EFFECT OF RENAL FAILURE ON LAUDANOSINE EXCRETION IN MAN


Although atracurium, *per se*, does not produce prolonged neuromuscular blockade in patients with renal failure (Hunter, Jones and Utting, 1982; Fahey et al., 1984), the influence of renal failure on the elimination of its metabolites has not been determined in man. Of the major metabolites of atracurium, laudanosine is of particular interest since it has central nervous system (CNS) stimulant properties in animals (Babel, 1899; Merrier and Merrier, 1955). We have determined the influence of renal failure on the excretion of laudanosine in patients receiving atracurium to provide muscle relaxation during surgical procedures.

PATIENTS AND METHODS

Sixteen patients were studied, after giving informed consent as approved by our Human Research Committee. Eight patients had normal renal function and were scheduled for elective surgery; the laudanosine concentrations in these patients were reported in an earlier publication (Fahey et al., 1984). The remaining eight patients had renal failure sufficient to necessitate haemodialysis. They were scheduled for cadaver kidney transplant and were dialysed within 24 h of surgery. All patients received diazepam 10 mg by mouth before surgery. Ninety minutes later, anaesthesia was induced with thiopentone 1–2 mg kg$^{-1}$ i.v. and the inhalation of nitrous oxide and halothane in oxygen via a face mask. The trachea was intubated without the use of neuromuscular blocking drugs, and ventilation controlled to maintain pH between 7.35 and 7.40. Anaesthesia was maintained with 0.6% end-tidal halothane and 60% nitrous oxide in oxygen, as measured continuously by mass spectrometry. Pharyngeal temperature was maintained at 37 °C with surface warming.

Once stable anaesthetic conditions had been achieved (approximately 30 min after endotracheal intubation) atracurium 0.5 mg kg$^{-1}$ was injected as in i.v. bolus. Venous blood samples were obtained from a separate i.v. cannula at 2, 4, 6, 8, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min after the injection of atracurium. These samples were heparinized, immediately acidified with sulphuric acid 3 mol litre$^{-1}$ so that the plasma achieved a pH of 5.0 ± 0.5, centrifuged in the operating room, and the plasma frozen to −20 °C until analysis. No additional doses of atracurium were given to maintain surgical relaxation; instead, suxamethonium was administered by infusion, as required.

SUMMARY

Patients with renal failure and undergoing a cadaver renal transplant were found to have plasma concentrations of laudanosine, following the administration of a single bolus dose of atracurium 0.5 mg kg$^{-1}$, higher than those found in patients without renal failure. Since laudanosine is a known central nervous system stimulant in a variety of animal species, its actions should be investigated further in man, and particularly in patients with renal failure.
Concentrations of laudanosine were determined using gradient ion-exchange liquid chromatography with a sodium sulphate 0.06 mol litre$^{-1}$ (pH 2.0) and acetonitrile mobile phase and N-methyl-laudanosine as an internal standard (Fahey et al., 1984). The assay was sensitive to a laudanosine concentration of 10 ng ml$^{-1}$ with a coefficient of variation of 9% at 15 ng ml$^{-1}$. Mean values for laudanosine concentrations for the two patient groups at each time interval were compared using the Mann–Whitney test (Zar, 1974). P < 0.05 was considered significant.

RESULTS
Mean plasma laudanosine concentrations were greater in the patients with renal failure between 90 min and 240 min after the injection of atracurium than those found in the patients without renal failure (fig. 1). There were no differences in mean plasma laudanosine concentrations before the 90-min sampling time. The highest laudanosine concentration in the patient group without renal failure was 327 ng ml$^{-1}$; that in the renal failure group was 758 ng ml$^{-1}$. These peak values were observed in the first 10 min following the administration of the atracurium.

The time from the administration of atracurium until perfusion of the transplanted kidney was between 50 and 120 min; renal function per se was not assessed until the day following surgery.

DISCUSSION
Patients with renal failure may have prolonged neuromuscular blockade from non-depolarizing neuromuscular blocking drugs because of the dependence of these drugs on the kidney for their elimination. However, neuromuscular blockade associated with atracurium is not prolonged in patients with renal failure, because its metabolic breakdown is independent of renal function (Fahey et al., 1984). However, unlike the parent drug, the metabolites of atracurium may not be rapidly eliminated, and may possess potentially harmful effects such as the CNS stimulation associated with laudanosine (Babel, 1899) and the tissue alkylation resulting from the acrylate metabolites (Nigrovic and Koechel, 1984). These toxic effects could be accentuated if renal or liver disease increased the blood concentrations of these metabolites.

Laudanosine has been a subject of scientific investigation for 85 yr (Babel, 1899; Mercier and
Mercier, 1955), the major finding of which is that laudanosine is a CNS stimulant in a variety of animal species. Its effects may include seizures or an increase in anaesthetic requirement, both of which could conceivably go unrecognized in the patient receiving atracurium.

Animal studies have shown that the i.v. dose of laudanosine necessary to produce seizure activity is species-dependent. Rabbits can exhibit seizure activity with an i.v. dose of 3 mg kg\(^{-1}\) of laudanosine (Shi et al., 1985), whereas dogs require four to six times that dose to display a similar response (Mercier and Mercier, 1955; Hennis et al., 1984). Plasma concentrations of laudanosine which induce seizures in these animals have not yet been determined. Thus, at the present time, it is not possible to determine whether the concentrations of laudanosine present in patients with renal failure, after a single i.v. dose of atracurium, could affect the CNS.

No patient in this study exhibited gross evidence of CNS stimulation that could be attributed to laudanosine. However, Duncan (1983) reported a paediatric patient in renal failure who received atracurium 0.6 mg kg\(^{-1}\) and, after attempted antagonism of neuromuscular blockade with neostigmine 20 min later, exhibited unexplained "jerky movements of his limbs" and sweating—a clinical picture that could be explained in part by the pharmacological action of laudanosine. However, since neuromuscular blockade may mask any CNS effects, studies using electroencephalographic monitoring may be needed to provide a definitive answer.

Our results show that renal failure leads to significantly higher concentrations of laudanosine following the administration of a single dose of atracurium. Although not considered in this study, it is possible that repeated doses of atracurium could lead to higher concentrations of laudanosine than those reported, and be more likely to cause CNS effects.

In conclusion, we have demonstrated increases in the concentration of laudanosine following the administration of atracurium to patients with renal failure. This suggests that the kidney is involved in the elimination of laudanosine. Since laudanosine is considered a potent CNS stimulant in animals, studies should be undertaken in man in case its potential CNS effects are masked by neuromuscular blockade and general anaesthesia.

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REFERENCES


