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The effects of physicochemical properties of pethidine and its basic metabolites on their buccal absorption and renal elimination

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The pK_a values, R_F values, partition coefficients between n-heptane and phosphate buffer (pH = 7·4), and buccal absorption tests of pethidine and its basic metabolites, norpethidine and pethidine *N*-oxide, have been determined. The amounts of these compounds recovered in the 48 h urine samples after intramuscular administration of pethidine (1·5 mg kg^{-1}) to six healthy subjects varies with urinary pH values: the recovery from acidic urine (pH 5·0) is 15·2 to 52·0%, 6·7 to 12·9% and 0·2 to 2·3% of dose for pethidine, norpethidine and pethidine *N*-oxide respectively; in alkaline urine (pH 8·0) the values are 0·8 to 1·8%, 0·6 to 2·8% and 0·3 to 2·1% respectively. The physicochemical properties (pK_a values, R_F values, partition coefficients) and buccal absorption of pethidine, norpethidine and pethidine *N*-oxide are in good agreement with the pattern of their renal elimination in acidic and alkaline urine conditions. The contribution of the physicochemical properties of pethidine and its metabolites to the drug's disposition in the body and the effect of urinary pH on its metabolism should be taken into account in pharmacokinetic studies and interpretation of intersubject variation in response to pethidine.

Pethidine is biotransformed, in man by demethylation to norpethidine, by hydrolysis to pethidinic and norpethidinic acids followed by glucuronide conjugation, by *N*-oxidation to pethidine *N*-oxide and by hydroxylation to 4-hydroxypethidine (Chan 1977). In a previous study on factors influencing the excretion and availability of pethidine in man it has been demonstrated that the amounts of pethidine excreted in acidic urine are directly proportional to plasma concentration and that even under these controlled conditions there is intersubject variation in the amount excreted (Chan et al 1975b). It is apparent that the physicochemical properties of pethidine and its metabolite together with the urinary environment will affect its disposition in the body.

I have set out to determine if there is a correlation between the pK_a values, R_F values, the partition coefficients and buccal absorption of pethidine and its basic metabolites (norpethidine and pethidine *N*-oxide) with their pattern of urinary elimination and whether it is necessary to consider these various factors in the pharmacokinetics of pethidine and the interpretation of the intersubject variation to this drug.

MATERIALS AND METHODS

Determination of pK_a values of pethidine N-*oxide*

Pethidine *N*-oxide was synthesized according to Bobranski & Pomorski (1966) and characterized as previously described (Mitchard et al 1972). A solution of the purified *N*-oxide (5×10^{-3} M) was prepared in carbon dioxide-free distilled water (25 ml). This solution of pethidine *N*-oxide as free base was titrated at 25 ± 1 °C with 0·05 M hydrochloric acid added in successive 0·1 ml quantities, the pH being recorded after each addition. The pK_a was taken as corresponding to the pH at 50% neutralization. Similarly, the pK_a values of pethidine and norpethidine bases were determined.

Thin layer chromatography of pethidine, norpethine and pethidine N-*oxide.*

T.l.c. glass plates (20 × 20 cm), spread to 0·25 mm with a 1 : 2 w/v mixture of Kieselgel, PF 254 (Merck) and water, dried for 10 min at 20 °C then activated at 110 °C, 1 h, were developed with benzene–methanol–diethylamine (75 : 15 : 10) after 50 µl of chloroform concentrate from the urine samples had been applied. After 30 min at 20°C in the dark spots were visualized with Dragendorff reagent.

The determination of partition coefficients of pethidine, norpethidine and pethidine N-*oxide using an n-heptane-buffer system*

Materials used were: n-heptane (Analar grade), saturated with Sörensen phosphate buffer (pH 7·4); pethidine hydrochloride (Roche, Welwyn Garden City, Gt. Britain); norpethidine hydrochloride (Sterling-Winthrope, Rensselaer, N.Y., U.S.A.); pethidine *N*-oxide (synthesized in own laboratory);

10 ml capacity glass centrifuge tubes with well-fitted screw caps lined with Teflon septa (Sovirel, Levallors-Perret, France); mechanical tilt shaker.

