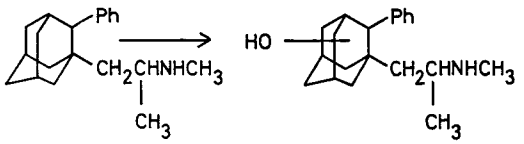
Plasma and urine concentrations of a new adamantane derivative

Amantadine hydrochloride, the salt of 1-aminoadamantane, was originally used in man as an anti-viral agent but has since proved valuable in the treatment of Parkinson's disease (Pearce & Pearce, 1971). A novel adamantane derivative, compound I (*N*-methyl-1-(2-phenyl-adamant-1-yl)-2-aminopropane hydrochloride, LRCL 1148), synthesized in these laboratories (Chakrabarti, 1972), was found in animals to have pharmacological properties that suggested that it might be superior to amantadine in the treatment of this disease (Cashin & others, unpublished observations).



I II (isomers a, b) acid-labile conjugates

We have studied the absorption, metabolism and excretion of the compound, taken in two No. 1 gelatin capsules each containing 50 mg of I and 207 mg lactose, by five healthy male volunteers who had fasted overnight, but had taken some water. Blood samples were taken hourly for 12 h via a heparinized indwelling intravenous needle and three further samples by venepuncture until 31 h. Urine was collected for 48 h.

Peak plasma concentrations of approximately 100 ng ml^{-1} of unchanged compound I occurred 2–5 h after dosage. Four subjects had further peaks 3 to 6 h after the initial peak (see Fig. 1 Subject 1).

The fluctuating plasma concentrations are probably the result of enterohepatic recycling since studies in dogs have shown that compound I is excreted in bile as an acid-labile conjugate, possibly an *N*-glucuronide (Chatfield & Green, unpublished observations) and double-peak blood levels found with carbenoxolone have been thought likely to be due to enterohepatic circulation of biliary excreted conjugates (Downer, Galloway & others, 1970). The peaks were barely apparent in subject 5 who had had a cholecystectomy and in whom biliary excretion and reabsorption might be expected to occur at a more uniform rate (see Fig. 1).

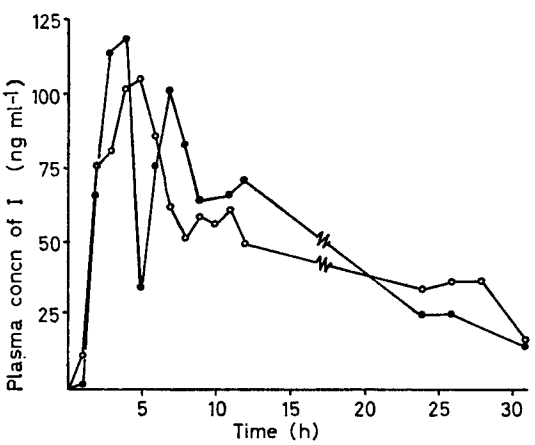


FIG. 1. Plasma levels of I in 2 subjects after 100 mg oral dose of I. ●——● Subject 1. ○——○ Subject 5.

Plasma concentrations of compound I were measured by a modification of the radioisotope derivative technique described by Hammer & Brodie (1967). The biological half-life was 18·1 ± 1·0 h as estimated by exponential regression analysis of the mean plasma levels observed from 4 to 31 h. That of amantadine was 9 to 15 h, based on urinary excretion data (Bleidner, Harmon & others, 1965).

Urinary concentrations of unchanged compound I and two metabolites (structure II, isomers a, b) were assayed by g.l.c. using a flame ionization detector, after chloroform extraction of the urine at pH 9 before and after acid hydrolysis. Compound I, unlike amantadine, was metabolized in man by mono-hydroxylation of the adamantane nucleus followed by conjugation (Chatfield & Green, unpublished observations).

After a single oral dose (100 mg) of compound I to five subjects the mean 48 h urinary excretion of unchanged I and its metabolites accounted for 33·3% (range 16·0–53·9%) of the dose. Less than 1% of the unchanged compound was excreted, most of the urinary material being present in two isomers of the hydroxylated product II, a and b, corresponding to different but as yet unknown positions of hydroxylation on the adamantane nucleus. The major urinary metabolite, considered as compound IIa, accounted for 30·5% (range 15·2–48·7% of the dose, only small amounts (1·9%, range 0·3–4·3%) of the isomer IIb being recovered. About half the total amounts of metabolites IIa and IIb were excreted as acid-labile conjugates.

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Isosalsolinol formation: a secondary reaction in the Pictet-Spengler condensation

1,2,3,4-Tetrahydroisoquinolines are formed non-enzymatically in the Pictet-Spengler condensation (Whaley & Govindachari, 1958) of a carbonyl compound with a phenethylamine. The condensation is almost certainly the first step in the biosynthesis of this series of alkaloids in plants, and a similar reaction has recently been described in man (Sandler, Bonham Carter & others, 1973). Typically, dopamine and acetaldehyde condense to form 1,2,3,4-tetrahydro-6,7-dihydroxy-1-methylisoquinoline (salsolinol, I) with cyclization occurring *para* to a hydroxyl group which is then at the 6 position of the resulting alkaloid.

Compounds belonging to this series have recently aroused considerable biomedical interest (Lancet, 1973) although three representatives only have so far come under close scrutiny in this context. Salsolinol itself (Heikkila, Cohen & Dembiec, 1971) and its non-methylated analogue, norsalsolinol (Cohen, Mytilineou & Barrett, 1972), are taken up into catecholamine binding sites and may act as false neurochemical transmitters (Greenberg & Cohen, 1973). There has been speculation that tetrahydropapaveroline, the pharmacologically active (Holtz, Stock & Westermann, 1964)