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Comparison of Renal Excretion of Pethidine (Meperidine) and its Metabolites in Old and Young Patients

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Summary. In a previous study old subjects were found to eliminate pethidine and its active metabolite norpethidine more slowly than young people. To investigate whether this was due to the decline in renal function with age, the urinary output of pethidine and its metabolites pethidinic acid, norpethidine and norpethidinic acid was compared in old and young patients. The cumulative urinary excretion of pethidine and pethidinic acid over 24 h was similar in old and young patients. The slower elimination rate of pethidine from plasma might therefore be due to slower biotransformation of pethidine to norpethidine and norpethidinic acid. The cumulative urinary excretion of norpethidine and norpethidinic acid during 24 h was significantly lower in old patients than in young: 2.7% versus 7.1% ($p < 0.001$), and 5.5% versus 10.5% ($p < 0.001$). The renal clearance of norpethidine was inversely correlated with age. Thus, the slower disappearance of norpethidine from plasma in old patients is due to slower renal excretion of this metabolite. The renal clearance of pethidine showed pH-dependence and was usually smaller than the creatinine clearance. In contrast, renal clearance of norpethidine was correlated with creatinine clearance and was of the same magnitude. The difference in renal handling may be explained by the more polar character of norpethidine compared to its parent compound. The present study shows that not only the excretion of unchanged drugs may decline with increasing age but also that of drug metabolites, which may therefore reach higher plasma levels in old patients. If they are pharmacologically active they will increase and prolong the response to medication and possibly increase the risk of side effects.

Key words: pethidine; drug metabolism, pethidine metabolites, renal excretion, pharmacokinetics, geriatrics, old age, meperidine

Drug disposition may differ in old and young patients (for reviews see Crooks et al. 1976; Richey and Bender 1977; Greenblatt et al. 1982). In an earlier study (Holmberg et al. 1982) a slower elimination rate of pethidine from plasma in old patients than in the young was demonstrated following a single intravenous dose. The plasma clearance was lower (9.13 ± 2.50 vs 16.18 ± 5.15 ml/min/kg) whereas the volume of distribution was similar. Plasma levels of the active metabolite norpethidine tendend to persist longer in the elderly. The question arose whether renal function, which is known to decline with increasing age (Davies and Shock 1950), could play a role in the slower disappearance of pethidine and norpethidine from plasma in the old. The present investigation is a comparison of the urinary output of pethi-

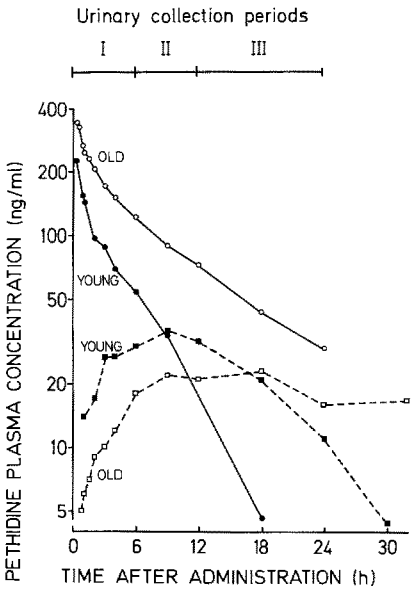

Fig. 1. Urinary collection periods and plasma concentration-time curves of pethidine (circles) and norpethidine (squares) in 1 old (RS) and 1 young (JH) patient

