The metabolism of dothiepin hydrochloride *in vivo* and *in vitro*

E.L. CRAMPTON, W. DICKINSON, G. HARAN, B. MARCHANT & P.C. RISDALL (introduced by P.A. BERRY)

Research Department, The Boots Co. Ltd., Nottingham NG2 3AA

Dothiepin hydrochloride (Prothiaden, 11-(3-dimethylaminopropylidene)-6, *H*-dibenzo(b,e)thiepin hydrochloride) is a tricyclic antidepressant currently used in the treatment of depression. In this study the metabolic fate of [^{14}C]-dothiepin hydrochloride has been studied after administration of a single oral dose to rat, dog and cat (2 mg/kg), baboon (5 mg/kg) and man (50 mg single dose). Absorption was rapid in all species studied and in the rat it was shown that the major site of absorption of dothiepin was in the small intestine. Elimination of radioactivity from the circulation, up to 24 h after a single oral dose of [^{14}C]-dothiepin hydrochloride was slower in man and the baboon than in the dog, cat or rat. In all species 49.0–61.7% of the dose was recovered in the urine and 14.9–41.0% in the faeces.

The biological transformation of dothiepin hydrochloride in the body was rapid, extensive and complex and large qualitative and quantitative species differences occurred in metabolites and conjugates. Twelve radioactive components were separated by thin-layer chromatography from basic heptane extracts of baboon and human urine. A smaller number of components have been separated from rat, cat and dog urine, of these, four coincided with non-radioactive markers of northiaden (mono-desmethyl dothiepin), northiaden S-oxide, dothiepin and dothiepin S-oxide. In man the major basic metabolites appeared to be northiaden S-oxide and dothiepin S-oxide. In rat and baboon northiaden S-oxide was present in the largest amount and in the cat dothiepin S-oxide was the major basic metabolite.

Some metabolites have been isolated from rat urine and rat liver subcellular fractions and identified by mass spectrometry and fourier transform nuclear magnetic resonance (F.T.n.m.r) spectroscopy. The major basic metabolite isolated from rat liver 10,000 *g* fractions was identified unequivocally as northiaden by mass spectrometry and F.T.n.m.r. spectroscopy indicating that demethylation is a major pathway of metabolism of this compound in rat liver. Demethylation in rat liver has also been reported for the tricyclic antidepressants imipramine (Dingell, Sulser & Gillette, 1964, Minder, Schnetzer & Bickel, 1971), amitriptyline (Hucker, 1962), nortriptyline (McMahon, Marshall, Culp & Miller, 1963) and desipramine (Bickel & Baggiolini, 1966). Evidence was also obtained for the presence of dothiepin S-oxide in rat liver cell fractions.

The major basic metabolite isolated from rat urine was identified unequivocally as dothiepin S-oxide. This confirmed the work of Horešovský, Franc & Kraus, (1967), who showed that dothiepin S-oxide appeared to be a metabolite in rat urine using U.V. spectroscopic analysis. It was also shown that the major polar metabolite in rat urine was a glucuronic acid conjugate and the aglycone of m/e 312 was tentatively identified as hydroxylated dothiepin.

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