the lungs using a Magill system proved impossible. A diagnosis of severe bronchospasm was made after exclusion of tube obstruction. The patient rapidly became extremely cyanosed and developed bradycardia. Four millilitre of 1:10,000 adrenaline was given i.v. Manual ventilation of the lungs with 100 % oxygen became easier almost immediately and the patient’s colour improved.

Throughout this period of approximately 20 min, the carotid and femoral pulses remained palpable, but surgery was abandoned and the patient was admitted to the ICU. Approximately 4 h after the adverse reaction, he was awake and orientated. Chest x-ray was normal.

Surgery was re-scheduled to take place 3 days later. After oral premedication with diazepam 10 mg, anaesthesia was induced with nitrous oxide, oxygen and halothane and tracheal intubation was accomplished without difficulty. Alcuronium 15 mg was given and anaesthesia was maintained with nitrous oxide, oxygen and supplements of fentanyl. Anaesthesia and surgery proceeded uneventfully. Intradermal testing was carried out 1 month later as described by Fisher [2]. Dilutions of thiopentone 1:100, atracurium 1:1000 and normal saline were used. The intradermal tests were negative after 30 min and the patient was again tested with atracurium diluted to 1:100, but again he showed no positive response.

Our second report is of a healthy 58-yr-old 50-kg woman (with no history of any significant previous illnesses) scheduled for elective total hip replacement. After premedication with oral diazepam 5 mg, thiopentone 200 mg was given, followed by a flushing dose of normal saline, atracurium 25 mg and tracheal intubation. Anaesthesia was maintained with nitrous oxide, oxygen and morphine supplements, 0.5 % isoflurane and an infusion of atracurium 10 mg kg⁻¹. Approximately 2.5 h after induction of anaesthesia, her systolic arterial pressure decreased inexplicably and suddenly to 60 mm Hg. Blood loss had been insignificant, she had received adequate fluids and a second unit of blood was being infused. The ECG monitor showed normal sinus rhythm and polymethyl methacrylate cement had not yet been applied. The end-tidal carbon dioxide concentration was unchanged, the patient appeared flushed and warm, and the ears and hands became markedly oedematous and hyperaemic. A tentative diagnosis of adverse reaction to blood transfusion was made.

Blood transfusion was stopped, additional volumes of Hartmann’s solution were infused, and the isoflurane discontinued. Hydrocortisone 100 mg and chlorpheniramine 5 mg were given i.v. The systolic arterial pressure gradually improved to 100 mm Hg over the next 30 min and surgery proceeded uneventfully. After operation she was admitted to the ICU, where she remained well. The blood used for transfusion showed no haematological incompatibility and no irregular alloantibodies were detected in the patient’s serum.

Four hours after the onset of acute hypotension blood was assayed for plasma immunoglobulin and complement C3 and C4 concentrations, but these were within the given normal range. One month later, intradermal skin testing was carried out for thiopentone and atracurium, with normal saline as a control. A florid positive reaction was seen with atracurium diluted 1:1000.

Nine previous communications have reported severe adverse reactions to atracurium [3]. Of our two patients, only the second showed a positive response to intradermal testing. Although there is no evidence that severe anaphylactoid reactions can be produced by histamine release in response to drugs given in normal doses, or that direct histamine release in response to drugs can produce severe bronchospasm [3], our first patient was very similar to the report by Stinton-Hopkins [1], where severe life-threatening bronchospasm followed the administration of atracurium to a patient with a history of eczema and asthma. Curiously, immediate cardiovascular collapse was not a feature in our first patient.

We note the view shared by Fisher [4] and by Rowlands [5] that “modification in anaesthetic technique based on the history of allergy, atopy or asthma is unlikely to reduce the likelihood of severe clinical anaphylaxis”. Nevertheless, we believe that the severe bronchospasm in our first patient resulted from histamine release, and atracurium should probably be avoided in such patients. The acute hypotension in our second patient was probably an anaphylactoid reaction to atracurium, as suggested by the intradermal testing. The clinical features of oedema, and warm vasodilated peripheries have been described previously. Interestingly, the onset was delayed and did not occur at induction, but this is not a unique feature [6].

