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Comparative Disposition of Pethidine and Norpethidine in Old and Young Patients*

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Summary. Pethidine was given as a single intravenous dose for premedication before minor surgery. Two groups of subjects were studied, old patients aged more than 65 years, and young patients aged 18–30 years. Blood samples were taken at fixed intervals for 30 h after the injection, and the plasma concentrations of pethidine and its major metabolite norpethidine were analyzed by gas chromatography. In comparison with the young the old patients had a lower plasma clearance for pethidine (9.13 ± 2.50 versus 16.18 ± 5.15 ml/min/kg), slower elimination rate β (0.101 ± 0.036 versus 0.211 ± 0.146), and a larger AUC (1935 ± 554 versus 1092 ± 277 h · ng/ml) but a similar volume of distribution (5.69 ± 1.54 versus 5.38 ± 1.75 l/kg). Norpethidine appeared later and reached its peak concentration later in the old patients than in the young. In several old patients it was still present at a plateau level after 30 h. The present study emphasizes that both parent drug and active metabolite must be taken into consideration when drug therapy is evaluated. The data do not provide pharmacokinetic support for a reduction in the dose of pethidine if it is given as a single intravenous dose. However, when repeatedly administered, it is advisable to reduce the total daily dose.

Key words: pethidine, norpethidine; analgesic, single-dose kinetics, plasma concentrations, drug disposition, geriatric patients

In recent years some studies have demonstrated differences in drug disposition between old and young patients; for review see Crooks et al. (1976), and Richey and Bender (1977). However, the influence of old age on pharmacokinetics has not been sufficiently evaluated. Pethidine, introduced nearly 40 years ago, is commonly used for premedication prior to surgery, and for analgesia in acute or chronic pain. On the basis of clinical experience elderly patients are often given lower doses of this drug than the young. Modern pharmacokinetic methods allow critical evaluation of this practice. Thus, Chan et al. (1975) studied plasma concentrations of pethidine after intramuscular administration and found considerably higher levels in old (> 70 years) than in young patients.

In the present study we have determined the disposition of pethidine in old and young patients after intravenous administration. Furthermore we have measured the plasma concentration of its active metabolite norpethidine in these two age groups.

Materials and Methods

Patients

Nine old and six young patients took part in the investigation (Table 1). In the old group there were five men and four women, with a mean age of 74.4 years. The young group consisted of four men and two women, with a mean age of 24.6 years. Fourteen subjects, apart from the reason for surgery, were healthy as judged clinically and by routine blood and urine laboratory tests. One older patient had mild hypertension. The mean value of creatinine clearance was 70 ml/min in the old patients and 119 ml/min in the young. The mean value and range of pH in urine for the old patients was 6.45 (5.85–7.40), and for the young patients 6.66 (5.30–8.00). The serum albumin and orosomucoid levels were within the normal range. Fourteen patients were non-smokers and one

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young man smoked 20 cigarettes per day (subject DK). None of the patients abused alcohol. Pethidine was given as premedication for cystoscopy or for minor surgery, mainly hand surgery, performed under regional anesthesia with prilocaine-adrenaline or lidocaineadrenaline. The operations were made in a bloodless field obtained by use of a tourniquet. As postoperative analgesic, pentazocine was administered to patients RS, JH and EÖ, whereas patients GE, IE and HP were given Distalgesic (a combination of dextropropoxyphene and paracetamol). Informed consent was obtained from each subject. The investigation was approved by the Ethical Committee of the Karolinska Hospital.

Methods

The dose of pethidine was 1 mg/kg given intravenously at a rate of 10 mg/min, about 15 min before the operation. Blood was drawn via an indwelling venous antebrachial polyethene chatheter, used exlusively for sampling. The samples (2 ml) were obtained before (0 h) and after 15, 30, 45, 60 and 90 min and 2, 3, 4, 6, 9, 12, 18, 24 and 30 h. Plasma was collected and frozen at −20 °C until assayed for its content of pethidine and norpethidine.

The 0 sample was analyzed for its content of creatinine and serum proteins. Urine was collected for 24 h. 10-ml samples of freshly voided urine was collected under oil and analyzed for pH. In the remaining portion of urine the creatinine content was determinded and the creatinine clearance calculated.