Pethidine, norpethidine and pethidine *N*-oxide together (2·5 mol ml^{-1} of each) in 5 ml phosphate buffer, pH 7·4, were placed in a glass centrifuge tube with 5 ml of n-heptane (saturated previously with the buffer). The tube was capped and shaken for at least 20 h at 25 ± 1°C. Tubes containing only buffer drug solution were similarly treated and also stored at −20 °C (controls). The experiment was in triplicate. After 20 h, the tubes were centrifuged to ensure complete separation of the phases. The partition coefficients (K) of each substance was then calculated from $K = (C_I - C_F)/C_F$. Where C_I is the initial concentration of drug in buffer and C_F is the final concentration of drug in buffer.

The buccal absorption tests (B.A.T.) of pethidine, norpethidine and pethidine N-*oxide*

These were, in general, according to Beckett & Triggs (1967). Solutions containing the compounds were prepared separately or as a mixture of the three, by dissolving the compounds in freshly distilled water. Each solution contained 5 mol (or 1·4 mg) drug ml^{-1}. The optimum mouth contact time for the B.A.T. of pethidine was 6 min and a 30 min interval between successive B.A.T. was considered sufficient for the absorbed pethidine to pass into the blood stream. Buffer solutions of pH 4·0 to pH 5·0 were prepared from sodium citrate/HCl (Sörensen); pH 5·0 to pH 8·0, from phosphate (Sörensen); and pH 8·0 to pH 9·0 from sodium borate/HCl (Sörensen).

The drug solution 0·5 ml (equivalent to 2·5 mol of drug or drugs) in a beaker was diluted with 24·5 ml of the appropriate buffer solution and the pH recorded. The solution was then circulated about 300 times around the mouth by movement of cheeks and tongue. After 6 min the solution was expelled into a beaker and the mouth rinsed with 10 ml of distilled water for 10 s. The rinse was expelled into a second beaker. The volume and pH of the expelled solution was measured immediately. The solutions were combined adjusted to 250 ml with distilled water and analysed for drug. During the waiting time between successive tests (at least 30 min) the mouth was rinsed with three changes of distilled water. Four subjects, one male and three female, took part.

The urinary recovery of pethidine and its basic metabolites

Three male volunteers and three male patients (ages 25 to 45), who gave informed consent, took part under medical supervision and with approval of the Medical Research Ethical Committee. All had normal renal and hepatic function and none were taking any medication that might have affected the results. For urinary studies, the bladder was emptied immediately before the drug dose. Cumulative urine samples were collected at 3 h intervals for 12 h and then 12 hourly to 48 h. All specimens were collected in plastic containers and stored at −20 °C. Two separate 1·5 mg kg intramuscular doses of pethidine were given to each of the subjects. On one occasion the urine was made acidic (pH less than 5·0) by ingestion of ammonium chloride tablets as described by Beckett & Triggs (1967) and on the other, the urine was made alkaline (pH more than 8·0) by ingestion of sodium bicarbonate 3 g (6 × 0·5 g capsules) every 2 h for 6 h before the study 2·5 g at 2 hourly intervals during the study, 3·0 g before bed time and 3·0 g on rising. The pH of each urine sample was checked immediately before storage.

Analysis of pethidine and metabolites

The concentration of pethidine, norpethidine and pethidine *N*-oxide in various samples were determined by g.l.c. procedure (Chan et al 1974).

RESULTS

pK_a values of pethidines

The pK_a values of pethidine, norpethidine and pethidine *N*-oxide were 8·5, 9·7 and 4·9 respectively. Previous reported values for pethidine and norpethidine are 8·63 and 9·68 (Asatoor et al 1963).

Thin layer chromatography

On t.l.c., three spots having R_F values of 0·65, 0·55 and 0·35 which corresponded to the R_F values for authentic samples of pethidine, norpethidine and pethidine *N*-oxide were obtained. Thus the basic metabolites norpethidine and pethidine *N*-oxide are more polar than the parent drug.

