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The absorption, distribution and excretion of pentazocine in man after oral and intravenous administration

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Gas-liquid chromatography is a sensitive technique for the analysis of pentazocine in biological samples. Dose for dose, the concentration in blood and the urinary excretion rate of pentazocine are much lower after oral administration than after intravenous administration. The recovery of the unchanged drug in faeces is low whether it is given by mouth or intravenously.

The analgesic potency of pentazocine in man is much less when given orally than parenterally (Beaver, 1968). This may be due to a slow or incomplete absorption of the orally administered drug, or both. Evidence to support this view is lacking for pentazocine, but has been obtained in animals for the related analgesics morphine and racemorphan which behave similarly (Cochin, Haggart & others, 1954; Fisher & Long, 1953). A gas chromatographic procedure for the evaluation of pentazocine in biological samples has now been used to investigate the disposition of the orally and intravenously administered drug in man.

EXPERIMENTAL

Analytical methods

Apparatus. A Perkin-Elmer F11 chromatograph fitted with a flame ionization detector and coupled to a 0 to 5 mV Leeds and Northrup Speedomax G (model S) recorder was used. The chromatographic column was glass tubing, $\frac{1}{4}$ inch o.d., 2 m long, packed with 80–100 mesh Chromosorb G which was acid-washed, treated with chlorodimethylsilane and coated with 2·5% w/w SE30. The column was conditioned for 24 h under the operating conditions: injection port temperature about 250°, oven temperature 200°, nitrogen (carrier-gas) flow rate 60 ml/min. The inlet pressures of the flame gases were 25 lb/inch^2 for hydrogen and 35 lb/inch^2 for air.

Reagents. Ammonium hydroxide solution, 1·0N; hydrochloric acid 0·1N; internal marker solution, the equivalent of 5 μg base/ml of α-3-hydroxy-6-dimethylamino-4,4-diphenylheptane hydrochloride in distilled water; freshly distilled reagent-grade benzene‡; reagent-grade *n*-butanol.

Treatment of biological samples. Urine (5 ml), combined with internal marker solution (1 ml), was adjusted to pH 8·5–9·5 with ammonium hydroxide solution and extracted three times with benzene (2·5 ml). These extracts were combined in a test-tube, finely tapered at its base (Beckett, 1966).

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‡ Some benzene samples gave GLC peaks which interfered with the analysis of pentazocine at high instrument sensitivity; treatment with activated charcoal and redistillation was necessary.

Blood (2 ml), mixed with distilled water (3 ml) and internal marker (1 ml) was made alkaline with ammonium hydroxide (0·2 ml) and extracted three times with benzene (2·5 ml). The extracts were combined and extracted with hydrochloric acid (2·5 ml). The acidic phase was retained, washed with benzene (2 ml) made alkaline and extracted in the same way as urine. For larger blood samples, blood (15 ml) mixed with distilled water (10 ml) was made alkaline with ammonium hydroxide solution (1·5 ml), extracted three times with benzene (15 ml) and the combined benzene extract concentrated to approximately 7·5 ml and treated as above.

Faeces (whole sample) were homogenized in two volumes of hydrochloric acid. The homogenate was treated in the same way as blood.

Chromatographic analysis. The bulked benzene extracts were concentrated by evaporation at 90° on a water-bath. The concentrate was taken up into n-butanol (10 μl) just before complete evaporation of benzene and an aliquot (2–4 μl) was injected onto the gas chromatographic column with a 10 μl Hamilton syringe. The amount of pentazocine present in a sample was determined by measuring the peak-height ratio of pentazocine to internal marker and relating it to a previously constructed calibration graph. Retention times relative to solvent fronts were pentazocine 5·3 min, internal standard 3·7 min.

The specificity and reproducibility of the assay for pentazocine in biological samples and the recovery of drug by extraction. (i) Blood and urine samples from ten subjects and faecal samples from four subjects who had not received pentazocine were analysed. 16 replicate analyses were made of standard solutions of pentazocine in blood (0·2 μg/ml) and urine (1·0 μg/ml).

