problems from this study are not going to be as great as was originally anticipated.

I return to my basic thesis that any patient on routine aspirin or NSAID medication [1] should have a bleeding time performed before an extradural is sited. If the bleeding time is prolonged beyond 10 min, then the anaesthetist must balance the advantages and disadvantages of siting the extradural in that particular patient.

R. Macdonald
Leeds


ATRACURIUM AND HISTAMINE

Sir,—I was interested to read the paper by Adt, Baumert and Reimann on the role of histamine in the cardiovascular effects of atracurium [1], in which work by myself and colleagues was quoted extensively [2, 3]. I would like to congratulate them on a well executed and researched project. The obvious question is, of course, how much one may infer about the true haemodynamic side effects of a drug when patients recruited to the study have been prescreened for cardiovascular medications? These drugs may well obtrude or exaggerate any haemodynamic event after i.v. administration of a large bolus dose of atracurium. I think the authors need to look in more detail at the individual patient responses and the preoperative medication. It is interesting, however, to observe the data on cardiac index and systemic vascular resistance.

R. P. F. Scott
Salisbury


Sir,—Thank you for the opportunity of replying to Dr Scott’s comments. Conditions for clinical studies are optimal when healthy individuals are investigated and all interfering medication is excluded. We represent a clinic for cardiac disease where all comments. Conditions for clinical studies are optimal when healthy individuals are investigated and all interfering medication is excluded. We represent a clinic for cardiac disease where all interfering medication is eliminated.

We have shown that a transient increase in plasma histamine concentration occurs after i.v. heparin, which could account for a cardiovascular reaction [1, 2]. In differing patients, different plasma histamine concentrations can occur, for which different preoperative medications may be partly responsible. However, there is no clear relationship between medication and cardiovascular reaction pattern; for example, patients with and without beta receptor blockers did not develop tachycardia, and the decrease in mean arterial pressure after histamine release was independent of antihypertensive premedication. Lorenz and Doenicke have demonstrated that, in approximately 3% of all patients undergoing surgery, serious to life-threatening plasma histamine concentrations occur—for example after administration of antibiotics—whereas the incidence of all types of histamine reactions may be as great as 20–30%. We believe that the variety of drugs administered during surgery is the cause of in calculable histamine release and that preoperative medication is of less importance for cardiovascular sequelae.

During coronary artery surgery there is a tendency to interpret intraoperative arrhythmias as cardiac ischaemia. However, Levi’s group have achieved very impressive results in animal studies, showing that cardiac anaphylaxis is an independent pathological phenomenon in which histamine often plays a lethal role [4, 5]. Similarly, preliminary results of an in vitro study of mast cells from human hearts show that these mast cells do, in fact, release histamine when perfused with drugs that are clinically suspected to be histamine liberators. These results underline that the influence of histamine on the heart is of a clinical importance which has not yet been completely investigated.

It is our philosophy to protect patients with a deficient cardiovascular system against histamine-mediated reactions, occurring during anaesthesia, by means of prophylactic administration of H1- and H2-receptor antagonists. The aim of the study under discussion was, first, to establish the amount of histamine released and the cardiovascular reaction induced by a clinical dose of atracurium and, second, to investigate if muscle relaxants used in these patients can be achieved safely following the above-mentioned “prophylaxis”. In our opinion, both questions have been answered adequately.

M. Adt
Berlin


PROBABLE RESISTANCE TO VECURONIUM INVOLVING THE 17-HYDROXY METABOLITE

Sir,—The editorial by Hunter [1] has prompted this report of a case of probable resistance to vecuronium accompanied by the detection of its 17-hydroxy metabolite. A 26-year-old waitress (weight 62 kg), being otherwise healthy, was to undergo knee surgery. She was not currently receiving medication and did not abuse alcohol or other chemical substances. Premedication comprised diazepam 10 mg orally and pethidine 50 mg i.m. After administration of glycopyrronium 0.2 mg and vecuronium 1 mg, anaesthesia was induced i.v. with thiopentone 250 mg and the trachea was intubated with the aid of suxamethonium 100 mg. The patient’s lungs were then ventilated manually with nitrous oxide and 1% endurane in oxygen. Vecuronium 4 mg was injected, but without effect: the peripheral neuromuscular showed no fade on train-of-four stimulation. A new ampoule of vecuronium, of the same batch, was prepared and a second 4-mg dose of the drug was administered, again without demonstrable neuromuscular block. As the patient was coughing on the tracheal tube, thiopentone 100 mg was given i.v. Venous blood samples were taken (which were sent to the laboratory for centrifugation and then stored at −70 °C). The patient then received pancuronium 3 mg which provided neuromuscular block sufficient for the 45-min surgery. The residual block was antagonized with neostigmine-glycopyrronium and the postoperative course was uneventful.

The blood samples, and ampoules of vecuronium belonging to the same batch as that given, were analysed at the University Hospital, Groningen. The serum and plasma samples, respectively, contained 17-hydroxy vecuronium 304 and 305 ng ml−1 and vecuronium 35 and 65 ng ml−1. The ampoules were found to contain only vecuronium, ruling out the possibility that the patient received any drug other than that stipulated.

In an effort to confirm the finding, the patient agreed to donate blood for an in vitro experiment. A solution of vecuronium 2.25 µg ml−1 was added to the patient’s plasma and 2-ml samples
CORRESPONDENCE

were taken from this mixture at nine intervals for up to 128 min. Each sample was immediately acidified, stored at -20 °C and subsequently transferred to Groningen for analysis. All samples revealed vecuronium without any of its breakdown products.

