PHARMACOKINETICS AND CLINICAL EXPERIENCE OF 20-H INFUSIONS OF METHOHEXITONE IN INTENSIVE CARE PATIENTS WITH POSTOPERATIVE PYREXIA

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SUMMARY
We have studied the pharmacokinetics of 20-h infusions of methohexitone in young patients with postoperative fever undergoing artificial ventilation of the lungs. The infusion rate was adjusted so that patients were unresponsive to vocal stimulation but reacted to tracheal suction. The mean steady state concentration of methohexitone required was 2.6 mg litre\(^{-1}\) (unbound 0.53 mg litre\(^{-1}\)). The mean (SD) total clearance of methohexitone was 16.3 (4.2) ml min\(^{-1}\) kg\(^{-1}\), which is greater than that for volunteers or normal surgical patients. The unbound clearance correlated positively with body temperature during the infusion (r = 0.796, P = 0.017). The terminal half-life of methohexitone was 6.3 (3.8) h and that of the 4'-hydroxy metabolite 5.8 (2.1) h. There were no marked haemodynamic effects of the infusion, and no excessive sedation after the infusion. However, the clearance of methohexitone was high and variable, possibly as a direct effect of postoperative fever. Consequently, the need for individual titration of the rate of infusion is emphasized.

KEY WORDS
Anaesthetics, intravenous: methohexitone. Pharmacokinetics.

The use of long-term or high-dose infusions of methohexitone for sedation or total i.v. anaesthesia is controversial. Undesirable haemodynamic effects [1, 2], excessive post-infusion sedation [3] and convulsions [2] have been reported following such infusions.

The pharmacokinetics of methohexitone in adults has been investigated after i.v. bolus in surgical patients [4, 5] and volunteers [5] and with short-term infusions in volunteers [6]; fairly consistent results have been obtained. However, studies with hexobarbitone [7] suggest that pharmacokinetic data from volunteers or "normal" surgical patients may not apply to intensive care patients, in whom physiological functions are altered by factors such as trauma, infection, fever and multi-drug treatment. Thus the clearance of methohexitone was found to be substantially greater in patients with hepatitis than in normal subjects [8]. During and after long-term (14 h) infusions in elderly patients recovering from major surgery, the clearance of methohexitone was comparable to that in volunteers recovering from hepatic surgery, while the volume of distribution was increased markedly and the terminal half-life prolonged [3].

The objectives of this investigation were to evaluate the pharmacokinetics and clinical performance of methohexitone in long-term infusions in young intensive care patients with postoperative fever.

PATIENTS AND METHODS
Design of study
The study was approved by the Ethics Committee of the University of Lund. Informed consent was obtained from 10 young patients (six male) aged 20–41 yr with normal heart, lung, kidney and liver function. All patients were undergoing surgery of the jaw and were operated on by the same surgeon. No patient was receiving any medication before surgery. Haemoglobin,
thrombocyte, leucocyte, liver enzyme and serum electrolyte concentrations were measured before and after operation. Patients were premedicated with pethidine 0.8–1.3 mg kg\(^{-1}\), dixyrazine (a major tranquillizer) 0.2–0.5 mg kg\(^{-1}\) and atropine 0.5 mg. General anaesthesia was induced with thiopentone 3–5 mg kg\(^{-1}\) and maintained with enflurane and 70% nitrous oxide in oxygen (\(F_{1_o2}\) 0.3) supplemented with fentanyl 0.01–0.02 mg kg\(^{-1}\). Suxamethonium 1.3–2.8 mg kg\(^{-1}\) was used to facilitate tracheal intubation.