Distribution and excretion of pentazocine in man

General conditions of the trials. Except where stated, trials conditions were essentially those described by Beckett & Rowland (1965). Four healthy male volunteers, aged 23 to 42 years, participated. Urine was maintained acidic by orally administered ammonium chloride (Beckett & Tucker, 1966).

Intravenous administration. Pentazocine (24 mg base as lactate) in sterile aqueous solution (2 ml) was injected into a vein of the right forearm.

Oral administration. Pentazocine hydrochloride (100 mg) was taken in distilled water (50 ml).

Collection of biological samples. Control samples were collected before drug administration and analysed. After drug administration, blood samples (5 ml) were collected from a left forearm vein into heparinized vials at 10 min intervals for 2 h and larger samples (20 ml) were collected hourly for 6 h thereafter. Urine was collected half-hourly for the first 4 h, hourly for the next 4 h, 2-hourly for the next 6 h, then at 24 h and 4-hourly thereafter up to 32 h. Faeces were collected as passed, for up to 48 h after drug administration.

RESULTS

Analytical method

Specificity and reproducibility of the assay and recovery of drug. Pentazocine-free samples of blood, urine and faeces, when analysed at high instrument sensitivity, did not produce chromatographic peaks at, or close to, the retention time of the drug. The standard deviations of the assays of standard solutions of drug in blood and urine were 5 and 3% respectively. The average recoveries of drug by extraction from blood and urine were 98 and 93% respectively.

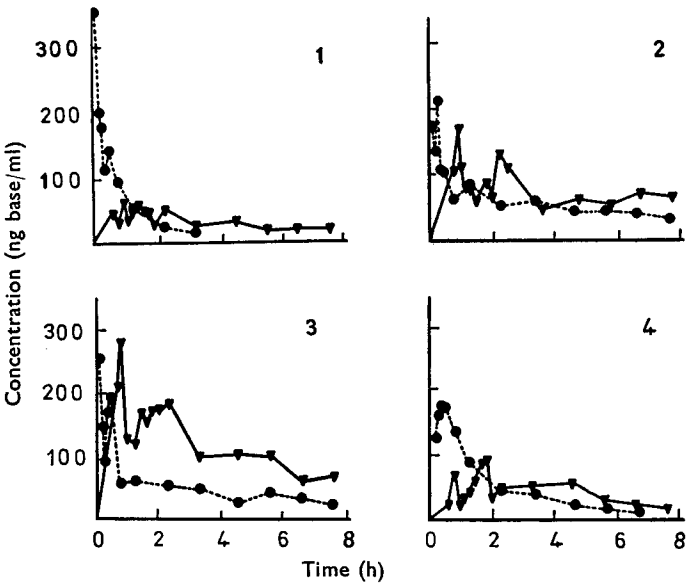

FIG. 1. Concentrations of pentazocine in blood after intravenous administration of 24 mg base as lactate (●– – –●) and oral administration of 88·7 mg base as hydrochloride (▼——▼). Subjects 1–4.

Distribution and excretion of pentazocine in man

Concentration of pentazocine in blood. The values for successive blood samples after intravenous and oral administration of the drug are shown in Fig. 1.

Urinary and faecal excretion of pentazocine. Under conditions of maintained acidic urinary pH, the 32 h urinary recoveries of the dose as unchanged drug were 8 to 24% after intravenous administration and 3 to 15% after oral administration (Table 1). In each subject the percentage urinary recovery of dose was greater after

Table 1. *Urinary recoveries, urinary excretion half-lives and faecal recoveries of pentazocine after intravenous and oral administration to man under conditions of maintained acidic urinary pH*

