PRELIMINARY METABOLIC STUDIES ON THE NEW ANALGESIC MEPTAZINOL

Meptazinol, *m*-(3-ethyl-1-methyl hexahydro-1H-azepin-3-yl) phenol hydrochloride (Figure 1) has been shown to possess potent analgesic activity in rats, mice and monkeys (Goode & White, 1971). Recent clinical studies have demonstrated that the compound is capable of relieving severe pain in man (Oosterlinck & De Sy, 1975).

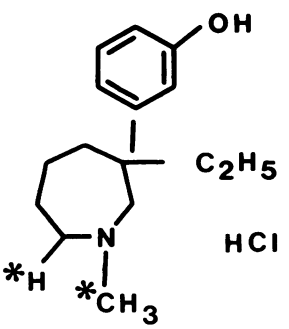

Figure 1 Structural formula of meptazinol hydrochloride with the asterisks showing the location of the radioisotopes.

Preliminary metabolic studies have now been carried out in human volunteers who took drug labelled with both radiocarbon and tritium. The material was labelled with [^{14}C] on the N methyl function and [^{3}H] on the 7 position in the azepine ring. This provided a convenient and sensitive way of investigating the extent of N demethylation, a likely route of metabolism for this compound.

Eight healthy male volunteers each swallowed a gelatin capsule containing 50 μCi [^{14}C] and 150 μCi [^{3}H] meptazinol hydrochloride at doses ranging from 50-200 mg. Blood samples and urine collections were taken at regular intervals during the first 24 h after dosing. Faecal samples were collected daily. Aliquots of plasma and urine were subjected directly to liquid scintillation counting while faecal samples were homogenized and small samples digested prior to counting by the method of Mahin & Lofberg (1966).

As shown by the attainment of peak plasma levels of radioactivity within 1-2 h of dosing,

Table 1 Plasma levels of total radiocarbon in male volunteers following ingestion of radiolabelled meptazinol

Time after dosing (h)	*Dose of meptazinol (mg)* 50*	100**	200**
0.25	0.05	no sample	no sample
0.50	0.55	2.95	1.89
1.00	1.39	5.24	6.56
2.00	1.23	4.20	6.74
3.00	0.86	2.90	4.92
4.00	0.56	1.85	3.78
6.00	0.33	1.25	2.12
8.00	0.25	0.84	1.54
12.00	0.17	0.59	1.08
24.00	0.12	0.29	0.53
48.00	no sample	0.17	no sample

Results expressed as μg equivalents meptazinol HCl/ml plasma
* mean value from four subjects
** mean value from two subjects.

Table 2 Urinary excretion of radioactivity by male volunteers after ingestion of radiolabelled meptazinol

Collection period (h)	*Dose of meptazinol (mg)* 50* [^{14}C/^{3}H]	100** [^{14}C/^{3}H]	200** [^{14}C/^{3}H]
0-3	39.53/34.13	40.84/34.42	24.43/21.73
3-6	17.30/16.98	24.19/22.73	34.03/29.68
6-9	5.43/5.35	7.23/7.78	14.30/14.14
9-12	1.98/2.22		
12-15	1.10/1.35	6.91/7.84	1.83/2.09
15-24	1.03/1.70		0.98/1.21
24-48	0.38/0.87	1.24/2.55	0.58/1.24
48-72	no sample	0.06/0.94	0.11/0.60
Totals	66.75/62.60	80.47/75.86	76.26/70.69

All results expressed as % administered dose
* mean value from four subjects
** mean value from two subjects.

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 [2-^{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