Before recovery, the patients were transferred from the operating theatre to the intensive care unit (ICU), where the lungs were ventilated artificially with air and oxygen (\(F_{1_o2}\) 0.3). Arterial \(P_{a/o2}\) was maintained at 15–18 kPa and \(P_{a/c02}\) at 4.6–5.6 kPa. An infusion of methohexitone for sedation was started just after the patient’s arrival in the ICU. Systemic arterial pressure was measured continuously via a radial artery cannula. Body temperature was measured by a rectal probe and recorded every 1 h. Venous blood samples were taken before and 4, 8, 12, 16 and 20 h after the start of the infusion and 0.5, 1, 2, 4, 8, 12, 16 and (if feasible) 24 h after the infusion was stopped. A solution of methohexitone sodium (Brietal) 2 g in 5% glucose 500 ml was delivered by a volume controlled IVAC infusion pump. The clinical status of the patient was evaluated at least every 1 h by a nurse who was in continuous attendance. The infusion rate was adjusted to provide sedation that allowed the patient to be unresponsive to vocal stimulation but react to tracheal suction, which was performed as needed. All changes in infusion rate were noted. The sedation was supplemented with analgesics (pethidine, phenoperidine or piritramide) when the patient was in pain. The total doses given were: pethidine 0.4–1.8 mg kg\(^{-1}\) (four patients), phenoperidine 0.02–0.22 mg kg\(^{-1}\) (eight patients) and piritramide 0.13–0.28 mg kg\(^{-1}\) (two patients). Paracetamol was used to decrease body temperature if it exceeded 39.5 °C. A neuroleptic drug (dixyrazine 0.7 mg kg\(^{-1}\) or droperidol 0.04–0.07 mg kg\(^{-1}\)) was administered if further sedation was needed and the systolic arterial pressure was 100 mm Hg or less. All patients were given cefuroxime 4.5 g i.v. in divided doses during the infusion.

**Assay of methohexitone**

The blood samples were centrifuged and plasma stored at −20 °C until assay. Methohexitone and its 4'-hydroxy metabolite concentrations were measured by gas–liquid chromatography with nitrogen-selective detection, after slight modifications to the original procedure [9]. Briefly, 0.2–1.0 ml samples of plasma were adjusted to pH 6.5 with Na\(_2\)HPO\(_4\) solution and extracted with cyclohexane:dichloromethane (1:1) 4 ml after addition of hexobarbitone 2 μg as internal standard. After evaporation of the solvents, the extracts were injected onto a gas chromatograph with an OV-17 packed column as described [9]. The coefficient of variation of the assay was around 4% over the range 0.13–2 μg per sample. The metabolite was identified by its chromatographic retention time relative to those of methohexitone and hexobarbitone [9], and by its presence only in plasma and urine samples from patients treated with methohexitone. As we did not have access to pure metabolite, it could not be assayed in absolute concentrations; however, its terminal half-life could be calculated from concentrations expressed in arbitrary units (peak height of metabolite vs that of the internal standard).

The unbound fraction (\(F_u\)) of methohexitone and the metabolite were measured using a Centrifree Micropartition System (Amicon, U.S.A.), as described previously [10].

**Pharmacokinetic calculations**

A model-independent approach was used for calculation of clearance and volume of distribution of methohexitone.

The area under the plasma concentration curve (AUC) and the area under the first moment curve (AUMC) were calculated by the logarithmic trapezoid method [11]. Total body clearance (\(C_{\text{B}}\)) was calculated as dose/AUC. The unbound clearance (\(C_{\text{Bu}}\)) was calculated as \(C_{\text{B}}/F_u\). The volume of distribution at steady state (\(V_{ss}\)) was calculated as:

\[
V_{ss} = \frac{Dose \cdot AUMC}{\left(AUC\right)^2}\frac{t \cdot Dose}{2 \cdot AUC}
\]

where \(t\) is the duration of the infusion (20 h) (cf [11]).

The terminal half-lives of methohexitone and the metabolite were determined by curve-stripping of the post-infusion concentration data followed by weighted non-linear regression. Redistribution half-lives were not characterized. Weighting of the data points was by concen-
Methohexitone Infusions in Intensive Care Patients

Table I. Individual characteristics of the patients, anaesthesia and methohexitone infusions. The total dose is given as the methohexitone free acid. † Mean (SD)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Age (yr)</th>
<th>Cigarette smoker?</th>
<th>General anaesthesia to start methohexitone (min)</th>
<th>End methohexitone to extubation (min)</th>
<th>Methohexitone final infusion rate (mg kg⁻¹ h⁻¹)</th>
<th>Total dose infused (g)</th>
<th>† Body temp. during infusion (°C)</th>
</tr>
</thead>
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<td></td>
<td>39</td>
<td>11</td>
<td>20</td>
<td>0.94</td>
<td>0.74</td>
</tr>
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</table>

The RSTRIP software (Micro Math Inc., U.S.A.) was used, giving half-lives as mean (SD).

Results

Data on individual patients, anaesthesia and infusion rates of methohexitone needed to maintain the pre-determined degree of sedation are shown in Table I, which also shows mean body temperatures during the infusion. The initial step-wise dose titration took between 1 and 8 h (median 4.5 h). It was then possible to maintain a reasonably constant infusion rate in most patients.

