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The absorption, blood concentrations and excretion of pentazocine after oral, intramuscular or rectal administration to man

A. H. BECKETT, P. KOUROUNAKIS*, D. P. VAUGHAN AND M. MITCHARD

Department of Pharmacy, Chelsea College (University of London), Manresa Road, London, S.W.3, U.K.

Blood concentrations, urinary excretion rates and faecal excretion of unchanged drug were measured after oral, intramuscular or rectal administration of pentazocine; *Significant inter-subject variation* was observed. Blood concentration-time curves are related to urinary excretion rates. Relative physiological availabilities by each route were determined.

The urinary excretion of pentazocine in man shows large inter-subject variation and only a relatively small amount of unchanged drug is excreted by this route (Berkowitz & Way, 1969; Beckett, Taylor & Kourounakis, 1970). We have attempted to evaluate the physiological availability† of pentazocine by different routes of administration using an acid urine to prevent reabsorption of unchanged drug in the kidney tubules (Beckett & Tucker, 1967) and have used each subject for a comparative study of different formulations.

Cumulative urinary excretion of unchanged pentazocine is used to assess the relative physiological availability by the different routes.

EXPERIMENTAL

The subjects (I–IV) and procedures of Beckett & others (1970) were used but, in the GLC analysis of pentazocine, dipipanone as well as α-methadol was used as an internal standard.

Pentazocine administration

Oral route. Tablets (Fortral, Bayer) instead of solutions (Beckett & others, 1970) were used. These were taken in a single dose (four tablets of pentazocine HCl equivalent to a total of 88·7 mg base), or as two doses, each equivalent to 88·7 mg base, separated by 2 h.

Intramuscular route. 1 ml of aqueous pentazocine HCl (≡40 mg base) was injected into the *gluteus maximus* muscle.

Rectal route. A suppository (100 mg pentazocine base as lactate in 1·661 g Suppocire AM, Gattefossé—sfpa) was inserted high into the rectum.

* Present address: Faculty of Pharmacy, University of Montreal, Case Postale 6128, Montreal 101, Canada.

† Physiological availability is interpreted as the amount of drug available from the preparation to give a pharmacological or clinical response, whereas, *biological availability* is interpreted as the amount of drug available in a form which can be absorbed.

RESULTS

Urinary and faecal excretion

The 24 h urinary recoveries of unchanged drug for all subjects and routes are presented in Fig. 1. Faecal recoveries of unchanged drug after oral and rectal administration, ranged from 0·1 to 0·8% of the administered dose. Data obtained after oral administration as a solution (Beckett & others, 1970) are included for comparison.

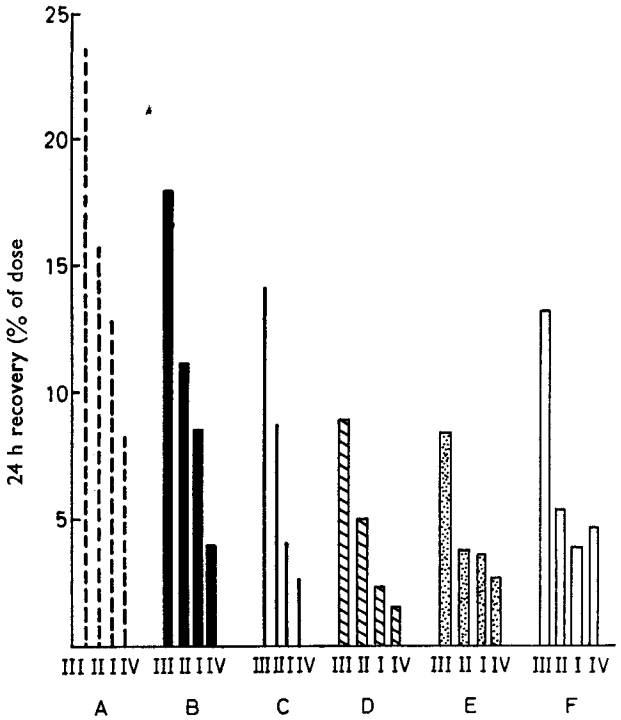

FIG. 1. 24 h Urinary recoveries of pentazocine expressed as a percentage of administered dose from four subjects: 1, III; 2, II; 3, I; 4, IV; after different routes of administration. A, i.v. (24 mg base)*; B, i.m. (40 mg base); C, oral (solution) (88·7 mg base)*; D, oral (tablets) (88·7 mg base); E, suppositories (100 mg base); F, two oral tablet doses (each 88·7 mg base) separated by a period of 2 h.

