Biochemical Pharmacology, Vol. 22, pp. 3128–3129. Pergamon Press, 1973. Printed in Great Britain.

Biliary excretion of ^{3}H-terbutaline in man

THE EXCRETION of drugs in the bile may be an important route of elimination and may lead to an enterohepatic recirculation of drugs. However, due to sampling difficulties few data are available on the "hepatic clearance" of various agents in man. This study reports the excretion of ^{3}H-terbutaline (1-[3,5-dihydroxyphenyl]-2-tert.-butylaminoethanol) in human bile. Terbutaline (Bricanyl®) is a selective β_2-receptor stimulator[1] of frequent use in asthma therapy.[2–4] Metabolic studies in rat and dog revealed a species difference in the amount of terbutaline that was excreted by the biliary route.[5] This finding emphasized the necessity of studying the biliary excretion of terbutaline in man.

Studies were performed on two female patients, GE and ILE and on one male patient, ÅL, on the fourth, fifth and second day respectively, after uncomplicated colecystectomy and common bile duct exploration with T-tube drainage. The patients were fully informed concerning the means and objects of the study and gave their consent. Prior to the experiment, the patient was asked to empty the bladder. With the patient resting comfortably on his back, the bile was drained by gravity through the T-tube. The patients were given intravenously 0·16 mCi in 0·73 μmole, 0·11 mCi in 0·50 μmole and 0·25 mCi in 0·89 μmole ^{3}H-terbutaline sulphate, respectively. These amounts correspond to 2·2, 2·2 and 1·9 μg terbutaline per kg body weight, which can be compared with the recommended dose of 250 μg terbutaline for subcutaneous administration to adult asthmatics.[6] The compound was dissolved in saline and sterilized before use. Bile and blood were then obtained as indicated in Fig. 1 and,

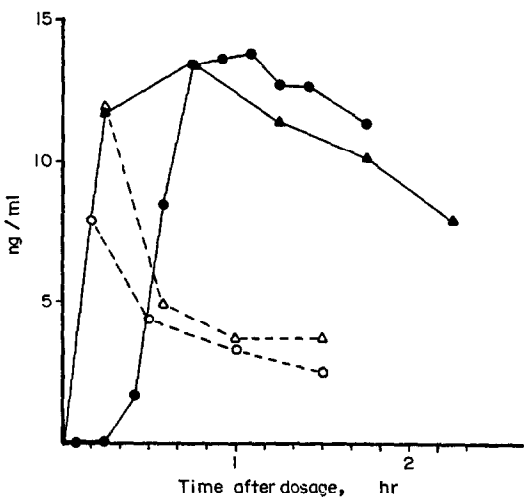

FIG. 1. Time course of concentrations of total radioactivity (expressed as terbutaline) in serum and bile after intravenous administration of 2·2 μg ^{3}H-terbutaline per kg body weight to female human patients. The bile values are given at the midpoint of the sampling period. GE: (●) bile. (○) serum; ILE: (▲) bile, (△) serum.

when possible, urine was collected and pooled. All samples were kept frozen until analyses could be performed.

Total radioactivity in serum and urine was determined by liquid scintillation counting and unchanged terbutaline in serum and urine was analysed by ion-pair extraction.[7] Total radioactivity in bile was determined by mixing 50–100 μl bile with 200 μl hydrogen peroxide (30%) in a counting vial, which was closed with a screw cap and kept at 40°C for 1–2 hr. After addition of scintillator solution the samples were adapted to darkness before counting. All samples were counted in a liquid scintillation spectrometer (Packard 3320).

The concentration of total radioactivity (expressed as terbutaline) in bile and serum after intravenous administration of ^{3}H-terbutaline sulphate to GE and ILE is given in Fig. 1. As indicated in

Fig. 1 for subject GE, whose bile was collected most frequently, there was a delay before the radioactivity appeared in the bile samples. This delay may illustrate the approximate time needed for the excreted bile to flow from the liver to the sampling barrels. The mean value of bile flow during the sampling period was 11 ml/hr for GE, 27 ml/hr for ILE and 14 ml/hr for ÅL. Of the administered dose GE excreted 0·36% in bile within 24 hr, ILE 0·68% within 2·5 hr and ÅL 0·73% within 24 hr. The fraction of unchanged terbutaline in serum was of similar magnitude as in an earlier intravenous study in human volunteers.[7] Initially the fraction of unchanged drug in serum for GE and ILE was high; mean 89%, and then declined to a mean of 50% 90 min after injection. No serum was obtained from patient ÅL.

The radioactivities recovered in urine were 59% of the dose (GE) and 72% (ÅL) in 24 hr, of which unchanged drug constituted 50% and 63%, respectively. ILE excreted 66% of the dose in urine within 3 hr, of which 77% appeared as unchanged drug. These data are also in accordance with the results obtained in human volunteers free from disease.[7]

The amount of terbutaline in human bile is of a similar magnitude to that found in dog, where approximately 2% of the i.v. dose was excreted, but differs from rat, which excreted approximately 40% of i.v. terbutaline in the bile. The present result suggests that biliary excretion of terbutaline after parenteral administration is of minor importance for the fate of the drug in man.

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Biochemical Pharmacology, Vol. 22, pp. 3129–3131. Pergamon Press, 1973. Printed in Great Britain.

Effect of hashish compounds on rat liver lysosomes *in vitro*

(*Received* 9 *April* 1973; *accepted* 25 *June* 1973)

Δ^1-TETRAHYDROCANNABINOL (Δ^1-THC) is the major psychoactive compound of hashish. Its precursor in synthesis and probably also in biogenesis, cannabidiol, does not exhibit psychoactive effects.[1]

The effect of hashish compounds on rat and human erythrocytes[2,3] and on rat liver mitochondria[4,5] has been recently described. A paramount feature of the effect is an interaction between the hashish compounds and the membranes of these cells or organelles. It has been shown that 1·5 hr after intraperitoneal injection of ^{14}C-tetrahydrocannabinol to a rat, most of the radioactivity accumulates in the liver.[6] Thus it was of interest to study the effect of hashish components on rat liver lysosomes, with a particular emphasis on a possible effect on the integrity of the lysosomal membrane.