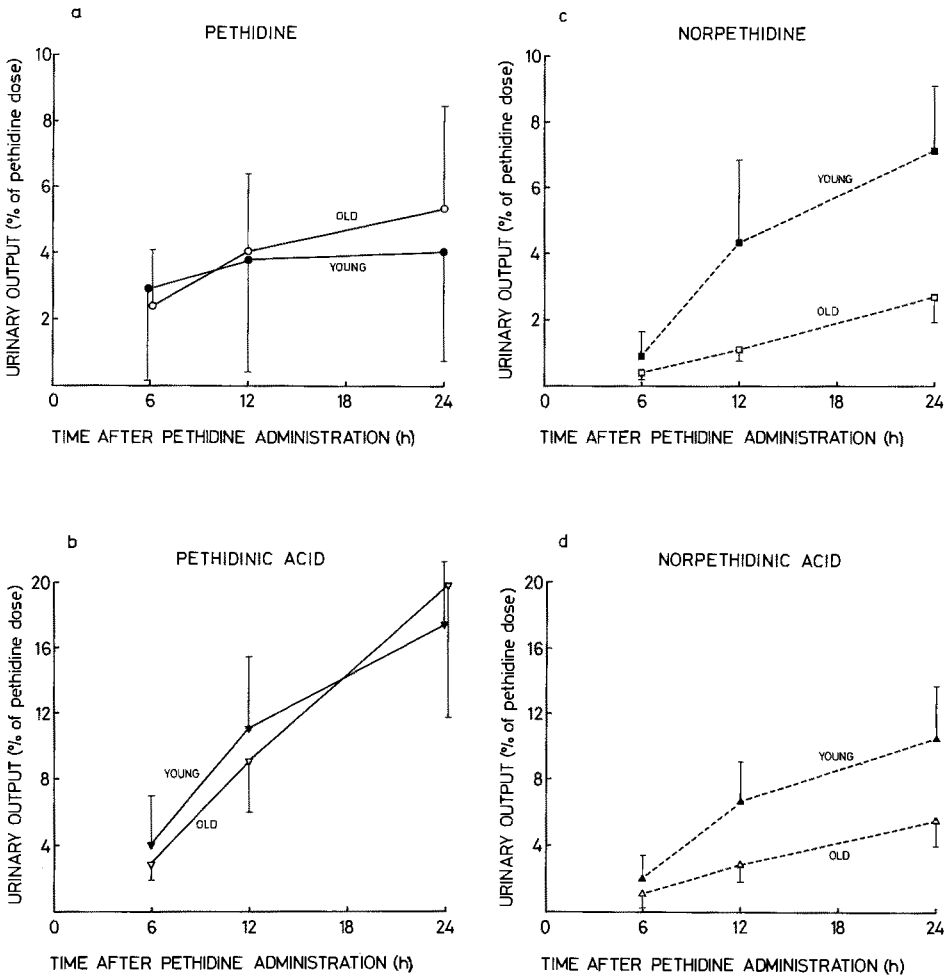

Fig. 2. Cumulative 24 hour urinary output of pethidine and pethidinic acid (**a, b**), norpethidine and norpethidinic acid (**c, d**) as percent of the given dose, m ± SD. The excretion of norpethidine and norpethidinic acid are lower in old than in young patients ($p < 0.001$)

dine and its metabolites pethidinic acid, norpethidine and norpethidinic acid in old and young patients.

Materials and Methods

Nine old and 7 young patients took part in the study after giving their informed consent. They received pethidine as premedication before minor surgery. The mean ages of the 2 groups were 72 years (range 70–83 years) and 24 years (range 18–29 years), respectively. The older group was composed of 5 men and 4 women, and the younger of 4 men and 3 women. They were admitted to the hospital for minor hand surgery or cystoscopy, but were otherwise healthy as judged clinically and by routine laboratory tests. One exception was 1 old patient who had mild hypertension. The mean creatinine clearance was 70 ml/min (range 56–94 ml/min) in the old subjects and 119 ml/min (range 86–164 ml/min) in the young. The mean urinary pH was similar in the 2 groups, 6.5 (range 5.8–7.4) in the old and 6.6 (range

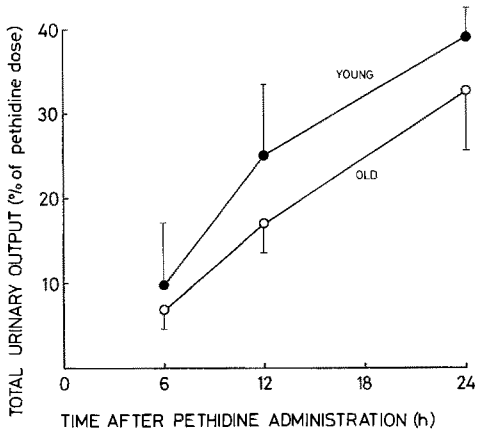

Fig. 3. Cumulative 24 hour urinary output of pethidine and its metabolites as percent of the given dose, m ± SD. The excretion is lower in old than in young patients ($p < 0.05$)

5.3–8.0) in the young. No attempt was made to control urinary pH.

Pethidine was given as a single intravenous dose of 1 mg/kg, at the rate of 10 mg/min, 15–30 min before operation. Blood was collected at regular inter-