The plasma concentrations of pethidine and norpethidine were measured by gas chromatography using electron capture detection as described by Hartvig et. al. (1977). Typical lower limit for detection was 10 ng/ml for pethidine and 2 ng/ml for norpethidine. From the log plasma concentration versus time curve pharmakokinetic parameters were calculated in accordance with a linear one-compartment model. The area under the plasma concentration-time curve (AUC) was estimated by the log trapezoidal method (0–30 h), and the area to infinite time was added by integration. The elimination rate constant of the terminal portion (β) of the curve was calculated by linear least-squares regression analysis from log plasma concentration versus time. The plasma clearance (Cl_{pl}) was determined according to the equation $Cl_{pl} = \frac{D}{AUC}$, where D is the dose. The apparent volume of distribution, V_d, was calculated from the equation $V_d = \frac{Cl_{pl}}{\beta}$. Terminal plasma half-life ($t_{½\beta}$) was also calculated ($t_{½} = 0.693/\beta$). The statistical significance of differences was evaluated by Student's t-test for unpaired data.

Table 1. Patient data

Subject	Age	Sex	Body weight (kg)	Operation	Creatinine clearance (ml/min)
Old					
(AÖ)	70	M	83	cyst	–*
(AJ)	75	M	64	h.s.	69
(TN)	70	M	70	h.s.	81
(KB)	83	M	72	pl.s.	58
(GE)	67	M	70	h.s.	80
(VC)	86	F	52	cyst	56*
(GF)	79	F	72	pl.s.	61*
(RS)	70	F	58	h.s.	63
(IE)	70	F	53	h.s.	94
Young					
(HP)	25	M	72	h.s.	119
(MO)	18	M	70	pl.s.	162
(DK)	20	M	78	h.s.	86
(JT)	26	M	72	h.s.	164
(JH)	25	F	60	pl.s.	92
(EÖ)	29	F	60	pl.s.	90

hs = hand surgery; pls = plastic surgery; cyst = cystoscopy

* Other drugs taken:
AÖ – methenamine hippurate 1 g tablets b.i.d. for two days before cystoscopy,
VC – bendroflumethiazide, 2.5 mg tablets, containing potassium chloride 570 mg once a day,
GF – chlorpromazine 10 mg tablets, two tablets t.i.d.

Results

The log plasma concentration versus time curves for the old patients are given in Fig. 1, and for the young patients in Fig. 2; mean values for the two patient groups are shown in Fig. 3. The initial plasma concentration of pethidine was generally slightly higher in the old patients than in the young (Figs. 1–3). The mean peak concentrations were 330 ± 86 SD ng/ml and 253 ± 49 SD ng/ml, respectively; the difference is not statistically significant. In the three young patients who had hand surgery, irregularities in the plasma concentration-time curve appeared during and after the application of the tourniquet and the surgery procedure. The plasma concentration time curve declined biexponentially in eight old subjects, and monoexponentially in one of the old subjects undergoing hand surgery. In two of the young subjects the plasma concentration curve declined biexponentially and in the remaining four monoexponentially.

Pharmacokinetic parameters are given in Table 2. The old patients had significantly longer plasma $t_{½}$, lower β, lower Cl_{pl} and larger AUC values than the young. The V_d was similar in the two groups.

The i. v. dose used was well tolerated except in one old patient (KB), who had nausea and vomited. Most patients showed the intended slight sedation during the first 15–20 min.

The time to the appearance of measurable norpethidine in plasma ranged from 0.5–1.5 h in the old and from 0.25–1.0 h in the young subjects; the difference was not statistically significant. The time to peak value was longer in the old patients (12.6 h) than in the young (7.5 h; $p < 0.05$; Fig. 3). The peak heights varied considerably between individuals. In several old patients plasma concentrations of norpethidine were still at a plateau level 30 h after the dose had been given (Fig. 1). In the remaining subjects concentration-time curves declined with great interindividual variation (Fig. 1).

In old patients pethidine levels exceeded those of norpethidine until about 30 h, when the two plasma concentration curves met without crossing. In the young subjects plasma concentrations of pethidine exceeded those of norpethidine only until about 9 h,

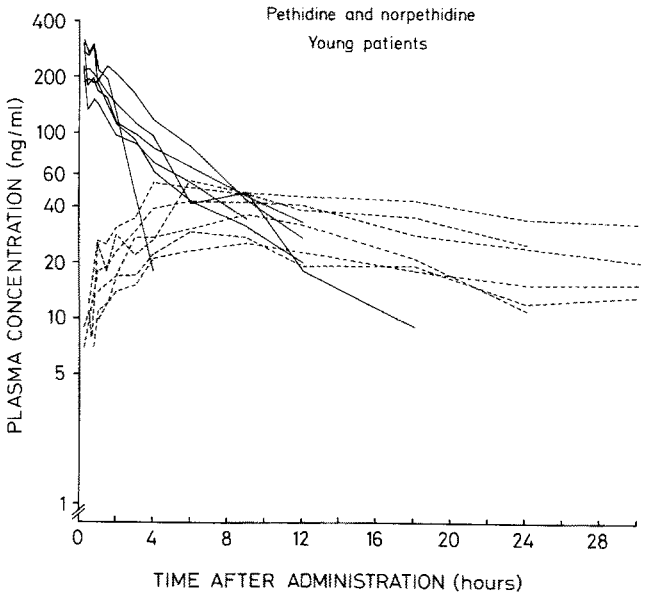

Fig. 2. Log plasma concentration of pethidine (full lines) and norpethidine (dotted lines) versus time in young subjects

