Dose dependent disposition of [^{14}C]-ICI 89,406 in the male rat: Is this due to a capacity limited excretory pathway for the drug into bile?

D.J. BARNFIELD, G.R. BOURNE, C. LOWERY & S.R. MOSS

Drug Metabolism Section, Safety of Medicines Department, ICI Pharmaceuticals Division Alderley Park, Nr. Macclesfield, Cheshire, SK10 4TG.

The metabolism and excretion of [^{14}C]-ICI 89,406 (1-(2-[^{14}C]-2-cyanophenoxy)-3-β-(3-phenylureido) ethylamino-2-propanol) a β-adrenoreceptor antagonist, has been studied in the male rat and using the isolated perfused rat liver. [^{14}C]-ICI 89,406 was dosed to rats orally (5 or 50 mg/kg), i.p. (5 mg/kg) and i.v. (0.6 mg/kg). The liver preparation was perfused with whole blood and ICI 89,406 (10 mg) introduced into the perfusate as a bolus injection.

Following oral administration of ICI 89,406 to the rat (5 mg/kg) urinary and faecal excretion accounted for 5.8 $\pm$ 0.7% (mean $\pm$ s.d.; n = 3) and 96.4 $\pm$ 2.1% of the dose. When the dose was increased to 50 mg/kg urinary and faecal excretion accounted for 14.0 $\pm$ 4.0% and 78.4 $\pm$ 2.4% of the dose. The proportions of unchanged drug and metabolites in urine were independent of the dose. The unchanged drug accounted for 81.6% of the faecal components after a dose of 5 mg/kg but this was reduced to 47.8% when the dose was increased to 50 mg/kg ICI 89,406. The proportion of two polar metabolites increased from 6.4% to 23.5% of the faecal radioactivity with increasing dose.

The mean clearance of [^{14}C]-ICI 89,406 from the isolated perfused rat liver was 4.1 $\pm$ 1.7 ml/min and the extraction ratio 0.34 $\pm$ 0.05. The fraction, F, of an 'hepatically' administered dose reaching the systemic circulation was 0.65 suggesting that ICI 89,406 undergoes a modest degree of 'first pass' metabolism. From *in vivo* studies F was calculated to be 0.68 from the ratio of unchanged drug excreted in urine after i.p. and i.v. administration. This is in good agreement with the perfused liver studies. Bile contained 52% of the radioactivity introduced into the perfusion system. ICI 89,406 and its glucuronide conjugate accounted for less than 10% of the radiolabelled components. This was also seen when the dose to the perfused liver was reduced to 75 µg.

The dose dependent disposition of ICI 89,406 in the male rat is apparently due to a limited capacity to excrete ICI 89,406 into bile either as a conjugate or unchanged drug. Studies in the perfused rat liver demonstrated that excretion of ICI 89,406 and its conjugate in bile is a minor route of elimination and may not account for the dose dependent disposition of this drug *in vivo*. ICI 89,406 undergoes conjugation with glucuronicacid thus the dose dependent pathway seen after oral administration of ICI 89,406 may be due to metabolism in the gut wall. As the dose is increased and a greater fraction of the dose is absorbed unchanged then a greater fraction of the dose is available for oxidative metabolism.

Changes in dopamine receptor status after denervation or chronic receptor stimulation

B. COSTALL & R.J. NAYLOR

Postgraduate School of Studies in Pharmacology, University of Bradford.

It has been shown that denervation or stimulation or striatal dopamine (DA) mechanisms can lead to changes in DA receptor status (see Cross, Longden, Owen, Poulter & Waddington, 1978; Quik & Iversen, 1978). It has also been shown that manipulation of DA mechanisms in the extrapyramidal system can influence DA metabolism (as measured by homovanillic acid) in an anatomically distinct area of the mesolimbic system (Costall & Naylor, 1979). Therefore, the present studies were designed to investigate possible changes in extrapyramidal, mesolimbic and cortical DA receptor status following destruction of the DA pathways to the extrapyramidal and mesolimbic areas, and after chronic striatal stimulation by DA. Changes in haloperidol receptor binding (Leysen, Tollenaere, Koch & Laduron, 1977) and in the activity of DA stimulated adenylate cyclase (Kebabian, Petzold & Greengard, 1972) were determined in the striatum (CP), tuberculum olfactorium (TUO), nucleus accumbens (ACB) and frontal cortex (FC) following denervation of the ascending DA pathways in the lateral hypothalamus (LH) (8 µg/4 µl 6-hydroxydopamine; Costall, Naylor & Pycock, 1975), and haloperidol binding was determined following chronic receptor stimulation caused by repeated intrastriatal DA administration (Costall, Naylor & Pinder, 1974). DA concentrations in the CP, TUO and ACB were also determined.

Male Sprague-Dawley rats (250 $\pm$ 25 g) with unilateral LH lesions, and exhibiting a maximum contralateral circling response to apomorphine, were selected