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.

Reference

CHANG, T. & GLAZKO, A.J. (1972). A gas chromatographic assay for ketamine in human plasma. *Anesthesiology*, **36**, 401–404.

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,