Partition coefficient and buccal absorption measurements

The mean partition coefficients between n-heptane and buffer (pH 7·4) of pethidine, norpethidine and pethidine *N*-oxide were 1·683, 0·374 and 0·105 respectively (n = 3). The partition coefficients between heptane and water can be used as a reliable criterion of the ability of substances to penetrate biological membranes (Brodie et al 1960; Hertz & Teschemacher 1971). Only a few partition coefficients of morphine-like substances have been determined

(Hertz & Teschemacher 1971). The present results indicate that pethidine was more lipid-soluble than its metabolites at physiological pH. Analysis of buffer solutions in control tubes (at 25 and −20 °C) indicates negligible decomposition or loss of the drugs during the experiment. These physicochemical parameters are compared with those obtained from the buccal absorption test in the discussion section. The effect of buffer pH on the buccal absorption of pethidine, norpethidine and pethidine *N*-oxide is shown in Fig. 1. The percentage of pethidine and

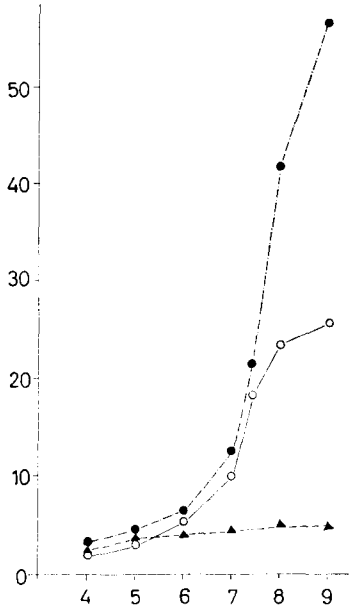

FIG. 1. The effect of buffer pH (abscissa) on the buccal absorption (ordinate: %) of pethidine (●) and its basic metabolites, norpethidine (○) and pethidine *N*-oxide (▲).

norpethidine absorbed, but not that of pethidine *N*-oxide, was increased as the buffer pH increased. There was little intersubject variation in the buccal absorption of these compounds. The percentage of buccal absorption of pethidine and its basic metabolites was similar whether determined alone or in a mixture of the three.

Urinary recovery of pethidine and basic metabolites

The 48 h recovery of pethidine, norpethidine and pethidine *N*-oxide from the urine of six subjects after an intramuscular dose (1·5 mg kg^{-1}) varied from 15·2 to 52·0%, 6·7 to 12·0% and 0·2 to 2·3% under acid urine and 0·8 to 1·8%, 0·6 to 2·8% and 0·3 to 2·1% under alkaline urine respectively (Table 1). The excretion of the unchanged drug and its more basic metabolite, norpethidine, is much higher in acid urine than alkaline urine ($t = 4·9$, $P > 0·0025$ for pethidine; $t = 6·6$, $P > 0·005$ for norpethidine), there was no difference for pethidine *N*-oxide ($t = 0·474$, $P > 0·35$).

Table 1. The 48 h urinary recovery of pethidine, norpethidine and pethidine *N*-oxide expressed as a percentage of dose in acid and alkaline urine from six healthy subjects after intramuscular pethidine (1·5 mg kg^{-1}).

	Pethidine (% dose)		Norpethidine (% dose)		Pethidine *N*-oxide (% dose)	
Subject	Acid urine	Alkaline urine	Acid urine	Alkaline urine	Acid urine	Alkaline urine
1	52·0	1·4	6·7	0·6	0·2	0·3
2	31·5	0·8	8·1	2·0	1·8	1·1
3	19·6	1·6	9·5	1·2	2·3	1·8
4	21·2	1·8	12·9	2·7	1·3	0·9
5	25·9	0·9	7·3	0·8	1·7	0·6
6	15·2	1·5	6·8	2·8	0·7	2·1
Average	27·6 ± 13·2	1·3 ± 0·4	8·6 ± 2·4	1·7 ± 0·9	1·3 ± 0·8	1·1 ± 0·7
	$t = 4·902$ $0·0025 < P < 0·005$		$t = 6·619$ $0·0005 < P$		$t = 0·474$ $0·35 < P < 0·30$	