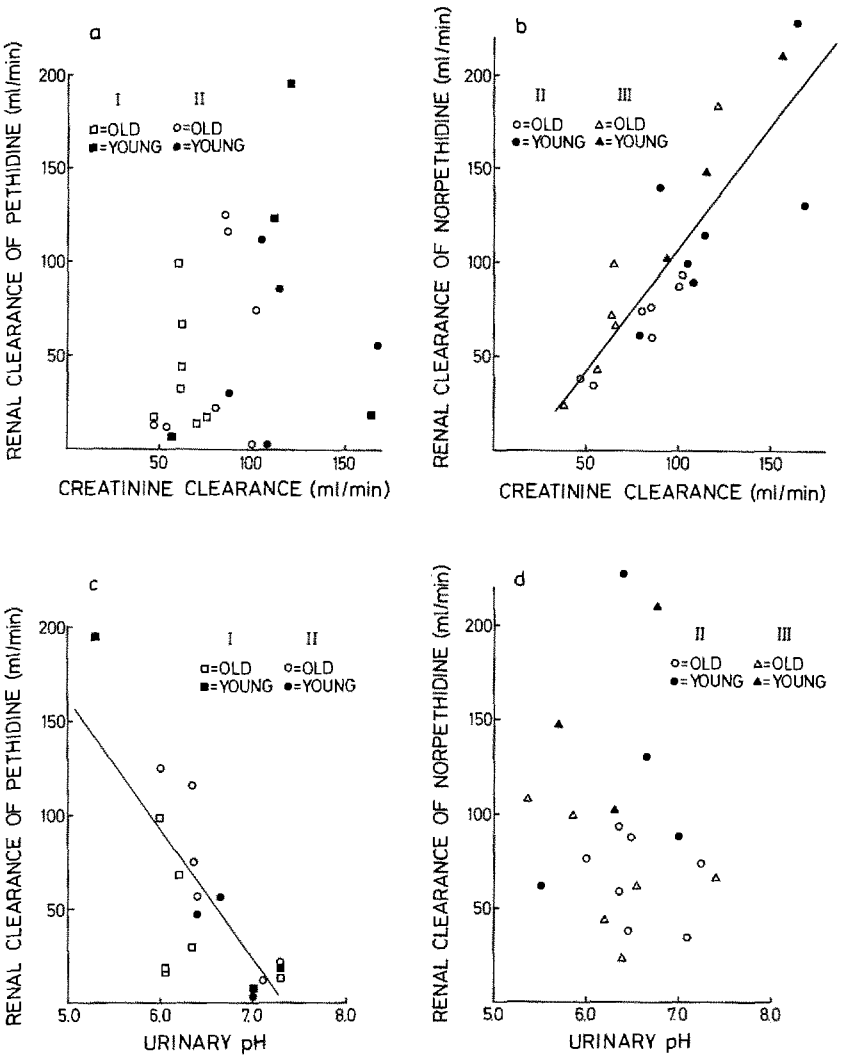

Fig. 4. Renal clearance of: **a** pethidine in relation to creatinine clearance ($r = 0.14$, n.s.); **b** norpethidine in relation to creatinine clearance ($r = 0.85$, $p < 0.001$); **c** pethidine in relation to urinary pH ($r = -0.73$, $p < 0.001$) and **d** norpethidine in relation to urinary pH ($r = -0.18$, n.s.)

vals from an indwelling polyethene antebrachial venous catheter used exclusively for sampling. Plasma was stored frozen at −20 °C until analysed for pethidine and norpethidine. Urine was collected for periods of 0–6 (I), 6–12 (II) and 12–24 (III) h after administration of pethidine (Fig. 1). For practical reasons urinary collection periods could not be extended beyond 24 hours. In each period a 10 ml sample of freshly voided urine was collected under oil and analysed for pH using an ordinary glass calomel electrode pH meter. From each portion a sample was taken for determination of creatinine and the creatinine clearance was calculated. The remaining portion of urine was stored frozen until analysed for pethidine and metabolites.

The plasma concentrations of pethidine and norpethidine were measured by gas chromatography using EC-detection (Hartvig et al. 1977). The urinary content of pethidine, norpethidine, pethidinic acid and norpethidinic acid was determined by gas chromatography-mass spectrometry according to Lindberg et al. (1980). Renal clearance of pethidine and norpethidine was calculated using midpoint values of the individual plasma concentration-time curves (Fig. 1). The plasma concentration data for most of the patients have already been published (Holmberg et al. 1982).

The investigation was approved by the Ethical Committee at the Karolinska Hospital.

Results

The cumulative urinary output of pethidine and of pethidinic acid was similar in old and young subjects (Fig. 2 a, b). The renal clearance of pethidine tended to be lower in the elderly than in the young but the difference was not statistically significant (46.1 ±

39.7 versus 84.1 ± 67.8 ml/min). The urinary output of norpethidine and norpethidinic acid was lower in old patients than in young (Fig. 2c, d). The renal clearance of norpethidine was lower in the old than the young (74 ± 36 vs 120 ± 50 ml/min, $p < 0.05$). The mean total urinary output (pethidine and metabolites) during 24 h was less in old than in young patients (32.6 ± 6.8% vs 39.1 ± 3.4%, $p < 0.05$; Fig. 3).

