ATRACURIUM OR VECURONIUM FOR MHS PATIENTS?

Sir,—I am writing in regard to comments made by Hunter [1] in her review entitled “Adverse Effects of Neuromuscular Blocking Drugs”, on the use of vecuronium and atracurium in malignant hyperthermia-susceptible (MHS) patients. She states that “satisfactory use of both agents has been reported in patients susceptible to malignant hyperpyrexia” and refers to papers by Buzello and colleagues [2] and Michel and Fronfield [3].

Buzello’s study was on MHS swine, not patients, and one of eight swine triggered in response to vecuronium. The explanations offered by the authors did not fit the facts as presented [4]. A literature search done for me by Organon Canada Ltd in December 1986 revealed no other studies in MHS swine or patients on the safety of vecuronium.

Michel and Fronfield [3] reported an 8 yr-old girl with a history of a previous MH crisis who was given atracurium for eye surgery without incident. There is other, more definitive proof of the safety of atracurium in MHS swine and patients. Skarpa and colleagues [5] reported that atracurium did not trigger MHS swine. Morrell and Harrison [6] have also shown that atracurium did not trigger MH in susceptible swine.

Hunter goes on to state that “it is considered preferable to allow spontaneous recovery from any non-depolarizing neuromuscular blocking agent”. Ørding and Nielsen [7] reported the safe use of atracurium in 40 MHS patients, in all of whom blockade was antagonized with neostigmine and glycopyrrolate without incident. It is our practice to antagonize neuromuscular blockade in MH patients whenever reversal would otherwise be indicated.

In conclusion, there is support in the literature for the safe use of atracurium in MHS patients. There is as yet no such support for vecuronium.

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REFERENCES

Sir,—When my review article was written the interesting paper by Ørding and Nielson [1] on the use of anticholinesterases in MHS patients given atracurium was not yet in print, so I was unable to refer to it. Their work is reassuring over the use of neostigmine in such patients, but the authors themselves state that the antagonism of neuromuscular block in such circumstances “is still controversial.” I doubt that allowing spontaneous recovery from neuromuscular block in the MHS patient could be considered anything but diligent practice.

At the Malignant Hyperthermia Workshop held during the European Congress in Vienna in 1986, Mauritz [2] stated that the safe non-depolarizing neuromuscular blockers to use in MHS patients were “alcuronium, pancuronium, vecuronium and atracurium”. Workers from Denmark substantiated this with respect to vecuronium [3].

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REFERENCES

THE COAGULATION AND FIBRINOLYTIC RESPONSE TO SURGERY

Sir,—The paper by Davis and colleagues [1] provides further evidence that performing hip surgery under regional anaesthesia which blocks the neuroendocrine response, results in less derangement of the coagulation system. This is obviously relevant to the explanation of a reduced incidence of DVT when hip surgery is performed under regional anaesthesia [2].

The difference in Thrombin Generation Index between GA and spinal groups during operation is in broad agreement with the results of a study I performed using another test of blood coagulability, the thromboelastograph. Characteristically, the thromboelastograph shortens during operation under GA, but is back to its preoperative value by the next day [3]. When hip surgery was performed under spinal anaesthesia, the thromboelastograph remained at preoperative values during operation,

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indicating that neuroendocrine activation of the coagulation system was being prevented, although this was not measured. Preliminary results have been reported [4].

The role of neuroendocrine mechanisms in the fibrinolytic response to trauma is much less clear [5]. Davies and colleagues [1] illustrated this by first stating that fibrinolytic activation is largely independent of catecholamines, and then explaining the difference between their study and that of Modig [6] by the latter’s use of adrenaline and ephedrine.

The fact that Modig and co-workers [6] found lower Factor VIII activation capacity in the extradural group, suggests that the adrenaline and ephedrine were not exerting any significant effect on the coagulation system.

It seems logical that, were fibrinolysis to be activated in the absence of coagulation, a hypocoagulable state would exist and lead to more blood loss, which is manifestly not the case with spinal blockade. Therefore, it seems likely that some component of neuroendocrine response is involved in fibrinolysis activation, and should be amenable to modification by regional block.

What we don’t know at present is the length of time the block needs to be continued to achieve maximum benefit in terms of reduction in thromboembolism. Spinal blocks have obvious limitations in this respect and a study directly comparing SAB and extended extradural block would be of interest.

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Sir,—Dr Lavies is correct to point out an apparent inconsistency in our discussion of the relationship between the neuroendocrine system and coagulation and fibrinolytic changes. Much of the understanding in this area comes from exercise studies in which, generally, the evidence is that there is no direct relationship between catecholamine concentrations and changes in fibrinolysis, as discussed. However, Colwell [1] has suggested that the fibrinolytic changes during vigorous exercise, whilst not directly related to catecholamines, result from haemodynamic changes and Factor XII activation that are themselves triggered by adrenaline. The evidence indicates parallel responses mediated by a Factor XII activation of the coagulation and fibrinolytic systems during acute strenuous exercise in normal humans and that these changes can be mimicked by adrenaline infusions, with evidence of additional modulation by glucocorticoids. It seems likely that similar conditions apply to the anaesthetic modification of the haemostatic response to surgery.

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REFERENCE


EFFECT OF ETOMIDATE AND METRONIDAZOLE ON PLATELET AGGREGATION

Sir,—Since imidazole is a very effective inhibitor of the thromboxane synthetase enzyme, it has become the basis for research into a suitable thromboxane synthetase inhibitor for clinical use [1, 2]. There are, however, a number of drugs frequently used by the anaesthetist which contain an imidazole structure. We decided, therefore, to investigate the thromboxane inhibitory effect of three such compounds—etomidate, midazolam and metronidazole. Both platelet aggregation and production of thromboxane were studied.

Platelet aggregation. Arachidonic acid (0.8 mmol litre−1 final concentration) was used to induce aggregation of platelet-rich plasma from blood to which was added varying concentrations of the compounds. Only at etomidate concentrations 100 times higher than peak concentrations seen upon i.v. administration (about 0.2 μg ml−1 [3]) was it possible to demonstrate an inhibition comparable to that produced by imidazole 1 nmol litre−1 (fig. 1). Midazolam 5 μg ml−1 and metronidazole 200 μg ml−1 (10 times normal plasma concentrations [4, 5]) showed no inhibition of platelet aggregation, but metronidazole did show a small degree of inhibition at the very high concentration of 500 μg ml−1 (fig. 2).

Sir,—Dr Lavies is correct to point out an apparent inconsistency in our discussion of the relationship between the neuroendocrine system and coagulation and fibrinolytic changes. Much of the understanding in this area comes from exercise studies in which, generally, the evidence is that there is no direct relationship between catecholamine concentrations and changes in fibrinolysis, as discussed. However, Colwell [1] has suggested that the fibrinolytic changes during vigorous exercise, whilst not directly related to catecholamines, result from haemodynamic changes and Factor XII activation that are themselves triggered by adrenaline. The evidence indicates

parallel responses mediated by a Factor XII activation of the coagulation and fibrinolytic systems during acute strenuous exercise in normal humans and that these changes can be mimicked by adrenaline infusions, with evidence of additional modulation by glucocorticoids. It seems likely that similar conditions apply to the anaesthetic modification of the haemostatic response to surgery.

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