COMPARATIVE PLASMA CONCENTRATION PROFILES AFTER I.V., I.M. AND RECTAL ADMINISTRATION OF PETHIDINE IN CHILDREN


The systemic bioavailability of pethidine is approx. 50% after oral administration because of considerable first-pass metabolism in the liver [1]. Several metabolites are formed including norpethidine, which has some analgesic activity [2-4].

Rectal administration of drugs is well established [5-8] and may be advantageous, especially in children, to avoid painful injections [9]. Furthermore, presystemic elimination may be reduced [8].

The aim of the present study in children was to describe the time-concentration profiles of both pethidine and norpethidine following rectal administration of pethidine, compared with those obtained after parenteral application.

PATIENTS AND METHODS

Twenty-five otherwise healthy children (age 7-13 yr, mean 10 yr) undergoing elective surgery (predominantly for undescended testis) were investigated. The study was approved by the local Ethics Committee and informed consent was obtained from both child and parents.

The general design of the investigation was an open, randomized study in three parallel groups. All patients received pethidine 1 mg kg⁻¹ i.v., i.m.

SUMMARY

Plasma concentration–time curves of pethidine and norpethidine were studied in 25 children allocated after operation to three groups to receive pethidine 1 mg kg⁻¹ i.v., i.m. or rectally. Peak concentrations occurred after 5 ± 1, 10 ± 2, and 60 ± 10 min, respectively, while the maximum concentrations amounted to 2800 ± 462, 1609 ± 367 and 531 ± 179 nmol litre⁻¹, respectively. The area under the curve (0-240 min) was similarly reduced in the group with rectal administration (P < 0.05). Compared with the i.v. data, approximately 40% systemic availability occurred after rectal application, although considerable individual variation was noted. In one child very high plasma concentrations were observed after rectal administration, possibly as a result of redistribution/recirculation phenomena. The average results are similar to those obtained when other opioids are given rectally.

or rectally. One hour before anaesthesia diazepam 0.2 mg kg⁻¹ was given orally as premedication. Anaesthesia was induced and maintained with halothane and 50% nitrous oxide in oxygen using a face-mask. The appropriate dose of pethidine (pethidine hydrochloride 10 mg ml⁻¹ in 0.9% sodium chloride, pH 7.5 (DAK, Copenhagen)) was given either parenterally i.v., or i.m. in the thigh. Rectal pethidine was applied with a syringe supplied with a blunt plastic applicator introduced 2-3 cm into the rectum.

The plasma concentrations of pethidine and its main metabolite norpethidine were analysed in blood samples drawn before and at 5, 10, 15, 40, 60, 90, 120, 180 and 240 min after the adminis-
tration of pethidine. Three millilitre of blood was collected into heparinized test tubes from an i.v. cannula (sited in the arm opposite to that used for i.v. injection) and centrifuged. Plasma was removed, frozen immediately and stored at −20 °C until analysed by gas chromatography/mass spectrometry in the positive chemical ionization mode. Plasma to which the internal standard, pentadeuterated pethidine, was added was made alkaline and extracted with tert-butylmethylether. The organic phase was evaporated and redissolved in ethanol. One microlitre was injected into a wide-bore capillary column HP-17 cross-linked 10 m × 0.53 mm × 2.0 μm film thickness. Column temperature was 180 °C and injector heated to 250 °C. Methane 4 ml min−1 was used as carrier and reactant gas. Pethidine, norpethidine and internal standard were monitored at (mass to charge) = 248.2, 234.2 and 253.3, respectively. Coefficient of variation (CV) on duplicates was 3% (mean concentration = pethidine 1039 nmol litre−1) and 18.6% (mean concentration = norpethidine 77 nmol litre−1). The latter CV reflects the fact that it was not possible to synthesize an appropriate internal standard. Limit of detection was 200 fmol for injected amount of pethidine and 1 pmol for injected amount of norpethidine. Further details of the assay will be published elsewhere.

Because of ethical problems and anticipated difficulties in co-operation from the children, the blood sampling period was limited to 240 min. A correct β-phase could, therefore, not be obtained and accordingly an elimination constant (or $T_{1/2}$) could not be calculated. Based on the resulting concentration–time curves of both components in all patients, the following variables were determined: maximum plasma concentration ($C_{\text{max}}$); time to peak concentration ($T_{\text{max}}$); the area under the curve AUC_{240} calculated by the trapezoidal rule method.

Statistical analyses were by Student's $t$ test for paired and unpaired observations after analysis of variance ($F$ test). A 95% level of significance was chosen. All results are given as mean ± one standard deviation (SD).

As pethidine is administered in milligram doses and pethidine and norpethidine are presented in molecular units, the following conversion factors may be used: Pethidine: nmol litre−1 × 0.247 = µg litre−1; µg litre−1 × 4.04 = nmol litre−1. Norpethidine: nmol litre−1 × 0.233 = µg litre−1; µg litre−1 × 4.29 = nmol litre−1.

RESULTS

There were no significant differences in patient characteristics between groups (table I).

