The urinary excretion of ketamine and its metabolites in the rat

A. LIVINGSTON & A.E. WATERMAN

Department of Pharmacology, Medical School, University of Bristol, Bristol BS8 1TD

The effect of altering urinary pH of adult male Wistar rats (250–300 g.b.wt.), on the duration of sleeping time following a single injection of ketamine (75 mg/kg i.p.) and the urinary excretion of ketamine and its metabolites was measured. The rats were divided into three groups of ten animals. The first group (A) were given 2% ammonium chloride to drink for 5 days, the second group (B) 2% sodium bicarbonate for 5 days and the third group (C) were given water. After this period the urine from animals in group A had a pH of 5.50 ± 0.34 (s.e. mean), group B had a pH of 8.80 ± 0.05 and the control animals a pH of 6.90 ± 0.23.

The rats were injected with ketamine and the sleeping time, that is the time between the loss and regaining of the righting reflex, was measured. The urine was collected for the two hour period following the injection and assayed for ketamine and its metabolites by a gas-liquid chromatographic method based on that described by Chang & Glazko (1972). There was no difference in the onset time of anaesthesia between the three groups, but the sleeping time was significantly prolonged ($P < 0.001$) in the group A animals to 31.1 ± 0.9 min compared to the control values of 21.9 ± 0.6 minutes. Group B were not significantly different to control with a sleeping time of 24.0 ± 1.3 minutes. The rate of excretion of ketamine, metabolite I (the demethylated metabolite) and metabolite II (the subsequent oxidation product) in the urine of control rats (Group C) was 1.00 ± 0.13, 3.19 ± 0.36 and 0.93 ± 0.13 μg/min respectively whilst in the group A rats these rates were 0.35 ± 0.03, 0.94 ± 0.15 and 0.34 ± 0.05 μg/min, all of which were significantly lower. In group B the rates of excretion were 1.81 ± 0.24, 4.90 ± 0.55 and 1.14 ± 0.15 μg/min, all of which were significantly higher than control.

However, the volumes of urine production were significantly lower in Group A than in both Groups B and C, and it was found that there was a great deal of variation in the concentration of ketamine and its metabolites in the urine of the various groups. It appeared that the low rate of excretion in Group A could be associated with the low volume of urine production. In order to test if the prolongation of sleeping time in Group A was associated with the low volume of urine produced an experiment was set up where one group of rats received an injection of vasopressin tannate (250 mu/rat i.m.) four hours before the injection of ketamine (75 mg/kg, i.p.) whilst the other group received an injection of the vasopressin vehicle only, the sleeping times were measured as before and no significant difference between the groups could be found, although the dose of vasopressin used abolished all urine production over the period of the experiment.

A.E.W. was a Wellcome Research Training Scholar and present address is Department of Pharmacology, Veterinary School, Bearsden, Glasgow G61 1QH.

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Influence of impaired renal function on the disposition of [^{14}C]fazadinium in the anaesthetized greyhound

D.R. BEVAN, J. CALDWELL, J. D'SOUZA & R.L. SMITH

Departments of Anaesthetics and Biochemical and Experimental Pharmacology, St Mary's Hospital Medical School, London W2 1PG

Drugs and their metabolites are generally ultimately cleared from the body by excretion in the urine and/or bile. Some compounds are cleared almost exclusively by one of these routes while others show a mixed elimination pattern, being excreted both in urine and bile. In such cases, the two pathways can be complementary to each other, so that deficiencies in elimination by one route are compensated by increased use of the other (Hirom, Millburn & Smith, 1975). The inter-relationship of the two elimination pathways for compounds showing mixed elimination pattern can be of clinical significance in patients with defects of one of the pathways. This obtains in the choice of neuromuscular blockers used for renal transplantation surgery. Using the dog as a model species,

we have examined the inter-relationship of urinary and biliary excretion for the elimination of fazadinium (Fazadon), a diquaternary ammonium neuromuscular blocker, and the consequences of alternatively occluding the two excretion routes for the disposal of the drug.

Adult female greyhounds (weight 25 ± 2.5 kg) were anaesthetized with thiopentone (30 mg/kg i.v.) and intermittent ketamine (10 mg/kg i.m.) and ventilated with O_2/air. The common bile duct was cannulated above the gall bladder, the ureters catheterized and cannulae placed in the femoral artery and vein. [^{14}C]-fazadinium dibromide (2.5 mg; 2.5 μCi) was injected i.v. and blood samples taken at frequent intervals for 1 h and then every 0.5 h for a further 4 hours. Urine and bile were collected hourly. The [^{14}C] content of plasma, urine and bile was determined by liquid scintillation spectrometry. In other experiments, the above was repeated except that the renal pedicles were ligated to prevent urine formation (5 dogs) or the common bile duct ligated above the cystic duct (3 dogs).

Table 1 shows the urinary and biliary excretion of [^{14}C]-fazadinium in the three groups of dogs. In 5 h, the control animals excreted some 65% of the dose (bile 47%; urine 19%). Ligation of the renal pedicles did not increase the biliary excretion of the drug, and similarly there was no increase in urinary excretion when the common bile duct was ligated. In both cases, the total excretion of drug was less than in the control dogs. The distribution half-lives for the plasma [^{14}C] in the three groups were similar, however, there were differences in the plasma elimination half-lives, which were as follows: 20 min (control), 22 min (renal ligated) and 30 min (bile duct ligated). The increase in plasma elimination half-life for the latter group can be attributed to decreased drug clearance due to prevention of biliary excretion. Examination of the urine and bile by thin-layer chromatography showed that the major excretion product was unchanged fazadinium together with smaller amounts of a metabolite formed by scission of the tetrazene link, 3-methyl-2-phenylimidazo-(1,2α)-pyridinium (Blogg, Simpson, Martin & Bell, 1973).

Thus, for the dog, the main pathway of elimination of the drug is via the bile, the ratio of hepatic to renal excretion being approximately 3:1. Furthermore, the two pathways are not complementary since one pathway does not compensate when the other is occluded. If biliary excretion of fazadinium predominates in man, the dog data suggests that its disposition should be relatively unaffected by impaired renal function, as does occur with *d*-tubocurarine (Miller, Mateo, Benet & Sohn, 1977; McLeod, Watson & Rawlins, 1976). This would suggest that from the drug disposition viewpoint fazadinium has advantages for patients with impaired renal function.

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Table 1 Urinary and biliary excretion of [^{14}C]-fazadinium in dogs

	% *Dose (± s.e. mean) excreted in 5 h*		
	Urine	*Bile*	*Total*
Control (n = 4)	18.6 ± 4.6	47.1 ± 4.0	65.7 ± 2.8
Ligated renal pedicles (n = 5)	—	52.8 ± 3.3	52.8 ± 3.3*
Ligated common bile duct (n = 3)	21.7 ± 5.0	—	21.7 ± 5.0**

* $P < 0.025$ cf control.
** $P < 0.005$ cf control; all others n.s.