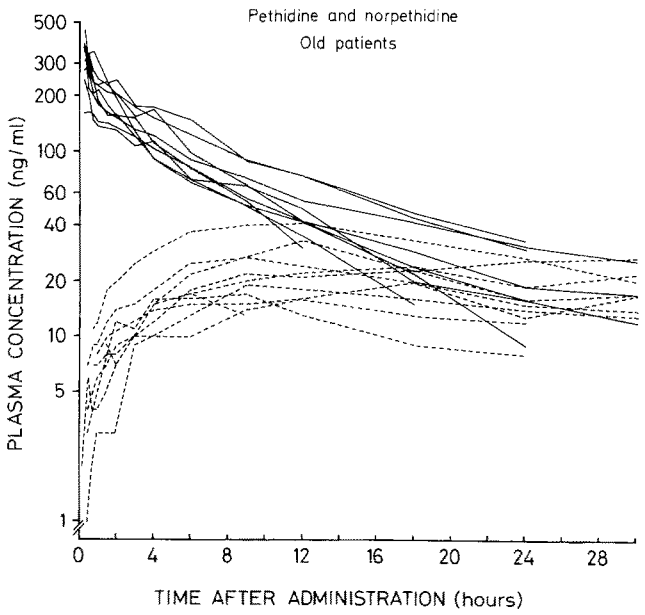

Fig. 1. Log plasma concentration of pethidine (full lines) and norpethidine (dotted lines) versus time in old subjects

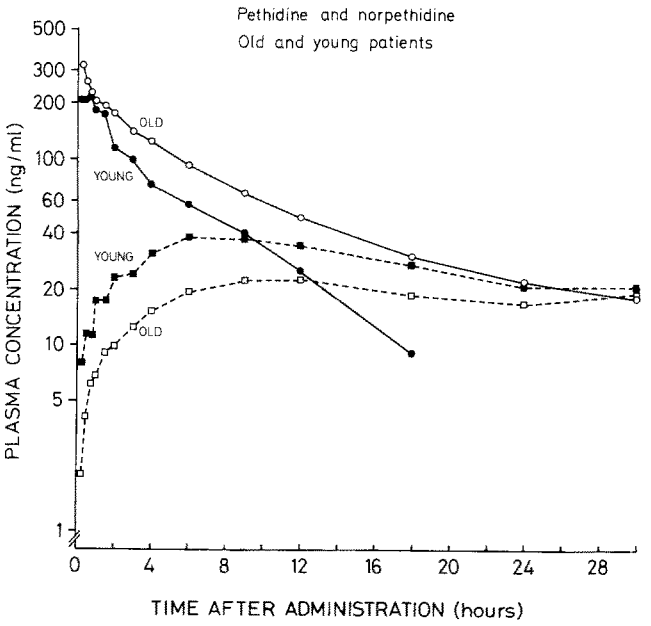

Fig. 3. Mean log plasma concentration of pethidine (circles) and norpethidine (squares) versus time in old and young subjects

Table 2. Pethidine – pharmacokinetic data (mean ± SD)

Patients	$t_{½}$ [h]	β_{el} [h^{-1}]	Cl_{pi} [ml/min/kg]	AUC [h · ng/ml]	$V_{d\ area}$ [l/kg]
Old $n = 9$	7.59 ± 2.37	0.101 ± 0.036	9.13 ± 2.50	1935 ± 554	5.69 ± 1.54
Young $n = 6$	4.18 ± 1.71	0.211 ± 0.146	16.18 ± 5.15	1092 ± 277	5.38 ± 1.75
Difference	3.41	0.110	7.05	843	0.31
Significance level	$p < 0.01$	$p < 0.05$	$p < 0.01$	$p < 0.01$	NS

and were not detectable after about 18 h, whereas norpethidine still remained at a measurable level after 30 h (Fig. 3).