Subject	Dose (mg base equivalent)	Route	Urinary pH	Urinary recovery of unchanged drug in 32 h (percentage dose)	Ratio of urinary recoveries (i.v./oral)	Urinary excretion half-life (h)	Faecal recovery of unchanged drug in 48 h (% dose)
1	24	i.v.	4·59–5·22	13·0	3·0	2·7	0·5
	88·7*	oral	4·70–6·25	4·4		2·5	0·4
2	24	i.v.	4·70–5·27	16·2	1·7	2·5	0·7
	88·7	oral	4·83–5·33	9·3		†	0·1
3	24	i.v.	4·67–5·31	24·0	1·6	6·0	0·7
	88·7	oral	4·67–5·41	15·1		5·5	1·5
4	24	i.v.	4·69–8·48†	8·4	2·8	†	0·1
	88·7	oral	4·87–5·41	3·0		†	0·5

* = 100 mg hydrochloride; † = non-linear terminal part of semi-log graph of excretion rate versus time.

† Less than 5·5 for most samples.

intravenous administration than after oral administration by a factor of 1·6 to 3·0. Excretion half-lives of pentazocine varied between subjects but not within subjects and appeared to be independent of the route of drug administration (Table 1). The 48 h recoveries of the dose as unchanged drug in the faeces were 0·1 to 2·0% and were apparently independent of the route of administration of drug (Table 1).

DISCUSSION

Effect of route of administration upon the entry of pentazocine into blood and excreta

Blood. Pentazocine given orally at a dose 3·7 times larger than that given intravenously produced blood concentrations only 1 to 2 times that following an intravenous dose (Fig. 1). Therefore, absorption of orally administered pentazocine is either slow or incomplete, or both. The concentrations of pentazocine in blood generally decline smoothly and exponentially with time after intravenous drug administration, but fluctuate with time after oral administration, the secondary and tertiary peaks indicating erratic absorption of drug.

Urine. The semi-logarithmic graphs of excretion rate versus time for intravenously and orally administered pentazocine were similar, despite the three-fold increase in oral dose, and almost linear after the initial absorption and distribution phases (Fig. 2), but some deviation can occur in the terminal part of the graph. These