Concentration of pentazocine in blood and urine

Blood concentrations for successive samples after oral, intramuscular and rectal administration are shown in Fig. 2 as are the urinary excretion rates for two of the four subjects (III and IV); the profiles for I were similar to those of IV whereas those for II were similar to those of III. The blood levels and urinary excretion rates after 2 × 88·7 mg of pentazocine base are shown in Fig. 3. The ratios of the total amount of pentazocine excreted in the urine during a 24 h period after intravenous injection (Beckett & others, 1970) relative to the amount excreted after the other routes of administration, are shown in Table 1. The approximate urinary elimination half lives ($t_{\frac{1}{2}}$) of pentazocine, obtained from semi-logarithmic plots of urinary excretion after the initial absorption phase, and the ratios of the areas under the urinary excretion curves to that under the blood curves (expressed in arbitrary but relative units for each route and subject) are also shown in Table 1.

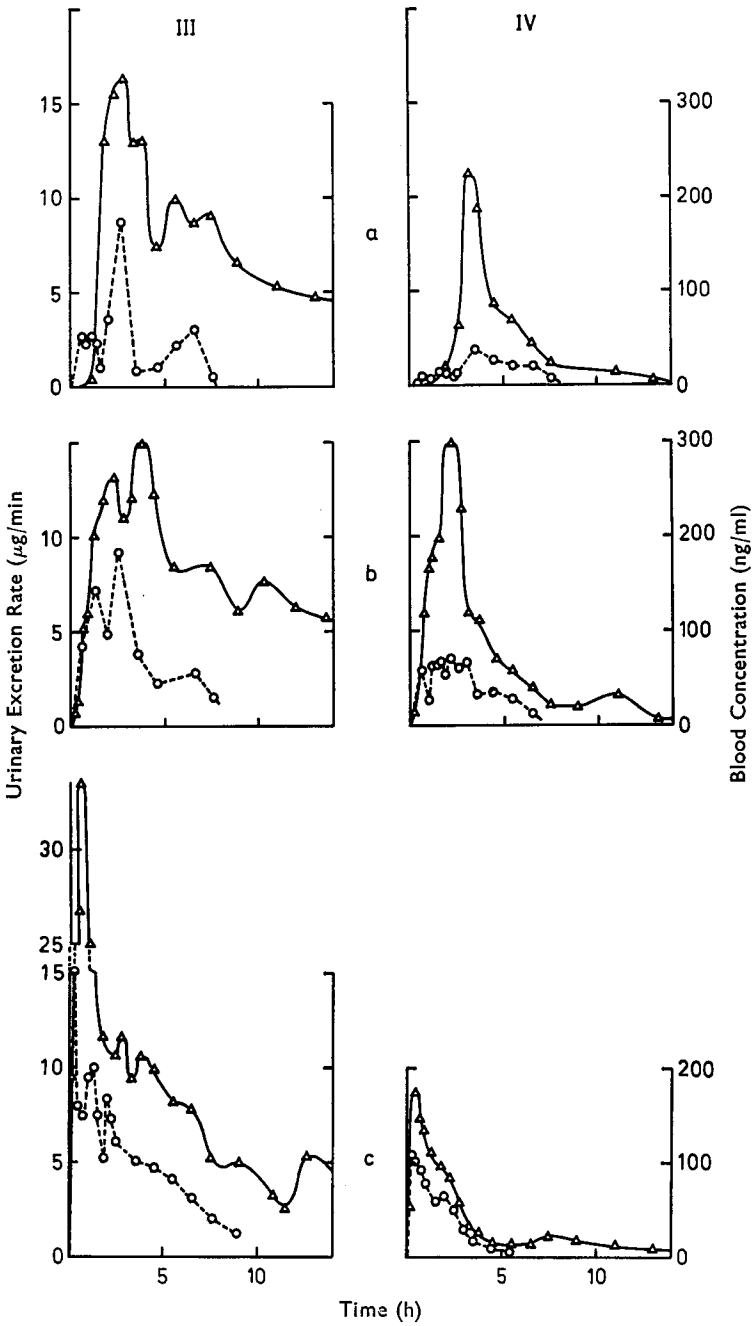

FIG. 2. Urinary excretion rates and the corresponding blood levels of pentazocine after administration of (a) oral tablets (88·7 mg base); (b) suppository (100 mg base) and (c) i.m. injection (40 mg base) to subjects III and IV, under conditions of acidic urinary pH. —△— Urinary excretion rates. —○— Blood concentration.

