PLASMA CONCENTRATION AND METABOLISM OF PHENOPERIDINE IN MAN

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SUMMARY

The plasma concentrations of phenoperidine were measured in five patients during general anaesthesia. The concentration of the drug decreased rapidly between 2 and 40 min and then declined more slowly. Detectable concentrations of phenoperidine were present in plasma for at least 3 h. In the five patients, the distribution half-life of the drug ranged from 3.19 to 14.23 min and the elimination half-life from 47.31 to 162.30 min. Unchanged phenoperidine and two identified metabolites (pethidine and norpethidine) were present in urine.

Phenoperidine may be used during the maintenance of general anaesthesia and may contribute to post-operative analgesia following surgical procedures. In addition, it is useful in intensive care units in the management of patients requiring prolonged mechanical ventilation. The effects of phenoperidine on respiratory function have been studied previously (Prys-Roberts and Kelman, 1967; Henderson and Parbrook, 1976). Its effects are maximal within 5-15 min, and the duration of action is usually less than 60 min. By contrast, little is known of the plasma concentration, elimination or metabolism of the drug in man. In the present study, we have investigated the clearance of phenoperidine from the circulation after its use as an adjuvant during general anaesthesia, and attempted to isolate the unchanged drug and its principal metabolites from urine.

METHODS

Five patients (three males and two females), who were undergoing e.n.t. or abdominal surgery, were studied. The ages ranged from 22 to 24 yr and the body weights from 65.3 to 80.7 kg. None had clinical or biochemical evidence of anaemia, hepatic or renal disease and none was receiving current systemic drug therapy.

All the patients were premedicated with nitrazepam 10 mg orally (given on the previous night) and diazepam 5-10 mg orally (given on the day of operation). Following the induction of anaesthesia with thiopentone 250-400 mg, either tubocurarine 40-45 mg or pancuronium 7-9 mg was administered. After tracheal intubation, anaesthesia was maintained with nitrous oxide 60-70% and halothane 0.5% in oxygen. Ventilation was controlled. Halothane was discontinued 10-15 min later and droperidol 5-10 mg administered. The duration of surgery was usually 60-90 min and there was little or no fluid loss or replacement. At the end of the operation, residual neuromuscular block was antagonized (neostigmine 5.0 mg and atropine 1.2 mg i.v.). Morphine sulphate 10 mg i.m. was used routinely for analgesia after surgery.

During surgery, an i.v. cannula was placed in a superficial vein and patency maintained by the intermittent infusion of small volumes of saline. Phenoperidine 2.0 mg was injected i.v. into a different vein and blood samples were withdrawn from the cannula after 2, 3, 4, 5, 7, 10, 15, 20, 40, 60, 80, 100, 120, 180 and 240 min, and placed in tubes containing lithium heparin. Collections of urine were made from 0 to 24 h and from 24 to 48 h following injection of the phenoperidine.

Unchanged phenoperidine was extracted from samples of plasma, and the concentration of the drug was determined by gas-liquid chromatography using a nitrogen detector. Phenoperidine and its basic metabolites were extracted from urine in alkaline conditions into a mixture of diethyl ether and dichloromethane (4:1, v/v); the concentrated extracts were resolved by thin layer chromatography on silica gel plates. After resolution, spots with $R_f$ values corresponding to phenoperidine and its
presumptive metabolites were eluted and analysed by gas–liquid chromatography (Chan, Murray and Calvey, 1979).

RESULTS

In the five patients studied, significant concentrations of phenoperidine (usually greater than 1 ng ml\(^{-1}\)) were detected in plasma for 2–3 h after the i.v. administration of the drug (2.0 mg). The plasma concentration of phenoperidine decreased from \(21.2 \pm 6.5\) ng ml\(^{-1}\) to \(4.6 \pm 1.0\) ng ml\(^{-1}\) (mean ± SEM) between 2 and 40 min, and then declined more slowly (fig. 1). During the first 5 min there were large variations in the concentration of phenoperidine in plasma between subjects, although marked inter-individual differences were not observed subsequently (fig. 1).

time was expressed as a bi-exponential equation of the form:

\[ C_P = A e^{-\alpha t} + B e^{-\beta t} \]

where \(C_P\) is the concentration of phenoperidine in plasma at time \(t\), and \(A, B, \alpha\) and \(\beta\) are constants (table I). Values for the distribution and elimination half-lives were calculated from the expressions:

- Distribution half-life: \(0.693/\alpha\)
- Elimination half-life: \(0.693/\beta\)

In the five patients, the distribution half-life of phenoperidine ranged from 3.19 to 14.23 min, and the elimination half-life from 47.31 to 162.30 min (table II).

