Pharm. Pharmac., 1975, 27, 235–241 *Received July* 29, 1974

Factors influencing the excretion and relative physiological availability of pethidine in man

K. CHAN, M. J. KENDALL, W. D. E. WELLS, AND M. MITCHARD

Department of Clinical Pharmacology and Therapeutics, Medical School, University of Birmingham, B15 2TJ. U.K.

Factors influencing the urinary excretion of pethidine, norpethidine and pethidine *N*-oxide have been examined. The proportion of a dose of pethidine excreted unchanged or as norpethidine depends on the urinary pH and the route of administration. Older people appear to metabolize more of the drug and therefore excrete less unchanged pethidine. The rate of excretion of pethidine in acid urine is directly proportional to the plasma pethidine concentration and under these conditions the relative physiological availability of pethidine has been determined. It has not been possible to explain variations in the amounts of pethidine excreted as the *N*-oxide.

Pethidine was introduced as a potent synthetic narcotic analgesic in 1939 (Eisleb & Schaumann, 1939) and is still used extensively particularly in obstetrics and for the relief of post-operative pain. A recent study (Bannister, 1974) concludes that "pethidine is probably the best drug for post-operative analgesia". Pethidine is metabolized by demethylation to norpethidine, by ester hydrolysis to pethidinic and norpethidinic acids (Burns, Berger & others, 1955; Plotnikoff, Way & Elliot, 1956) or by *N*-oxidation (Mitchard, Kendall & Chan, 1972). A proportion is also excreted in the urine unchanged.

In clinical practice the response to pethidine is variable; some patients remain alert and unaffected whilst others may deteriorate markedly and even become shocked. The frequency of these adverse effects is unknown since it is often impossible to differentiate the effects of drugs from those of the underlying disease process. The variation in response is probably partially due to the wide variation in blood levels of pethidine attained after a standard intramuscular dose which was noted by Fochtman & Winek (1969) and which we have confirmed. This variation could be due to differences in distribution or in the rates of excretion and/or metabolism. Such differences do occur since the pattern of excretion may be affected by the urinary pH (Asatoor, London & others, 1963), and the rate of metabolism may be affected by pregnancy, for Crawford & Rudofsky (1965) have shown that pregnant women excrete proportionally less norpethidine than pethidine whilst non-pregnant females excrete more norpethidine than pethidine.

We have tested the hypothesis that inter-patient variations in blood pethidine concentrations and clinical results can be related to differences in the pattern of metabolism and excretion of the drug. We have, therefore, examined the urinary excretion of pethidine and two of its metabolites, norpethidine and pethidine *N*-oxide in man to find out the amount of variation, the effect of modifying pH and the variability in subjects whose urinary pH has been controlled. We have also looked at the influence of

the route of administration and have determined the relative physiological availability of pethidine after intramuscular and oral administration. Finally we investigated the pattern of excretion after administering norpethidine.

MATERIALS AND METHODS

Subjects. Three volunteers and seven patients in the Queen Elizabeth Hospital who gave informed consent took part. All were shown to have normal renal and hepatic function and none were taking drugs which might have affected the investigation. The studies were carried out under medical supervision and with the approval of the Medical Research Ethical Committee. The study was carried out in three parts:

(1) *The effect of urinary pH on the amount of pethidine and its metabolites excreted in urine after intramuscular administration*

(a) Urine was collected for 48 h from seven patients after a 1·5 mg kg^{-1} intramuscular dose of pethidine: no attempt was made to modify the urinary pH.

(b) Urine samples were collected for 48 h from three subjects (one volunteer and two patients) after two separate 1·5 mg kg^{-1} intramuscular doses of pethidine. On one occasion the urine was made acid (pH less than 5·25) by giving ammonium chloride as described by Beckett & Tucker (1967) and on the other the urine was made alkaline (pH more than 7·0). The two patients received 3 g of sodium bicarbonate (6 × 0·5 g capsules) every 2 h for 6 h before the study, but the volunteer, in whom it was found difficult to make the urine alkaline, was given sodium bicarbonate (300 m equiv) by slow intravenous infusion over a 2 h period immediately before the study. It was then found possible to maintain the urine alkaline by giving 2·5 g of sodium bicarbonate orally to all three subjects at 2 h intervals during the study.

