THE EFFECT OF FLUPHENAZINE DECANOATE (MODECATE^R) ON HEPATIC MICROSOMAL ENZYME ACTIVITY IN MAN

Many chronically administered centrally acting drugs have been shown to affect the activity of the hepatic microsomal drug metabolizing enzymes in animals and man. The pharmacological implications of such effects were recently reviewed by Conney (1967) and Kuntzman (1969). Although various anticonvulsant drugs, for example, phenytoin and phenobarbitone, induce hepatic enzyme activity in man (Latham, Millbank, Richens & Rowe, 1973), many phenothiazine-like major tranquillizers potentiate the action of other drugs. Chlorpromazine was reported to inhibit the metabolism of amphetamine (Sulser & Dingell, 1968) and guanethidine (Mitchell, Cavanaugh, Dingell & Oates, 1970) in rats, and phenytoin in man (Kutt & McDowell, 1968). Similar inhibitory properties of several phenothiazines on the metabolism of propranolol in rats were demonstrated by Shand & Oates (1971), who suggested that the underlying mechanism was competitive inhibition of hepatic enzyme activity.

In view of the long term effects of some chronically administered centrally active drugs on hepatic microsomal enzyme activity, we have assessed the effect of fluphenazine decanoate (Modocate^R, E.R. Squibb & Sons Ltd) in schizophrenic patients receiving long-term maintenance therapy. The excretion of urinary D-glucaric acid has been employed as an index of hepatic microsomal enzyme induction (Aarts, 1965; Hunter, Maxwell, Corrella, Stewart & Williams, 1971; Latham *et al.*, 1973). In addition we have determined serum quinine half-lives and the half-life of its hydroxylated metabolites as an index of hepatic hydroxylating enzyme capacity (Padgham, unpublished data).

Six male out-patients, aged between 25 and 52 years, who had been receiving monthly 25 mg fluphenazine decanoate intramuscularly for at least twelve months, were selected for study.

A complete 24 h urine collection was received from each patient. The volume was measured, an aliquot taken and stored at -15°C and the D-glucaric acid excretion, as lactone inhibitor, subsequently assayed by a method adapted from that of Marsh (1963). The following day 600 mg (2×300 mg capsules) quinine dihydrochloride was taken orally with water. Venous blood (5 ml) was withdrawn 4, 5, 6 and 8 h after dosage. The serum was separated and stored at -15°C prior to estimation. The concentrations of quinine and its metabolites were then measured by a method

based on that of Saggars, Hariratnajoithi & McLean (1970).

In this laboratory, previous studies have indicated a normal mean value $\pm$ s.d. for urinary D-glucaric acid excretion, as inhibitor lactone, of $17.0 \pm 10.7 \mu\text{mol}/24 \text{ h}$ ($n = 19$), a normal quinine half-life ($T_{1/2}$) of $8.5 \pm 2.0 \text{ h}$ ($n = 25$) and a normal quinine metabolite $T_{1/2}$ of $9.5 \pm 2.7 \text{ h}$ ($n = 25$).

In the present study, the mean D-glucaric acid excretion, as inhibitor lactone, was $12.0 \pm 6.8 \mu\text{mol}/24 \text{ h}$ ($n = 6$), the quinine $T_{1/2}$ $8.6 \pm 2.2 \text{ h}$ ($n = 6$) and the quinine metabolite $T_{1/2}$ $8.4 \pm 2.9 \text{ h}$ ($n = 6$). These results are not significantly different from the control values ($P > 0.1$, Student's *t* test).

The absence of a significant effect suggests that fluphenazine decanoate does not cause a change in hepatic microsomal enzyme activity in man.

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A.N. LATHAM & CHERYL PADGHAM

Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE

RITA HENRYK-GUTT

Shenley Hospital, Shenley, St Albans, Herts

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