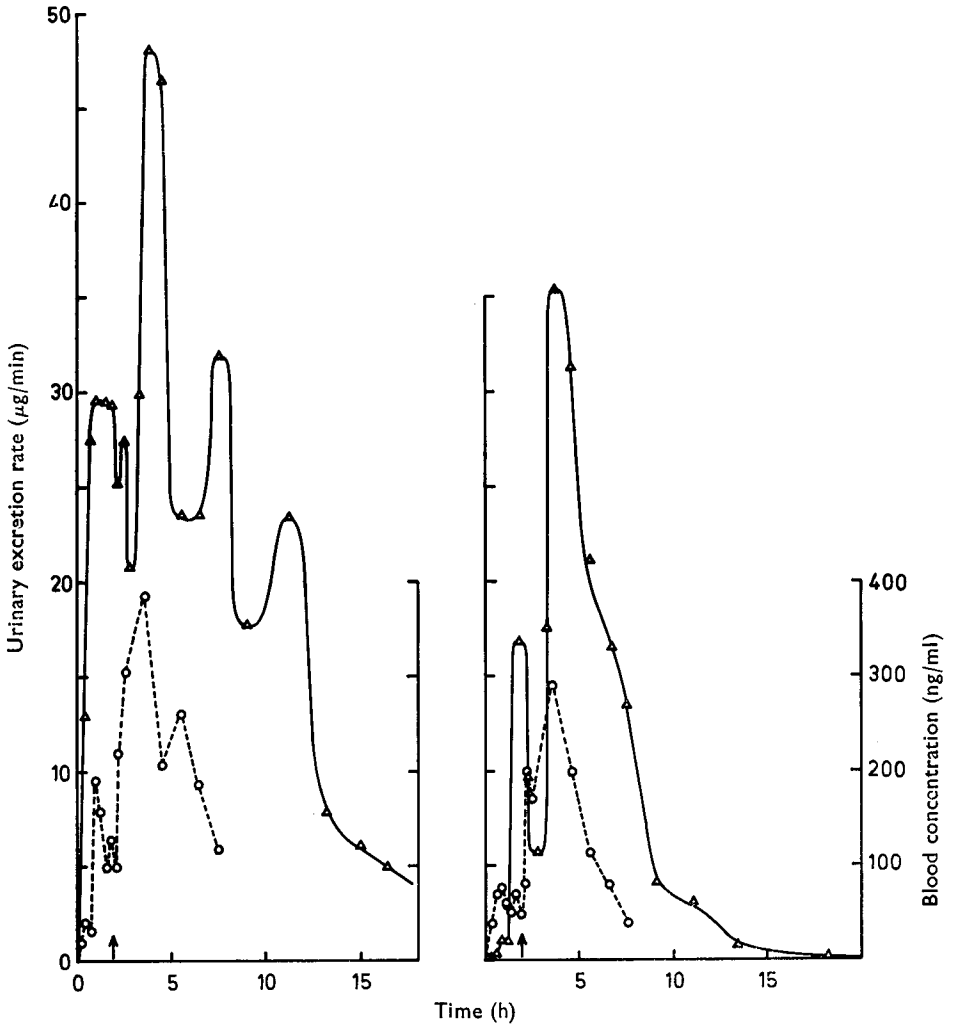

FIG. 3. Urinary excretion rates and the corresponding blood levels of pentazocine after administration of two oral tablet doses (each 88·7 mg base) to subjects III and IV under conditions of acidic urinary pH. —△— Urinary excretion rate. —○— Blood concentration.

DISCUSSION

Figs 2 and 3 indicate that when the urine is acid, blood concentrations are related to urinary excretion rates as with amphetamine (Beckett & others, 1969). Consistent inter-subject variation in blood concentrations and urinary excretion rates was observed for the various routes of administration of pentazocine; for example, subject III always had higher blood concentrations and a greater percentage recovery of unchanged drug in urine than did subject IV for comparable routes (Fig. 1). Thus unlike many other basic drugs, the determination of the relative physiological availability of pentazocine from various pharmaceutical forms must involve studies in each individual.