(c) A third study was carried out in ten subjects (three volunteers and seven patients, three of whom had participated in the studies described under 1a and 1b) from whom a 48 h urine maintained acid by administering ammonium chloride as in 1b, was collected after a 1·5 mg kg^{-1} intramuscular dose of pethidine. This provided a repeat study under acid conditions in three subjects.

(2) *The effect of route of administration on the amount of pethidine and metabolites excreted in acid urine*

In addition to the samples collected after intramuscular doses, 48 h samples were collected from two subjects (whose urine was made acid by taking ammonium chloride) after the intravenous (0·5 mg kg^{-1}) and oral (1·5 mg kg^{-1} as a solution) administration of pethidine. During the intravenous study on these two subjects urine was collected at frequent intervals and blood samples were obtained from a cannula in the forearm vein.

(3) *The excretion of norpethidine in acid urine after a dose of norpethidine*

The urine of the two volunteers was maintained acid and samples were collected for 48 h after the intravenous administration of norpethidine (0·5 mg kg^{-1}).

In all studies, the bladder was emptied immediately before the drug dose and urine samples were collected at 3 h intervals for 12 h and then at 12 h intervals to 48 h.

All specimens were collected in clean plastic containers and stored at −20° until analysed.

Analysis

The concentrations of pethidine and norpethidine in the plasma and urine and pethidine *N*-oxide in the urine samples were determined by the gas liquid chromatographic method using 8% carbowax 20M and 2% potassium hydroxide as the stationary phase. The method has been described in detail (Chan, Kendall & Mitchard, 1974). The blood urea and serum creatinine were determined for each of the persons participating in their study.

RESULTS

(1) *Urinary pH*

The recovery of pethidine, norpethidine and pethidine *N*-oxide in the 48 h urine of seven patients after an intramuscular dose (1·5 mg kg^{-1}) of pethidine varied from 6 to 28%, 0·2 to 7·0% and 0·0 to 0·6% respectively. The actual amounts expressed as a percentage of the dose are shown in Fig. 1A. Fig. 1B shows that acidifying the urine

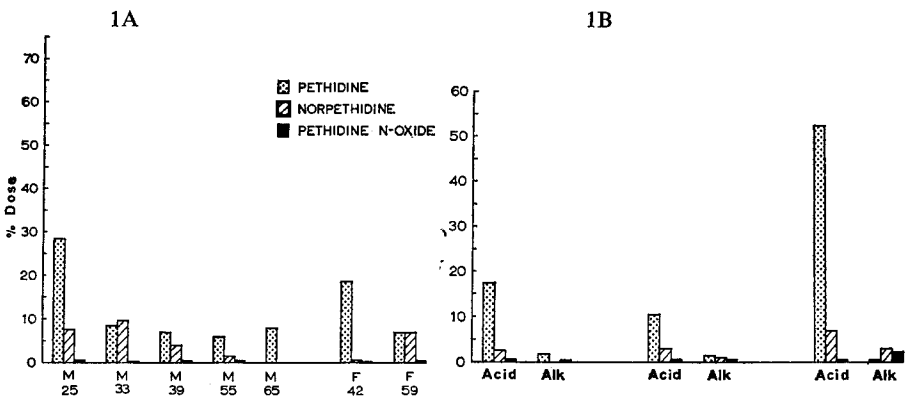

FIG. 1A. The amounts of pethidine, norpethidine and pethidine *N*-oxide expressed as a percentage of the dose recovered from the 48 h urine of seven patients after pethidine (1·5 mg kg^{-1} i.m.). The sex and age in years of each patient is indicated under their respective data.
B. 48 h urinary recovery of pethidine, norpethidine and pethidine *N*-oxide expressed as a percentage of the dose in alkaline and acid urine obtained from three subjects after pethidine (1·5 mg kg^{-1}, i.m.).