Unlike the 3-hydroxy metabolite, neither of the two other metabolites of vecuronium (17-hydroxy and 3,17-dihydroxy vecuronium) have been detected previously in biological material [2]. The 17-hydroxy vecuronium in this patient’s blood may suggest an alternative metabolic pathway. However, this statement must be taken with caution, as her original samples were not acidified, and a sample of blood had not been collected before she received vecuronium. Finally, the sensitivity and selectivity of the analytical methods may have been at least partly responsible for 17-hydroxy vecuronium not having been demonstrated earlier in human material.

It is, nevertheless, of interest that 1 yr earlier, the same patient had required a general anaesthetic. According to the anaesthetic chart, she had been given vecuronium 4 mg and, about 5 min later, pancuronium 4 mg. Although there was no comment on the record as to why the two agents were administered in such short order, it is very likely that on that occasion also, no effect was seen with vecuronium. Final confirmation of her resistance to vecuronium and the detection of 17-hydroxy metabolite obviously can only be obtained if this particular patient requires a general anaesthetic again.

Anaesthetists confronted with apparent resistance to vecuronium which cannot be explained on more classical grounds should ask for plasma vecuronium analysis for the patient in question.

D. A. COZANITIS
Helsinki


REPEATED RESISTANCE TO NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN A PATIENT WITH MULTIPLE MYELOMA

Sir,—We read with interest the article by Tatman, Wrigley and Jones [1] and the accompanying editorial by Hunter [2] on the subject of resistance to non-depolarizing neuromuscular blocking agents, and now report a similar case.

A 62-year-old man with a 7-yr history of multiple myeloma, persistent haematuria, thrombocytopenia and clot retention was referred for cystoscopy and evacuation of clot under general anaesthesia. Current medication included ranitidine, nifedipine, acyclovir, fluconazole and cromolnixazole. Anaesthesia was induced with thiopentone 350 mg, fentanyl 100 µg and vecuronium 7 mg. Three minutes later, the patient started coughing on attempted laryngoscopy. The anaesthetist resumed manual ventilation with 70% nitrous oxide in oxygen supplemented by 1% isoflurane. Second doses of vecuronium 3 mg and thiopentone 150 mg were administered and laryngoscopy was performed after an additional 3-min. Tracheal intubation was unsuccessful, although it was noted that the cords were still not fully relaxed. During anaesthesia, further boluses of vecuronium 2 mg were necessary at 10-min intervals to suppress ventilatory efforts. A total of vecuronium 18 mg was given over a period of 90 min. Neuromuscular block was not monitored.

The following morning, the patient presented again with persistent clot retention, and a rapid sequence induction was carried out using thiopentone 250 mg, fentanyl 100 µg and suxamethonium 100 mg. Tracheal intubation was uneventful at 1 min. Neuromuscular block was maintained with atracurium 40 mg, but breathing started 15 min later, and another dose of atracurium 10 mg was administered. Neuromuscular monitoring was commenced, and after the second dose of atracurium all four twitches of the train-of-four were present. Another dose of atracurium 20 mg was needed to ablate the third and fourth twitch responses. During the 1-h procedure, atracurium 80 mg in total was needed to maintain relaxation. At the end of surgery, all four twitches of the train-of-four were present.

Protein electrophoresis performed later revealed results which were consistent with myeloma (normal values in parentheses): IgG 42.6 g litre^{-1} (5.3-16.5 g litre^{-1}), IgA 0.24 g litre^{-1} (0.80-4.00 g litre^{-1}), IgM 0.5 g litre^{-1} (0.5-2.0 g litre^{-1}), paraproteins 36.2 g litre^{-1} (normally absent); beta-2-microglobulin 7.6 mg litre^{-1} (0.0-2.6 mg litre^{-1}); albumin 32 g litre^{-1} (35-50 g litre^{-1}); alpha, acid glycoprotein (AAG) 0.8 g litre^{-1} (0.6-1.2 g litre^{-1}). Serum electrolyte concentrations before the second anaesthetic were: sodium 133 mmol litre^{-1}, potassium 3.4 mmol litre^{-1}, creatinine 148 µmol litre^{-1}, calcium 1.8 mmol litre^{-1} (2.15-2.55 mmol litre^{-1}).

Little is known about altered drug responses in patients with paraproteinaemia secondary to multiple myeloma. It has been speculated that the presence of abnormal circulating immunoglobulins and decreased plasma albumin concentrations could result in altered responses to drugs normally bound to protein [3], although a standard text does not mention that paraproteinaemia presents a significant anaesthetic problem [4]. The extent of plasma protein binding of both vecuronium and atracurium is similar, but different authors have expressed varying views on which plasma proteins are implicated [2].

It is expected that neuromuscular blocking agents would bind mainly to AAG. This is thought to be the basis of the resistance to atracurium in the case reported by Tatman, Wrigley and Jones. However, in this patient, AAG was normal and serum albumin reduced slightly, which may potentiate block. Although other factors such as drug interactions may be involved, it is likely that the altered response to neuromuscular blocking drugs is caused by increased binding to paraproteins, including possibly IgG or beta-2-microglobulin. It is important to note that there was no apparent change in the response to suxamethonium.

We would welcome further comments on the subject of altered pharmacodynamics in patients with multiple myeloma.

C. IP YAM
P. WOOD
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