Our two case reports support the usefulness of intradermal skin testing if clinical anaphylaxis occurs following administration of a number of drugs. Measurement of plasma immunoglobulin and complement C3 and C4 concentrations was not useful in our second patient. This was not unexpected, as a moderate amount of blood had been lost and approximately 2 litre of crystalloids had been infused. Once again, the importance of administering adrenaline without delay in severe life-threatening clinical anaphylaxis is evident.

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SUXAMETHONIUM AND MALIGNANT HYPERThERMIA

Sir,—The letter by Dr Nelson [1] concerning the in vitro response of human skeletal muscle to suxamethonium deserves comment. Dr Nelson reports that skeletal muscle from three family members testing positive for malignant hyperthermia (MH) responded with contractures when challenged with suxamethonium 5 (one patient) or 50 (two patients) mmol litre⁻¹. He states that “Further studies are needed to clarify these effects of suxamethonium on MHS muscle”. The results reported contrast with those from Dr Denborough’s laboratory [2], with our own results [3, 4] and with the results of several other investigators [see 3, 5]. Dr Nelson also reports that gracilis muscle from four MH susceptible pigs exhibited contracture responses to suxamethonium 50 mmol litre⁻¹ [1]. This is in contrast to Dr Denborough’s [2] results and our negative findings with gracilis muscle from six pigs (F1 generation from a Yorkshire x Duroc cross) challenged in vitro with halothane to verify MH susceptibility (unpublished studies).

The results obtained by Dr Nelson in porcine muscle in vitro may be explained by differences between breeds in muscle responses to agents associated with MH, as suggested in his letter. An example of a possible breed difference in response to halothane has been reported by Gallant [6]. In this latter study, halothane caused a small plasmalemmal depolarization in muscle from MH-susceptible Poland China pigs. However, this depolarization was not observed in MH-susceptible Pietrain pigs. Certainly, Dr Nelson’s results obtained in the pig cannot relate specifically to MH, as some breeds do not show a contracture to suxamethonium. Perhaps the response to suxamethonium is the manifestation of some other skeletal muscle correlate of the MH defect expressed only in the breed used by Dr Nelson.

We know that skeletal muscle (diaphragm) from animals not susceptible to MH can exhibit contractures to suxamethonium. Previously we have reported occasional contractures to suxamethonium in rat diaphragm preparations [7] and, more recently, we have observed consistent and large (25-33 % twitch height) contractures to suxamethonium 50 mmol litre⁻¹ in mouse (male Swiss-Webster albino) diaphragm preparations (unpublished observations) which closely resemble those in human skeletal muscle and the “small” contracture in porcine skeletal muscle reported by Nelson [1]. We have only observed occasional small (one patient = 0.4 g; two patients = 0.3 g; two patients = 0.2 g) contractures to suxamethonium 50 mmol litre⁻¹ in muscle from 97 patients diagnosed as MH susceptible ([3, 4] and unpublished observations). These contractures were similar in magnitude to suxamethonium contractures observed by other investigators [5]. Therefore, we do not believe that a contracture to suxamethonium relates to MH.

The fact that the three patients exhibiting contractures to suxamethonium in the Nelson study were from the same family suggests that this family possesses some abnormality unrelated to the MH defect. This abnormality is not shared by the three MH susceptible patients who were not family members in the same study. We find the observations of Dr Nelson interesting. However, we do not believe that contractures to suxamethonium relate specifically to MH.

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Sir,—Drs Fletcher, Lizzo and Rosenberg state that they do not believe that in vitro muscle contractures to suxamethonium (we observe in MH human and pig muscle) relate specifically to MH. This view is based on interpretation of our data which I believe is incorrect. Based on their experience of contracture-testing of six pigs compared with our experience of 200, they suggest that a breed difference may explain our results. We did suggest that a genetic, but not a breed, difference may be involved. In fact, we have observed these in vitro contractures to suxamethonium in gracilis muscle from MH phenotype H in pure bred Poland China and Pietrain pigs. Thus it is difficult to find substantiation for their statement “results obtained in the pig cannot relate specifically to MH...” It is interesting that, in their own studies, these authors have observed five of 95 MH positive diagnostic human patients whose muscles also produced in vitro contractures to suxamethonium 50 mmol litre⁻¹. If they have observed no suxamethonium contractures among