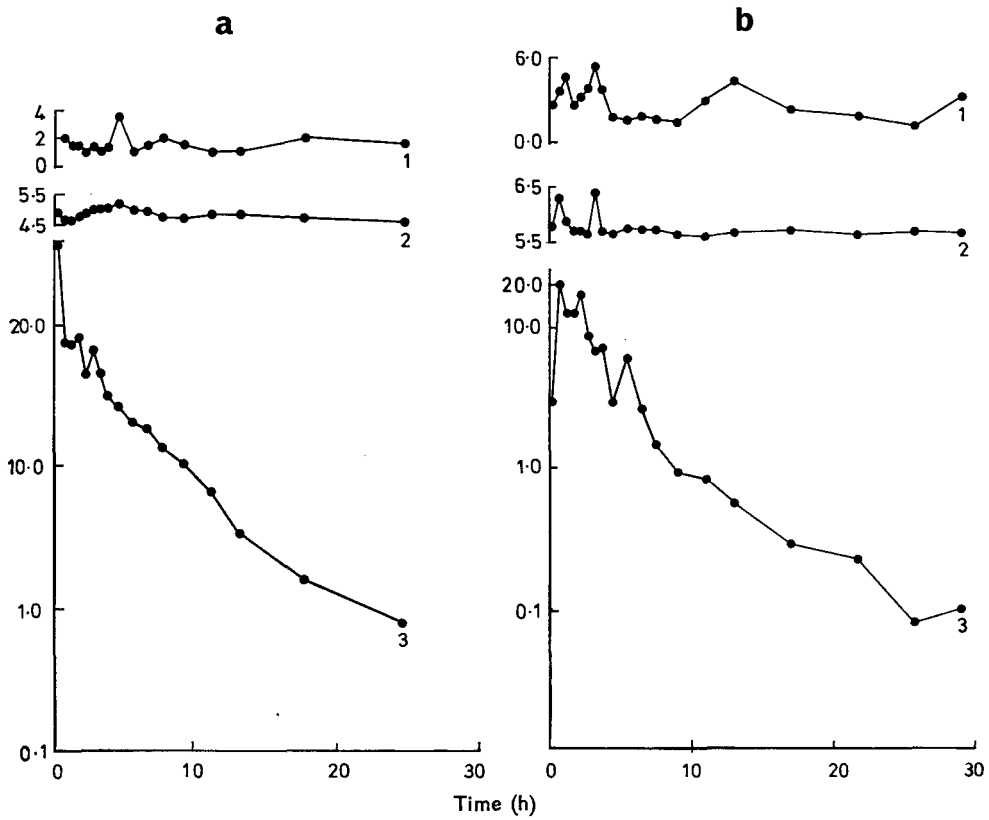

FIG. 2. Urinary excretion rate of pentazocine in μg/min (3), with corresponding urinary pH (2) and urine flow rate in ml/min (1) after (a) oral administration of 88·7 mg pentazocine base as hydrochloride; and (b), intravenous administration of 24 mg pentazocine as lacetate. Subject 1. Acid urine control.

observations confirm that pentazocine uptake from the gastrointestinal tract is impeded and erratic; slow absorption is unlikely to be the governing factor because the semilogarithmic plot of excretion rate versus time does not show the convex decreasing curvature considered indicative of this effect by Wagner (1963). Furthermore, if the urinary recovery of pentazocine under the described conditions is proportional to the amount of drug originally entering the body, the results (Fig. 3) indicate that about one to two thirds of the orally administered drug is absorbed to become distributed in the same way as an intravenous dose, i.e. there is incomplete absorption or organ clearance during absorption of 30 to 65% of the oral dose.

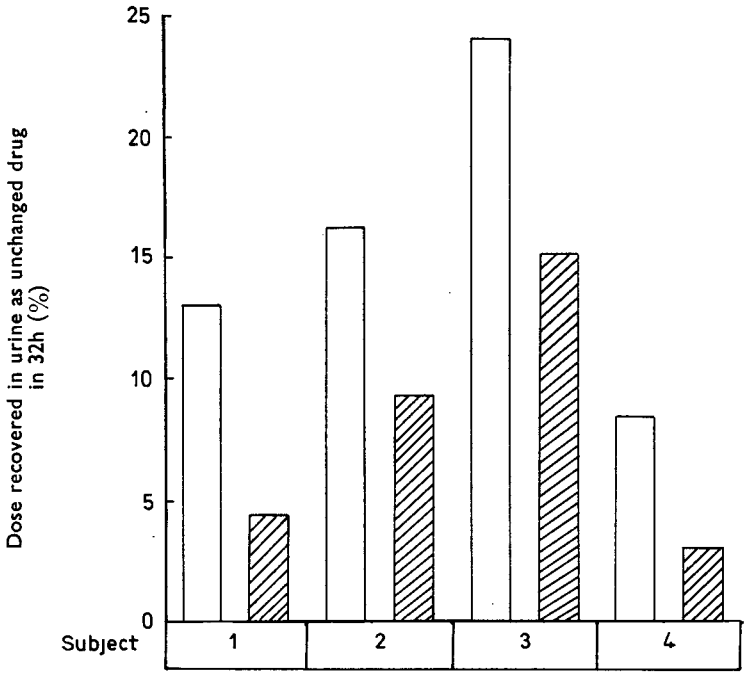

FIG. 3. Urinary recoveries of pentazocine after intravenous administration of 24 mg base as lactate (open columns), and oral administration of 88·7 mg base as hydrochloride (hatched columns) to man under conditions of maintained acidic urinary pH.

Faeces. The faecal recoveries of unchanged drug after administration by the intravenous and oral routes were low: 0·1 to 2·0% of the dose (Table 1). Therefore the "apparently" unabsorbed fraction of the oral dose is not accounted for in the faeces. These findings could be due to organ clearance of drug by metabolism during absorption, or biotransformation of the unabsorbed pentazocine by intestinal microorganisms. However, the second explanation is considered unlikely because metabolism by micro-organisms is generally confined to reductive and hydrolytic processes (Scheline, 1968) and pentazocine is metabolized by oxidation (Pittman, Rossi & others, 1969).

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