ROYAL ACADEMY OF MEDICINE IN IRELAND

SECTION OF ANAESTHESIA

Proceedings of meeting held on Friday, 13th October, 1989.

MUSCLE RELAXANTS IN THE INTENSIVE THERAPY UNIT (ITU)

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Although muscle relaxants are not as important as sedative and analgesic agents in intensive therapy, they can be useful in the management of the critically ill patient with poor lung compliance, usually due to adult respiratory distress syndrome. With this pathology, the hypoxic drive to breathing is so great that it may be impossible to achieve adequate artificial ventilation with the use of analgesics and sedatives alone. Muscle relaxants are also used regularly in paediatric and neurosurgical intensive care and in the management of certain discreet conditions such as tetanus. For many years, intermittent bolus doses of such non-depolarising muscle relaxants as alcuronium or pancuronium were used satisfactorily in these circumstances. such practices had their limitations however; especially in the patient who was also in renal failure, when recovery from neuromuscular blockade could be prolonged despite peritoneal or haemodialysis, delaying weaning from the ventilator. This has been described with alcuronium [1] and pancuronium[2].

Following the advent of atracurium and vecuronium, Which do not rely primarily on the kidney for elimination, it was therefore decided to study the use of both these drugs by constant infusion in the critically ill patient in renal and respiratory failure, whose clinical condition necessitated the use of muscle relaxants. This work had the approval of the Committee of Safety of Medicines and the Hospital Ethics Committee. Initially two pharmacodynamic studies were carried out; the first five patients were given a bolus of atracurium 0.6mg kg^{-1} followed by a constant infusion of atracurium 0.6mg kg^{1} hr^{-1} and neuromuscular function was monitored continually by the train-of-four (TO4) twitch technique. The second group of seven patients received a bolus dose of vecuronium 0.1mg kg^{-1}, followed by vecuronium 0.05mg kg^{-1} hr^{-1} by constant infusion and were monitored in the same way. All twelve patients also received a constant infusion of both morphine and midazolam throughout the study period. After the infusion of muscle relaxant had been stopped, recovery of the TO4 to control values occurred in a mean time of 60 min in the atracurium group[3], but in the vecuronium group recovery took a mean time of over 18hr.[4], a different order of magnitude. Indeed, the recovery of the TO4 after a infusion of atracurium for a mean time of 23 hr., was little different from that after a single bolus of the drug in the absence of an anticholinesterase. Atracurium therefore seemed much more appropriate for use by infusion in the ITU than vecuronium and a rapid recovery, so useful for cerebral assessment or for weaning from artificial ventilation, could be relied upon with atracurium.

It was realised however that one of the metabolites of atracurium, laudanosine, which is known to cause cerebral irritability in high doses in animals[5] and to be excreted at least in part by the kidney, may accumulate in such critically ill patients. Although the plasma levels of laudanosine after a bolus dose of atracurium are much lower than those known to cause cerebral irritation in animals, even in renal failure patients (200 ng ml^{-1} compared with 14ug ml^{-1} [6], the plasma levels of laudanosine after several hours even days, of an atracurium infusion had not been fully defined. Yate and his colleagues[7] reported laudanosine levels in five intensive care patients receiving atracurium infusions for up to six days. The highest recorded level (in a patient who was not in renal failure), was 5. lug ml^{-1}. No evidence of cerebral irritation was reported.

We therefore decided to undertake a pharmacokinetic study of atracurium and laudanosine in critically ill patients receiving infusions of the drug in the ITU. Fourteen further patients have now been reported, seven of whom were in renal failure and seven of whom had normal renal function[8]. The infusion of atracurium (0.6 mg km^{-1} hr^{-1}) was given for between 11 nad 47 hr. In all fourteen patients the plasma atracurium levels plateaued out within 30 min. of starting the infusion and disappeared within 120 min. of stopping the drug. Thus no evidence of cumulation of atracurium was found; results in keeping with those from the pharmacodynamic study. In the patients with normal renal function, the plasma laudanosine levels rose for the first 10-15 hr., before plateauing out at 1.5-2. Oug ml^{-1}. In the sicker patients with renal and respiratory failure, there was a greater range in the laudanosine levels; the highest recorded was 4.3 ug ml^{-1}, in keeping with Yate's study[7]. The plasma laudanosine level fell steadily over 12hr. after stopping the atracurium infusion in the patients with normal renal function, but in those with multisystem organ failure the decline was slower. Although the volume of distribution was greater and the elimination half-life of laudanosine longer in the renal failure group, there was no difference in the clearance of the metabolite between the two groups. Excretion of laudanosine in humans does not depend solely on renal function; the liver may also be involved. No evidence of cerebral irritation was seen even after the infusion of atracurium had been stopped and neuromuscular recovery had occurred; laudanosine still present in the plasma was not seen to have any untoward effect.

Further studies of atracurium infusions in the ITU are required, especially in patients with lever failure, but at present there is no evidence of cumulation of this drug even in the critically ill. The rapid recovery on terminating the infusion is useful for cerebral assessment and for rapid weaning from the ventilator. In contrast, because of the risk of cumulation, vecuronium should only be given by bolus doses in the ITU. It has little to offer over the older non-depolarising muscle relaxants in these circumstances and is of course, much more expensive.

Laudanosine levels are higher when infusions of atracurium are given than after bolus doses, but at the present time there is no evidence of cerebral irritation from the metabolite. The toxic level of laudanosine in man remains unknown.

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