The decrease in the plasma concentration of unchanged phenoperidine with time was resolved into both two and three exponential components, using a computer program. In three patients, the experimental data were best expressed as a tri-exponential equation (as assessed by the sum of the squared deviations between the experimental and the computer-derived points); in the other two patients, a bi-exponential solution was more appropriate. In all five patients, the differences between the bi-exponential and tri-exponential solutions were not significant statistically. In consequence, the decline in the plasma concentration of phenoperidine with

![Fig. 1. Plasma concentration of phenoperidine after i.v. injection. Each point and vertical bar represents the mean and standard error of five observations.](image)

Thin layer chromatograms of extracts of urine showed the presence of seven spots. Three of these spots have \(R_F\) values corresponding to unchanged phenoperidine, pethidine and norpethidine and gas–liquid chromatographic data indicate that these spots have retention times identical to the authentic compounds. The identity of the remaining spots is unknown.
DISCUSSION

In this study, the decrease in the plasma concentration of phenoperidine after i.v. injection was resolved into two exponential components. The half-life of the initial phase ("distribution half-life") ranged from 3.19 to 14.23 min, and presumably depended mainly on the distribution of phenoperidine in tissues (including the central nervous system). Similar interindividual differences in the initial half-life were observed after the rapid injection i.v. of other drugs, such as edrophonium and neostigmine, and probably reflect uneven drug distribution in plasma (Calvey et al., 1976; Calvey et al., 1979).

In general, the half-life of the initial phase is consistent with the rate of onset of drug action; maximal respiratory depression usually occurs after 5–15 min (Prys-Roberts and Kelman, 1967). By contrast, the half-life of the terminal phase ("elimination half-life") ranged from 47.31 to 162.30 min and there was a 10-fold difference in the plasma concentration of phenoperidine in the five patients studied. This phenomenon cannot be attributed to variations in drug distribution, and presumably reflects significant individual differences in drug metabolism or excretion. Similar differences are known to occur with numerous other drugs.

In the present studies in anaesthetized and artificially ventilated patients, no assessment of the pharmacological effects of phenoperidine could be made. Nevertheless, it is considered generally that the action of the drug lasts for 45–60 min, suggesting that plasma concentrations of 5 ng ml⁻¹ or more are required to produce any action in man.

Although little is known of the metabolism or elimination of phenoperidine, it has been suggested that the drug is metabolized partially to pethidine (Schnieden, 1966). This was confirmed in the present study; both unchanged phenoperidine and pethidine (and norpethidine) were identified in urine by thin layer chromatography and gas–liquid chromatography. The other four spots may represent diazepam, nitrazepam or other weak bases that were present in the urine extract. We hope to establish the nature of these unknown spots.

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REFERENCES


CONCENTRATIONS DE PHENOPERIDINE DANS LE PLASMA ET METABOLISME DE LA PHENOPERIDINE CHEZ L'HOMME

RESUME

On a mesure les concentrations de phénopéridine dans le plasma de cinq malades au cours de leur anesthésie générale. La concentration du médicament a diminué rapidement entre 2 min et 40 min, mais elle a baissé plus lentement par la suite. Des concentrations de phénopéridine ont été décelées dans le plasma pendant au moins 3 h. Sur les cinq malades, la demi-vie de répartition du médicament s’est échelonnée entre 3,19 et 14,23 min, et la demi-vie d’élimination entre 47,31 et 162,30 min. La phénopéridine intacte, ainsi que deux métabolites identifiés (pétidine et norpétidine) étaient présents dans l’urine.

PLASMAKONZENTRATIONEN UND METABOLIE VON PHENOPERIDIN BEIM MENSCHEN

ZUSAMMENFASSUNG


CONCENTRACIONES EN EL PLASMA Y METABOLISMO DE LA FENOPERIDINA EN EL HOMBRE

SUMARIO

Se llevaron a cabo mediciones de las concentraciones de fenoperidina en el plasma de cinco pacientes en el curso de la anestesia general. La concentración de la substancia
bajó rápidamente entre 2 y 40 min y después bajó más lentamente. Se encontraron concentraciones perceptibles de fenoperidina en el plasma durante 3 h por lo menos. En los cinco pacientes, la media vida de repartición de la substancia variaba entre 3,19 y 14,23 min y la media vida de eliminación entre 47,32 y 162,30 min. Se hallaron en la orina fenoperidina no modificada y dos metabolitos identificados (petidina y norpetidina).