In the entire series the renal clearance of norpethidine was correlated with creatinine clearance ($r = 0.87$, $p < 0.001$; Fig. 4b). In contrast, the renal clearance of pethidine was not correlated with creatinine clearance ($r = 0.14$, n.s.; Fig. 4a).

The renal clearance of pethidine was inversely correlated with urinary pH ($r = -0.73$, $p < 0.001$; Fig. 4c). The renal clearance of norpethidine, however, was independent of pH ($r = -0.18$, n.s.; Fig. 4d).

The renal clearance of norpethidine was inversely correlated with age ($r = -0.72$, $p < 0.01$) and so was creatinine clearance ($r = -0.77$, $p < 0.001$).

Discussion

To a minor extent pethidine is excreted unchanged (about 5 to 7%) via the kidneys (Lindberg et al. 1980; Verbeeck et al. 1981). Most of the drug is metabolized to pethidinic acid, norpethidine and norpethidinic acid. Of those metabolites norpethidine has been demonstrated both in plasma and urine, whereas the other metabolites are found only in urine (Hartvig et al. 1979). Norpethidine is a pharmacologically active metabolite (Dahlström et al. 1979; Kinn et al. 1982).

In a previous study differences were found in the pharmacokinetics of pethidine in old and young subjects (Holmberg et al. 1982). The present study has shown that he rate of renal excretion of pethidine and pethidinic acid is similar in old and young patients. The previous finding of a slower elimination rate of pethidine from plasma in old patients (Holmberg et al. 1982) may, therefore, be explained by the slower biotransformation of pethidine to norpethidine and norpethidinic acid.

The present investigation has also demonstrated that the cumulative urinary excretion of norpethidine and norpethidinic acid is significantly lower in old than in young patients. Thus, the previously observed slower disappearance of norpethidine from plasma in old patients is due to slower renal excretion of these metabolites. The plasma levels of norpethidine in old patients would have been even higher if they had been able to demethylate pethidine at the same rate as the young. The findings are in accordance with those of Szeto et al. (1977), who demonstrated an increased plasma level of norpethidine in patients with impaired renal function.

The renal clearance of norpethidine is correlated with creatinine clearance and both are inversely correlated with age; the renal excretion of norpethidine will gradually decline with increasing age, due to the fall in renal function that normally takes place with aging (Davies and Shock 1950). Consequently, the very old carry the greatest risk of a high plasma norpethidine level after repeated doses of pethidine, which might induce central nervous excitation (Szeto et al. 1977).

Pethidine is a non-polar, lipophilic substance with a pKa of 8.7. In the renal tubules it undergoes nonionic diffusion into tubular cells. Thus, its renal clearance is usually smaller than the creatinine clearance, as demonstrated in the present study. Also the renal excretion of pethidine will decrease with increasing pH, as found in the present study and as previously reported (Asatoor et al. 1963; Verbeeck et al. 1981). The renal excretion of pethidine will vary with physiological changes in urinary pH, with certain diseases (e.g. acidosis), and with drug therapy that alters urinary pH. However, this will have little effect on the plasma level of pethidine, as only 5% of the dose is excreted unchanged (Verbeek et al. 1981). In contrast, urinary change in pH with have little influence on norpethidine excretion. In the present study the renal clearance of norpethidine was dependent on kidney function and was of the same magnitude as creatinine clearance. Thus, norpethidine, after being filtered through the glomeruli, is only affected to a minor extent by tubular mechanisms. This is due to the fact that norpethidine is a more polar substance than its parent compound (Hartvig et al. 1977). This finding is in accordance with those by Verbeeck et al. (1981), who demonstrated that urinary acidification increased the urinary output of pethidine twenty-two-fold compared to urinary alkalinisation, whereas the excretion of norpethidine was increased only four-fold.

The total urinary excretion of pethidine and its metabolites in young patients during 24 h was slightly lower than that observed in a previous study of pregnant women during delivery (Lindberg et al. 1980). This might be due to different rates of metabolism and of renal excretion in pregnant women compared to other subjects of the same age group.

It is well-known that due to the decline in renal function in old age drugs that are excreted unchanged via the kidneys have a slower elimination rate in old patients. Therefore, lower doses of these drugs are required than in young patients (Crooks et al. 1976; Greenblatt et al. 1982). Little attention has

been paid to the slower elimination of drug metabolites. The accumulation of metabolites might lead to an increased and prolonged therapeutic effect if they were active, or to side effects at lower doses than in young patients. This phenomenon is exemplified by the lower rate of renal excretion of norpethidine demonstrated here.

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