The metabolism of ranitidine in animals and man

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Ranitidine hydrochloride [N-[2-[[5-(dimethylaminomethyl)]furan - 2 - yl]methy|[(thio)ethyl]} - N\(^2\)-methyl - nitroethene - 1,1 - diamine hydrochloride] is a new histamine H\(_2\) receptor antagonist effective in decreasing hypersecretion of gastric acid (Bradshaw et al., 1979; Peden et al., 1979). This compound has a novel structure and does not contain the imidazole nucleus, which has been regarded as essential for H\(_2\) receptor blockade (Ganellin et al., 1976).

The metabolism of [\(^1^4\)C]ranitidine hydrochloride (labelled as indicated in Scheme 1) has been studied in the rat, dog, mouse, rabbit and marmoset after oral administration of 10-100 mg (base)/kg body wt. In the dog, up to 80% of the administered radioactivity was recovered in urine in 3 days, the bulk of this being excreted in 24 h. In the other animal species, between 30 and 60% of the administered radioactivity was rapidly excreted in urine, the balance being recovered in faeces. After oral and intravenous doses of 25 mg/kg to the mouse, 48 and 64% of the radioactive dose respectively was excreted in urine collected for 3 days. The corresponding values for excretion of radioactivity in the faeces were 36 and 25%. Biliary-cannulation studies in the anaesthetised rat showed that, in this species, up to 17% of an intravenous dose was excreted in the bile during 4.5 h. Whole-body radioautography of the rat has confirmed the rapid excretion of radioactivity by the renal and biliary routes. Highest tissue concentrations of radioactivity after oral administration were found in the gut wall, liver and kidneys.

Peak plasma total radioactivity of 2-17 \(\mu\)g equivalents of ranitidine/ml and unchanged drug concentrations of 1-9 \(\mu\)g/ml (determined by high-pressure liquid chromatography; Carey & Martin, 1979) were attained within 30 min of oral administration of \(^1^4\)Cranitidine hydrochloride (50 mg of base/kg) to the rat. Absorption was slower in the dog, the peak amounts of radioactivity and unchanged-drug concentrations were respectively 19-28 and 10-14 \(\mu\)g/ml between 1 and 2 h after administration of dose. In each species the drug and its metabolites were rapidly cleared from plasma. The compound was not bound to plasma protein to any significant extent in any of the species investigated. Urine collected from animals housed in metabolism cages can be contaminated with micro-organisms that could metabolize ranitidine. To prevent this, the urine used for chromatographic analysis was collected from rabbits and dogs by using an indwelling catheter and from rats in which the ureters were cannulated. Metabolism cages had to be used for marmosets and mice and therefore the urine was collected in containers cooled with solid CO\(_2\). The drug and its metabolites were isolated from urine by adsorption on Amberlite XAD-2 resin. The residue from the methanol eluate was examined by t.l.c., with Merck 0.25 mm prelayered plates [system A: Kieselgel 60F\(_{254}\), solvent system methanol/NH\(_4\)OH 49:1 (v/v); system B: aluminium oxide F\(_{254}\) (type E), solvent system chloroform/methanol/water 75:15:1 (by vol.)].

Samples of pure ranitidine, ranitidine N-oxide (I) (desmethyl ranitidine) (II) and ranitidine S-oxide (III) were used as standards.

In the radiochromatograms from all species, ranitidine was the major radioactive component; the amount varied from 27 to 45% of 0-24 h-excreted radioactivity. Ranitidine was mainly metabolized by N-oxidation in the dog and only small amounts of compounds (II) and (III) were present in dog urine. Approximately equal amounts of compounds (I), (II) and (III) were present in the urine of the other species (Scheme 1). T.l.c. examination of human urine, collected after oral administration of 400 mg of unlabelled ranitidine hydrochloride per day to male volunteers has shown that unchanged drug is the major component and compound (I) the major metabolite. Only small amounts of compounds (II) and (III) were present.