Discussion

In the present study, old patients were found to have a different disposition of pethidine compared to young patients. However, the differences in plasma levels between old and young subjects were less pronounced than those found by Chan et al. (1975) after intramuscular administration of pethidine to old and young subjects. The fact that an alpha phase was detected in most of the old subjects, but usually not in the young, may have been due to more rapid distribution in the young, which was already completed before the first sample 15 min after dosing. This agrees with the suggestion by Castleden and George (1979), that in old patients propranolol has a decreased rate of distribution to tissues. The apparent volume of distribution of pethidine was similar in old and young subjects. This is in accordance with the finding for propranolol (Castleden and George 1979). In contrast, change in V_d with age has been found for some drugs, such as propicillin K (Simon et al. 1972), diazepam (Klotz et al. 1975) and chlormethiazole (Nation et al. 1976).

In the present study, old patients had a slower elimination rate of pethidine than the young, and their total plasma clearance was reduced. Pethidine is mainly eliminated by metabolism in the liver. Hepatic clearance is dependent on liver blood flow and liver extraction ratio. Pethidine has been classified as a drug exhibiting non-restrictrive hepatic clearance, "a high clearance drug" (Wilkinson et al. 1975). The reduction in its plasma clearance in old age would then to a large extent be due to diminished liver blood flow, but impaired liver extraction is probably a contributory factor. A dependence on liver function of pethidine disposition has been shown by some authors, who found a slower elimination rate of pethidine in patients with liver cirrhosis, and in others with acute viral hepatitis (Klotz et al. 1974, McHorse et al. 1975, Neal et al. 1979).

The pharmacokinetic data for pethidine in the present study are in agreement with those found by Mather et al. (1975) after a single i.v. dose; the values of V_d are similar. The present values for $t_{½\beta}$ and Cl_{pl} in young subjects are similar to those found by Mather et al. in patients with a mean age of 40 years. In a study of pethidine administered as repeated i.v. doses to patients with severe, long-standing pain, Dahlström et al. (1980) found values of Cl_{pl}, $t_{½}$ and V_d similar to those for old patients in our study.

Norpethidine is the only metabolite found in plasma and it is of clinical interest since it is pharmacologically active. It has some analgesic activity, but only a third of that of pethidine in the rat (Dahlström et al. 1979). It has also been found to have a spasmolytic effect in man (Kinn et al. 1982). When present in high concentration, especially in patients with impaired renal function, it can cause seizures (Szeto et al. 1977). In the present study the appearance of norpethidine was slower in the old patients than in the young, suggesting a decreased rate of metabolism of pethidine. The later peak concentrations of norpethidine in old patients could be explained by its slower formation from pethidine, as well as by a slower rate of elimination of norpethidine, or a combination of both. In several old patients norpethidine still remained at a plateau level 30 h after the administration of pethidine. It is possible that this slow elimination is due to impaired renal excretion of the metabolite. In general, plasma concentration-time curves of norpethidine varied considerably between individuals. The factors influencing these curves, such as rate and amount of formation of the metabolite, its volume of distribution and its elimination rate are probably all subject to considerable individual variation. These data could not be calculated for norpethidine, because the amount of metabolite formed was unknown, and the 30-h observation period was too short in some of the old patients. The possibility of altered plasma levels of drug metabolites in old age has been little studied, but old patients have been reported to develop increased levels of 3-hydroxyamylobarbitone (Irvine et al. 1974).

The renal excretion of pethidine and norpethidine are dependent on urine pH. Acidic urine enhances and alkaline urine impairs their excretion (Asatoor et al. 1963). In the present study the variation in urinary pH between individuals did not seem to influence the plasma concentration curves. One young patient (JT) had remarkably acidic urine (pH 5.47), but his elimination rate of pethidine was no more rapid than that of the other young subjects. The old patient with the lowest urinary pH (5.85) was one of the subjects with an extremely slow elimination rate of norpethidine. Renal function, measured as creatinine clearance, was lower in the old patients than in the young, in accordance with the gradual decrease in glomerular filtration rate and tubular function known to occur with increasing age (Davies and Shock 1950). It has not yet been established whether this is the reason for the slower elimination rate of norpethidine in some old patients.

The present study does not provide pharmacokinetic support for a reduction in the dose of pethidine when given as a single intravenous dose to old

patients. The slower elimination rate might result in a longer duration of action, which would be an advantage in the relief of pain. When old patients are given repeated doses, however, the plasma concentration of pethidine might reach a high level due to the lowered plasma clearance. The high level increases the risk of toxic symptoms, such as nausea and respiratory depression. Some old patients may also develop a gradual increase in the plasma level of norpethidine. This might add analgesic and spasmolytic activity, but it could also cause signs of central nervous system excitation. Thus, in the treatment of old patients with repeated doses of pethidine, a reduction in the total daily dose seems advisable.

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