DISCUSSION

Abdel-Monem & Portoghese (1971) demonstrated that the potency of some pethidine analogues could be correlated with lipid solubility and the rate of metabolism of the drugs. The R_F values on the t.l.c. system are a useful expression of molecule polarity. Obviously pethidine *N*-oxide and norpethidine are more polar than the parent drug, pethidine which at physiological pH pethidine has the higher lipid solubility. The order of partitioning of pethidine, norpethidine and pethidine *N*-oxide, as determined by the n-heptane buffer system, is in good agreement with the results from the buccal absorption test (Table 2).

The shape of the buccal absorption - pH curves (Fig. 1) apparently indicate that the compounds can be classified into two types. The first includes pethidine and norpethidine and corresponds to class four

Table 2. Urinary elimination of pethidines and its correlation with their physicochemical properties and buccal absorption.

	% Dose excreted in 48 h urine					
Compound	Acid urine	Alkaline urine	pKa	R_F	Part. coeff. at pH 7·4	% buc. abs. at pH 7·4
Pethidine	27·6 ± 13·2	1·3 ± 0·4	8·5	0·65	1·68	20
Norpethidine	8·6 ± 2·4	1·7 ± 0·9	9·7	0·55	0·37	15
Pethidine *N*-oxide	1·3 ± 0·8	1·1 ± 0·7	4·9	0·35	0·11	<5

of Beckett's group (Beckett & Triggs 1967). The percentages of the drugs absorbed are a function of the buffer pH. Both pethidine and norpethidine are weak bases with pK_a 8·6 and 9·7 respectively and are partially ionized in acidic solutions and therefore the rate of diffusion through the buccal membrane is slow. The opposite is true when the compounds are in alkaline buffer. The second type, and pethidine *N*-oxide, is in class two of Beckett's grouping and the percentage of buccal absorption shows little pH-dependence. The weak basicity of the *N*-oxide (pK_a 4·9) in comparison with the parent drug is due to the sharing of the nitrogen free electron pair by the oxygen which introduces an ionic character to the bond and therefore increases the polarity of the molecule.

The renal excretion of pethidine and its metabolites under acidic and alkaline urine conditions in six healthy subjects correlates well with the buccal absorption of these compounds (Table 2). The excretion of the unchanged drug and its more basic metabolite norpethidine is very much higher in acidic than alkaline urinary conditions. This difference is statistically significant (Table 1). Apparently, at alkaline urinary pH, the re-absorption of pethidine and norpethidine via the renal tubules is greater and therefore less of each drug is recovered in the urine. The opposite picture is found at acidic urinary pH. However, the renal excretion of the less basic metabolite, pethidine *N*-oxide, appears to be independent of urinary pH.

Although there may be variation in the rate of metabolism of pethidine among the six subjects, the renal elimination of pethidine and its basic metabolites norpethidine and pethidine *N*-oxide correlates well with their buccal absorption pattern and their physicochemical properties. Significantly less pethidine and norpethidine were recovered under alkaline urinary pH conditions. This is probably because after re-absorption into the blood stream both pethidine and norpethidine are also metabolized by hydrolysis to pethidinic and norpethidinic acid in the liver.

In clinical practice the response to pethidine is variable. This variation in response is probably partially due to the wide variation in the blood concentrations of pethidine attained after a standard intramuscular dose (Fochtman & Winek 1969; Chan et al 1975a). However the present study indicates that one should also appreciate the contribution of physicochemical properties of pethidine and its metabolites to the disposition of the drug in the body and the effect of urinary pH on the metabolic elimination of this drug. It is, therefore, important to consider these factors when one considers the clinical pharmacokinetics of pethidine and interprets the intersubject variation in response to the drug.

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