While $C_{\text{max}}$ of 2800 ± 462 nmol litre−1 (i.v.) (fig. 1) and 1609 ± 367 nmol litre−1 (i.m.) (fig. 2) occurred after 5 ± 1 min and 10 ± 2 min,

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>I.v. ($n = 10$)</th>
<th>I.m. ($n = 6$)</th>
<th>Rectal ($n = 9$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>9.6 (2.6)</td>
<td>10.2 (2.8)</td>
<td>9.6 (2.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>32.9 (7.6)</td>
<td>30.3 (5.8)</td>
<td>31.8 (8.9)</td>
</tr>
<tr>
<td>Pethidine Dose (mg)</td>
<td>33 (8)</td>
<td>30 (6)</td>
<td>32 (9)</td>
</tr>
<tr>
<td>Applied volume (ml)</td>
<td>3.3 (0.8)</td>
<td>3.0 (0.6)</td>
<td>3.2 (0.9)</td>
</tr>
<tr>
<td>AUC_{240} (nmol litre−1 h)</td>
<td>3769 (96)</td>
<td>3951 (110)</td>
<td>1327 (667)*</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (nmol litre−1)</td>
<td>2800 (462)</td>
<td>1609 (367)</td>
<td>531 (179)*</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>5 (1)</td>
<td>10 (2)</td>
<td>60 (10)*</td>
</tr>
<tr>
<td>Norpethidine $C_{\text{max}}$ (nmol litre−1)</td>
<td>137 (60)</td>
<td>103 (32)</td>
<td>135 (65)</td>
</tr>
<tr>
<td>Norpethidine $T_{\text{max}}$ (min)</td>
<td>90 (17)</td>
<td>120 (23)</td>
<td>180 (25)</td>
</tr>
</tbody>
</table>

**FIG. 1.** Semilogarithmic plot of pethidine (O) and norpethidine (●) concentrations against time in 10 patients receiving pethidine i.v.
respectively, $C_{\text{max}}$ of only $531 \pm 179 \text{nmol litre}^{-1}$ (fig. 3) occurred $60 \pm 10 \text{min}$ after the rectal administration (table I). The mean peak plasma concentration of norpethidine was reached after $90 \pm 17 \text{min (i.v.)} 120 \pm 23 \text{min (i.m.)}$ and $180 \pm 25 \text{min (rectal)}$ (table I). If the mean AUC$_{240}$ value of the i.v. group is used as reference the average systemic bioavailability after rectal application of pethidine was approximately $40\%$ with a range of variability in the nine patients of $32-81\%$.

![Fig. 2. Semilogarithmic plot of pethidine (○) and norpethidine (●) concentrations against time in six patients receiving pethidine i.m.](image)

![Fig. 3. Semilogarithmic plot of pethidine (○) and norpethidine (●) concentrations against time in nine patients receiving pethidine rectally.](image)

![Fig. 4. Pethidine (○) and norpethidine (●) concentration-time profile for one patient with an unusually high plasma concentration after rectal administration of pethidine.](image)

The pethidine plasma concentration–time profile of one child in the rectal group differed in demonstrating three peaks (fig. 4) and concentrations far exceeding the i.v. results. However, after $90 \text{min}$ the values were comparable to those of the rest of the group. At that time the norpethidine concentration was also similar to the average value in the group.

**DISCUSSION**

When given orally, approx. $50\%$ of pethidine becomes systemically available because of presystemic metabolism [1]. While i.v. and, to some extent, i.m. routes provide the most predictable results in this respect, drugs administered via the rectum may also avoid presystemic metabolism [8, 10]. However, the time to reach peak plasma concentrations in the present study reveals that the rate of absorption of pethidine was grossly delayed after rectal application compared with the i.m. or i.v. routes. Furthermore, both the maximum concentrations and the AUC$_{240}$ demonstrate that the amount of pethidine (in the relevant period) available for analgesic action after rectal administration was approx. $40\%$ of the amount available after parenteral administration. Poor absorption from the rectum is clearly the main reason for this discrepancy, although a minor
contribution may be some degree of presystemic metabolism. The faster appearance of norpethidine in the rectal group (figs 1–3) may support this, although no data demonstrate it directly. Difficulties in placing the drug correctly in the short rectum of the child, adsorption by faecal content and loss of the drug via the anus are probably the main reasons for the delayed or incomplete absorption of the drug.

Rectal administration of other opioids has been investigated, for example morphine in adults [11, 12] and children [13], pentazocine [14, 15], ketobemidone [16] and oxymorphone [17]. In all instances, the bioavailability was similar to that of pethidine given rectally in the present study.

Although it was not possible to determine the elimination constant, the average curves of the i.v. and i.m. groups (figs 1, 2) suggest half-lives (3–4 h) similar to those quoted elsewhere [1, 18]. This is not the case for the rectal group, suggesting that the drug was still being absorbed at these times after rectal administration (fig 3).

The very high plasma concentration of pethidine in one child following rectal administration (fig. 4) may have been caused by redistribution of blood from the visceral to the peripheral pool following induction of anaesthesia. However, abnormal vasculature of the rectum or deficiency of pethidine carboxylesterase in the liver cannot be excluded. The double peaks (fig. 4) are seen not uncommonly with opioids and an explanation may also depend on entero-hepatic recirculation.

The results of the present study in children demonstrate slow absorption rate and low bioavailability following rectal administration of pethidine. The latter problem may be overcome by increasing the dose, but the large individual variability of the plasma concentration–time profiles mitigates against this manoeuvre in this group.

The i.m. route of administration is also thought to be associated with erratic absorption, but this was only partly confirmed in the present study.

In conclusion, we recommend that the parenteral route of administration, preferably i.v., should be used for pethidine in the postoperative phase rather than the rectal route.

ACKNOWLEDGEMENTS

We are grateful to Mrs Anne B. Ryager for excellent technical assistance (pethidine assays) and to Lars Dalgaard PH.D. (Royal Danish School of Pharmacy) for synthesizing norpethidine.

REFERENCES