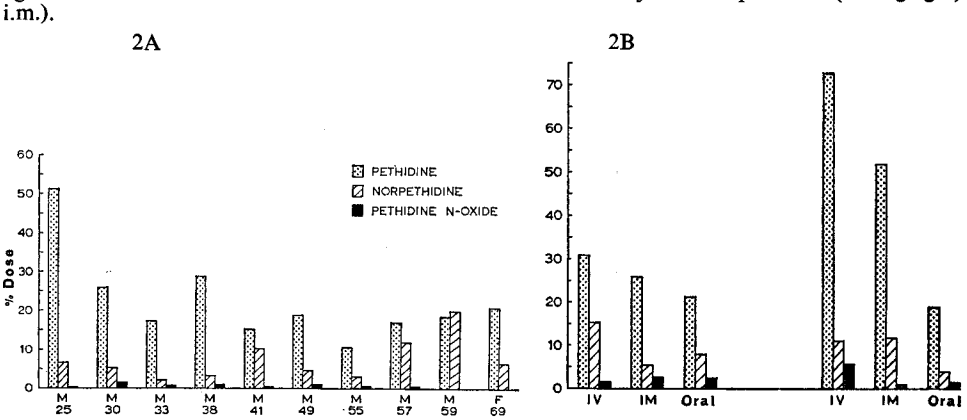

FIG. 2. A. The amounts of pethidine, norpethidine and pethidine *N*-oxide expressed as a percentage of the dose recovered from the 48 h acid urine of ten subjects after pethidine (1·5 mg kg^{-1}, i.m.). The sex and age in years of each subject is indicated under their respective data.
B. The amounts of pethidine, norpethidine and pethidine *N*-oxide expressed as a percentage of the dose recovered from the 48 h acid urine of two subjects after (0·5 mg kg^{-1}, i.v.), (1·5 mg kg^{-1}, i.m) and oral (1·5 mg kg^{-1}) pethidine.

increases the excretion of pethidine and norpethidine, whereas very little of these substances are excreted in alkaline urine. Fig. 2A shows that the recovery of pethidine and norpethidine from 10 subjects whose urinary pH was maintained constant at pH 4·8 to 5·25 varied between 10–50% and 2–20% of the dose respectively. More pethidine appeared to be recovered in the urine of young and more norpethidine in the older subjects. The amounts of pethidine *N*-oxide excreted in urine varied considerably and were not related to urinary pH.

(2) *Route of administration*

The amounts of pethidine, norpethidine and pethidine *N*-oxide expressed as a percentage of the dose recovered from the acid urine of two subjects after intravenous, intramuscular and oral administration are presented in Fig. 2B. In each case less pethidine was recovered after intramuscular and even less after oral administration.

(3) *Norpethidine study*

The results of urinary analysis after the intravenous administration of pethidine and norpethidine to two subjects are presented in Table 1. It has been assumed that the percentage of the dose unaccounted for has been metabolized to products not measured in this study, i.e. by hydrolysis to pethidinic and norpethidinic acids. A high proportion of the dose, whether pethidine or norpethidine, was hydrolysed by subject 1, whereas the corresponding values for subject 2 were consistently low. Similarly, subject 1 excreted a relatively low amount of unmetabolized drug in both studies and subject 2 a relatively high amount.

Table 1. *The urinary excretion of pethidine, norpethidine and their metabolites expressed as a percentage of the dose recovered in the 48 h acid urine of two subjects after an intravenous dose of pethidine or norpethidine (0·5 mg kg^{-1}).*

	Subject 1				Subject 2			
	% of dose recovered as:				% of dose recovered as:			
Drug (0·5 mg kg^{-1})	Pethidine	Norpethidine	*N*-Oxide	Hydrolytic products	Pethidine	Norpethidine	*N*-Oxide	Hydrolytic products
Pethidine i.v.	32	15	1·4	51·6	73	12	5·7	9·3
Norpethidine i.v.	—	56	—	44	—	82	—	17

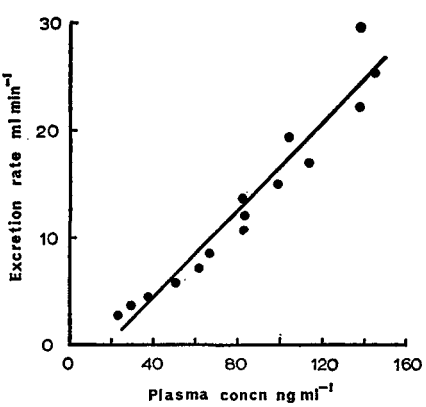

FIG. 3. Relation between excretion rate of pethidine in acid urine and plasma pethidine concentration.