Two subjects in this study had a smooth urinary excretion curve and blood concentrations that did not fluctuate greatly (I and IV), two showed fluctuations in both

Table 1. *The relative physiological availabilities, half lives and urine excretion curve areas relative to blood curve areas obtained in man after different routes and forms of administration*

	Relative physiological availabilities‡ (RPA) and urinary excretion half lives ($t_{\frac{1}{2}}$ h)								Area under urine excretion curve / Area under blood concentration curve (in arbitrary units)			
	I		II		III		IV					
Route	RPA	$t_{\frac{1}{2}}$	RPA	$t_{\frac{1}{2}}$	RPA	$t_{\frac{1}{2}}$	RPA	$t_{\frac{1}{2}}$	I	II	III	IV
Intravenous* ..	1	2·8	1	2·5	1	6·0	1	1·7	1·25	0·89	1·42	0·63
Intramuscular ..	1·5	3·0	1·4	1·5	1·3	5·2	2·1	1·9	0·71	0·80	0·84	0·67
Oral solution* ..	3·1	2·5	1·8	2·0	1·7	5·5	3·1	1·8†	1·17	0·96	1·42	0·71
Oral tablets ..	5·4	3·2	3·1	2·5	2·6	6·5	5·2	2·3	1·00	1·33	1·54	1·50
Rectal suppository	3·5	3·1	4·1	2·2	2·8	6·4	3·1	2·4†	0·89	1·00	1·00	1·20
Two oral doses	3·2	ND	2·9	ND	1·8	ND	1·7	ND	1·13	1·00	1·30	1·10

† Estimated from a line of best fit because of non-linear terminal part of semi-log graph of excretion/time.

‡ Relative physiological availability ≡

The 24 h urinary excretion of unchanged drug after intravenous administration expressed as a percentage of the dose

The 24 h urinary excretion of drug administered by a different route, or as different formulations, expressed as a percentage of the dose.

* Data from Beckett & others (1970).

ND—Not determined.

aspects (II and III) (Figs 2 and 3). The latter two subjects excreted the greater amount of unchanged drug in the urine (Fig. 1). The similarity of the profiles for blood concentrations and urinary excretion rates (acidic urine) for each of the subjects using the different routes of administration indicates that the fluctuations in blood concentrations are not artifacts arising from sampling or analytical techniques.

Despite the relatively small amount, it is proposed to compare the relative amounts of unchanged drug excreted in the urine (cumulative 24 h) in each subject by each route as a method for assessing the relative physiological availability of pentazocine by each route. This is done because:

(*a*) the areas under the blood curves and urinary excretion curves gave similar ratios for each method of drug administration to each individual (Table 1); (*b*) although the subjects showed variation in the 24 h urinary excretion of pentazocine expressed as a percentage of the administered dose, there was no inter-subject variation between the *relative* physiological availabilities obtained for each route of administration or formulation; (*c*) the large differences in blood concentrations and in the urinary excretion of unchanged drug using different routes of administration cannot be accounted for by a failure to make the drug available for absorption because faecal recoveries of unchanged drug were negligible; (*d*) the apparent urinary elimination half lives ($t_{\frac{1}{2}}$) for pentazocine after intravenous and intramuscular administration are similar to the apparent $t_{\frac{1}{2}}$ values obtained after oral and rectal administration, the $t_{\frac{1}{2}}$ being different for each individual (Table 1); the absorption of pentazocine into the systemic circulation is complete after 2–3 h by oral or rectal routes.

Table 1 shows that changes from intravenous to intramuscular route, to oral solution and then to oral tablet requires an increase in the dose of 1·5, 2–3 and 3–5 times respectively, to obtain similar cumulative urinary excretion profiles and similar

blood levels. Rectal administration shows a greater variation, about twice the dose being required by this route than by mouth using a solution for subjects II and III whereas approximately equal doses are required for subjects I and IV (Fig. 1).

When two doses of pentazocine (each of four tablets ≡ 88·7 mg base) were given 2 h apart there was an increase in the percentage of unchanged drug in the urine compared to that obtained from a single oral tablet dose (Fig. 1). This increase indicates that the percentage of the dose metabolized has been reduced. Substrate inhibition or saturation of the enzymes involved in the transformation of pentazocine may be responsible for the reduction in the percent metabolized. Thus the reduction in apparent biological availability from an oral tablet dose, relative to an oral solution dose (1·7 for *all* subjects, see Fig. 1) may be due to the slow release of pentazocine in the gastrointestinal tract. Slow release implies lower concentrations of pentazocine at the enzymatic sites and hence a greater proportion metabolized.

Unlike some other drugs, e.g. fenfluramine (Brookes, 1968), it is therefore necessary to give different amounts of pentazocine by the different routes to provide similar physiological availabilities from the different formulations.

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