absorption of the drug from the gastrointestinal tract was rapid (Table 1). Furthermore, absorption appeared to be near complete as shown by the negligible amounts of radioactivity in the faeces (< 5.0%) and the concomitantly good recovery of radioactivity in the urine. Excretion was very rapid, approximately 50% of the administered radioactivity appearing in the urine between 0-6 h after dosing. Urinary excretion was virtually complete within 24 hours.

The very similar recovery of both tritium and radiocarbon indicated that N demethylation did not occur to any significant extent (Table 2). The major metabolite of the drug appeared to be the glucuronide conjugate of the parent drug. A minor metabolite amounting to 5-10% of the administered dose was observed to contain very little tritium, suggesting that reaction had occurred at the 7 position of the azepine ring. Comparative thin layer chromatography of this metabolite with 6-ethyl-6-(*m*-hydroxyphenyl)-1-methylhexahydro-azepin-[2H]-2-one showed the two compounds to behave very similarly. Isolation of larger amounts of this minor metabolite from the urine of two further volunteers who had ingested 1.2 g of the drug enabled the infra-red spectrum to be determined. Again the minor metabolite and the 7 oxo compound appeared to be very similar. These data, together with a report of a structurally similar metabolite of the closely related analgesic profadol (Chang, Howell & Glazko, 1968), provides substantial evidence to identify the minor metabolite of

meptazinol as 6-ethyl-6-(*m*-hydroxyphenyl)-1-methylhexahydro-azepin-[2H]-2-one.

A comprehensive report of this work will be presented in due course.

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PHARMACOKINETIC STUDIES ON WY 23409 HCl

Wy 23409 HCl, 10-(*m*-chlorophenyl)-2,3,4,10-tetrahydropyrimido[1,2a]indol-10-olhydrochloride (Figure 1), is a new compound whose pharmacological properties in animals indicate that it may be useful as an antidepressive agent in man, devoid of unwanted side effects (Beckett, Southgate & Sugden, 1973; Sugden, 1974).

The pharmacokinetics and metabolism of the drug have been studied after oral administration of [^{14}C] Wy 23409 to human volunteers.

Three healthy volunteers, two male and one female, ingested gelatin capsules containing either 5 μCi or 50 μCi of radiolabelled drug in a total dose of 25 mg. Samples of venous blood were taken at frequent intervals during the first 24 h and then daily for up to three days. All urine was

collected, initially over short periods during the first day and daily thereafter. Daily faecal collections were made.

Radioactivity present in the plasma and in the urine samples was determined by liquid scintillation counting, and that present in the faeces was estimated similarly after portions had been digested by the wet oxidation technique of Mahin & Lofberg (1966). Plasma and urine samples were adjusted to pH 10 using NaOH and extracted with toluene. The radioactivity present in these extracts was taken to represent Wy 23409, since studies with animal samples had shown that this technique was specific for the unchanged drug.

Absorption of Wy 23409 from the gastrointestinal tract appeared to be rapid, since peak

Figure 1 Wy 23409-HCl (10 - (*m* - chlorophenyl) - 2,3,4,10 - tetrahydropyrimido [1,2a] indol-10-ol hydrochloride).

Asterisk denotes position of ^{14}C label in the [2- ^{14}C] Wy 23409 used in these studies.

plasma levels both of total and of toluene extractable radioactivity occurred between 2 h and 4 h after dosing. Furthermore, the small amount of the dose that was recovered in the faeces (< 15%) indicated that the drug had been extensively absorbed.

Removal of radioactivity from the plasma took place in a monoexponential fashion with a half-life of $50.3(\pm 3.3 \text{ s.e. mean})$ hours. The decline in free drug concentration was also monoexponential, but had a somewhat shorter half-life of $37.7(\pm 3.5 \text{ s.e. mean})$ hours. Urinary excretion of radioactivity, which was the major route of elimination, proceeded in a monoexponential manner with a half-life of $32.2(\pm 0.8 \text{ s.e. mean})$ hours.

During the first 24 h after ingestion of the dose, unchanged drug accounted for $72.4(\pm 2.2 \text{ s.e. mean})\%$ of the total radioactive materials in the plasma and $29.6(\pm 2.4 \text{ s.e. mean})\%$ of the radioactivity in the urine. These observations, together with the relatively long half-lives both of removal of Wy 23409 from the plasma and of renal elimination of radioactivity, indicate that the drug is metabolized relatively slowly and somewhat incompletely.

Investigation into the metabolic profile of the drug was carried out using the first-day urines. Ethanolic extracts from XAD-2 columns were subjected to silica-gel thin-layer chromatography either in solvent (a) chloroform-acetone-acetic acid-water (60 : 20 : 20 : 5 by vol.), (b) toluene-ethanol-ammonia (80 : 20 : 1 by vol.) or (c) dioxan-cyclohexane-ethanol-water (60 : 40 : 10 : 5 by vol.).

Scans of the chromatograms, produced using a Panax radiochromatogram scanner, revealed the presence of at least three metabolites in addition to Wy 23409, which was also detectable. In cases where the XAD extracts had been incubated with β -glucuronidase before thin-layer chromatography, no differences in the patterns were apparent, indicating that glucuronide conjugates were not excreted. The possibility that conjugates other than those with glucuronic acid are involved cannot, however, be excluded.

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