(4) *Renal clearance*

The urine sampling periods do not allow accurate flow rates to be calculated. The average rates varied from 30 to 190 ml h^{-1}, but there was no apparent relation between urine flow rate or between blood urea or serum creatinine and the amount of pethidine, norpethidine or pethidine *N*-oxide excreted in acid urine.

A plot of plasma pethidine concentration against urinary excretion rate (Fig. 3) shows that the rate at which the drug appears in urine is directly proportional to the plasma concentration.

DISCUSSION

There is a significant intersubject variation in the amount of pethidine, norpethidine and pethidine *N*-oxide excreted in 48 h by both male and female subjects. The amounts expressed as a percentage of the dose varied from 6–29% of pethidine from 0–10% of norpethidine and 0–1% of pethidine *N*-oxide (see Fig. 1A).

This study shows that at least four factors contribute to this variation.

The influence of the ionized:unionized ratio of weak acids or bases on their partition between lipid/water systems and the relevance to the renal tubular reabsorption of drugs was reviewed extensively by Milne, Scribner & Crawford in 1958. Subsequently, Milne carried out a study (Asatoor & others, 1963) which examined the influence of urinary pH on the excretion of pethidine and its derivitives in patients receiving the drug as an analgesic. These workers showed that more pethidine and norpethidine were recovered in acid than in alkaline urine; between 10 and 30% of the dose being recovered as pethidine. It appears that between 10 and 35% was recovered as norpethidine but it is not easy to obtain this information from their paper as the norpethidine figures are always quoted as a total with the pethidine.

The recoveries obtained in our study show a similar pattern but the variation was greater, one individual excreting over 50% of the dose as pethidine (Fig. 1B) in acid urine. The average recovery of norpethidine (2–20%) would appear to be significantly lower in the present study (see Fig. 3), although this may be related to a difference between the ages of the subjects used in the two studies (*vide infra*). In both studies less than 5% of the dose was recovered as pethidine or norpethidine under alkaline conditions.

A number of studies (Beckett & Rowland, 1965; Vaughan & Beckett, 1973) show that the intra-subject variation in the percent of weakly basic drugs recovered unchanged in urine is reduced under acid conditions. There appears to be little comment on the effect on inter-subject variation. When we repeated the studies in three subjects under acid conditions it was shown that similar amounts of pethidine were excreted unchanged and as norpethidine. However, Fig. 3 shows that there is still a considerable inter-subject variation in the amount of both pethidine and norpethidine recovered even when the urinary pH is controlled. The variation appears to be age related. The younger subjects excrete more pethidine than the older whilst the older subjects excrete relatively more norpethidine. The average percentages of pethidine and norpethidine recovered in the under 40 and over 40 year old males are 31·2 and 4·5. ($n = 4$) and 16 and 9·9 ($n = 5$) respectively. Analysis shows that the difference for pethidine is significant ($0{\cdot}1 > P > 0{\cdot}05$) but that for norpethidine is less ($0{\cdot}25 > P > 0{\cdot}1$). However, the small numbers and high s.d.s. make it difficult to comment positively on this observation until further studies have been carried out. The older group also appears to eliminate a higher proportion of the drug by other routes.

It was not possible to demonstrate any relation between difference in renal function as indicated by the blood urea or serum creatinine and variation in the amount of pethidine or norpethidine recovered in acid urine. However, Fig. 2A shows that as with amphetamine (Beckett, Salmon & Mitchard, 1969) the amounts of pethidine excreted in acid urine are directly proportional to the plasma concentration. The variation in the cumulative amounts of pethidine excreted by different individuals under these conditions therefore reflects differences in their plasma pethidine concentrations.

This age-related difference between the relative amounts of pethidine excreted is therefore not produced by deterioration in renal function in the elderly but reflects an age influenced change in the metabolism of this drug.

The influence of the route of administration on the urinary excretion of pethidine, norpethidine and pethidine *N*-oxide in two subjects is shown in Fig. 2B. As expected in both subjects least unchanged pethidine is recovered after the oral solution due to the "first pass" effect. The data are similar to that reported for pentazocine by Beckett, Kourounakis & others (1970) and the relative physiological availabilities* of pethidine (oral solution 1·4 and 3·6; i.m., 1·2 and 1·4) are similar to the values for pentazocine (1·7–3·1 and 1·3–2·1 respectively) given in that paper. The reason for the extremely large differences in the amounts of unchanged pethidine recovered in the urine of these two subjects is not clear but could be due in part to the fact that subject 1 was Caucasian and a heavy smoker, subject 2 was Asiatic (the only non-european) and a nonsmoker.

A comparison of the data obtained after the intravenous administration of pethidine and norpethidine to two subjects as presented in Table 1 demonstrates that there is an inter-subject difference in the amounts of drug metabolized by hydrolysis. The urinary pH, glomerular filtration rate and rate of demethylation were similar in both subjects but one excreted over 70% of pethidine and 80% of norpethidine unchanged. This subject only hydrolysed about 10% of the drug as calculated by difference whereas the other subject hydrolysed about 50% of both drugs and excreted correspondingly less unchanged: a similar pattern was obtained when intramuscular pethidine was given to these subjects (see Fig. 2B) although the difference was not so marked after oral administration.

The results therefore show that more pethidine and norpethidine are excreted in acid urine but that considerable inter-subject variation remains in the amounts excreted even when urine pH is maintained acid. The variation is due in part to individual differences in the amounts of the drug metabolized; older people appearing to metabolize more of the drug.

The amount of pethidine appearing in urine is related to the plasma concentration and variation in age, metabolism and urinary pH, all, therefore, contribute to variation in plasma concentrations and response to this drug.

The proportion of pethidine excreted as *N*-oxide is variable; sometimes it is not detectable, sometimes it accounts for 3 to 5% of the dose. The variation did not appear to be related to any of the factors examined in the course of this study and is the subject of further investigation.

Acknowledgements

M. J. K. is an M.R.C. Clinical Research Fellow.

* Relative physiological availability has been defined as the percentage of the dose recovered in 24 h urine after an intravenous dose divided by the percentage recovered after administration by another route.

REFERENCES

ASATOOR, A. M., LONDON, D. R., MILNE, M. D. & SIMENHOFF, M. L. (1963). *Br. J. Pharmac. Chemother.*, **20**, 285–298.

BANNISTER, E. H. D. A. (1974). *Anaesthesia*, **29**, 158–162.

BECKETT, A. H. & ROWLAND, M. (1965). *J. Pharm. Pharmac.*, **17**, 59–60.

BECKETT, A. H. & TUCKER, J. F. (1967). *J. Mond. Pharm.*, **3**, 181–202.

BECKETT, A. H., KOUROUNAKIS, P., VAUGHAN, D. P. & MITCHARD, M. (1970). *J. Pharm. Pharmac.*, **22**, *Suppl.*, 169S–174S.

BECKETT, A. H., SALMON, J. A. & MITCHARD, M. (1969). *Ibid.*, **21**, 251–258.

BURNS, J. J., BERGER, B. L., LIEF, P. A., WOLLACK, A., TAPPER, E. M. & BRODIE, B. B. (1955). *J. Pharmac. exp. Ther.*, **114**, 289–298.

CHAN, K., KENDALL, M. J. & MITCHARD, M. (1974). *J. Chromatog.*, **89**, 169–176.

CRAWFORD, J. S. & RUDOFSKY, S. (1965). *Br. J. Anaesth.*, **37**, 929–933.

EISLEB, O. & SCHAUMANN, O. (1939). *Deut. Med. Wochenschr.*, **65**, 967–968.

FOCHTMAN, F. W. & WINEK, C. L. (1969). *J. forensic Sci.*, **14**, 213–217.

MILNE, M. D., SCRIBNER, B. H. & CRAWFORD, M. A. (1958). *Am. J. Med.*, **24**, 709–729.

MITCHARD, M., KENDALL, M. J. & CHAN, K. (1972). *J. Pharm. Pharmac.*, **24**, 915.

PLOTNIKOFF, N. P., WAY, E. L. & ELLIOT, H. W. (1956). *J. Pharmac. exp. Ther.*, **117**, 414–419.

VAUGHAN, D. P. & BECKETT, A. H. (1973). *J. Pharm. Pharmac.*, **25**, *Suppl.*, 104P–108P.