The plasma concentration curves of methohexitone are shown in figure 1 and the pharmacokinetic parameters of methohexitone in the 10 patients in Table II. The total plasma concentration needed for adequate sedation varied between 1.5 and 8.6 mg litre⁻¹ (mean (SD) 2.6 (1.1) mg litre⁻¹). The corresponding range for unbound concentration was 0.35-1.89 mg litre⁻¹, (mean 0.53 (0.18) mg litre⁻¹). The mean total plasma concentration at the end of infusion was 4.1 (2.0) mg litre⁻¹ (unbound 0.80 (0.33) mg litre⁻¹).

In patient No. 3, $C_{\text{area}}$, $Cl_{\text{area}}$, total and unbound concentrations needed for sedation, in addition to total and unbound concentrations of methohexitone at the end of infusion, deviated by 2.33-7.43 SD from the mean values cited above and in Table II. $V^u$ deviated by 2.08 SD. These data were therefore not included in the calculations of mean values.

Fig. 1. Plasma concentration curves of methohexitone in individual patients.
Comparison of the half-life of the metabolite with that of methohexitone was complicated by the fact that the decay curves of methohexitone were markedly poly-exponential, while those of the metabolite were mainly mono-exponential. This was especially true for patient No. 8, in whom a late, long half-life could be defined for methohexitone but not for the metabolite. However, the turnover of the metabolite is apparently formation rate limited.

In two patients (Nos 1 and 7) the decline in plasma concentration of methohexitone was not smooth, and no terminal half-life could be defined. In patient No. 4 there was a minor secondary plasma concentration peak.

Figure 2 shows two primary pharmacokinetic parameters in individual patients plotted against the mean body temperature during the infusion. Smokers had a significantly greater unbound clearance of methohexitone than non-smokers (91 (16.5) vs 66 (11.5) ml min\(^{-1}\) kg\(^{-1}\); \(P < 0.05\), two-tailed \(t\) test, patient No. 3 excluded).

Recovery from sedation was smooth in all patients. Artificial ventilation was discontinued 48 (20) min after the infusion (table I), and patients were fully awake (orientated in time and space and able to give name and date of birth) within 1.5 h.

All patients had varying degrees of postoperative pyrexia (table I, fig. 2). Moderate tachycardia and increased pulse pressure caused by the pyrexia complicated assessment of the haemodynamic effects of the methohexitone infusion. As is apparent from table III, the infusion had marginal, if any, effect on mean arterial pressure.

Patients Nos 1–9 showed no evidence of liver impairment during or after the infusion of methohexitone. Circulating aspartate aminotransferase (AST) and bilirubin remained within normal values and showed no tendency to increase. However, in patient No. 10, exposed
previously to halothane anaesthesia in her childhood, some pallor and a 28-mm Hg reduction in mean arterial pressure were observed at the end of the infusion; liver enzymes increased to maximum values of: AST 8580 u litre\(^{-1}\) (normal < 35 u litre\(^{-1}\)); alanine aminotransferase 11420 u litre\(^{-1}\) (normal < 35 u litre\(^{-1}\)); lactate dehydrogenase 7400 u litre\(^{-1}\) (normal < 500 u litre\(^{-1}\)). Serum bilirubin was 130 µmol litre\(^{-1}\) (normal < 20 µmol litre\(^{-1}\)) 4 days after the end of the infusion. All liver function values returned to normal within 3 weeks. Tests for viral hepatitis were negative.

**DISCUSSION**

The total plasma concentration of methohexitone needed to maintain deep sedation (1.5–8.6, mean 2.6 mg litre\(^{-1}\)) is slightly less than the therapeutic window for hypnotic effects (3.4–10.7 mg litre\(^{-1}\)) reported by Lauven, Schwilden and Stoeckel [12]. Sporadic administration of opioid analgesics may have led to a decreased demand for methohexitone in our patients compared with that of unpremedicated volunteers in Lauven’s study. The plasma concentrations in our patients can be compared also with reported target methohexitone concentrations for i.v. anaesthesia, in conjunction with 67 % nitrous oxide in oxygen, of 10 mg litre\(^{-1}\) [13] or 5 mg litre\(^{-1}\) [14].

The mean clearance of methohexitone in our patients (16.3 ml min\(^{-1}\) kg\(^{-1}\)) was greater than in young volunteers (12.1 ml min\(^{-1}\) kg\(^{-1}\)) [6], surgical patients (10.9 ml min\(^{-1}\) kg\(^{-1}\)) [4]; 8.2–9.3 ml min\(^{-1}\) kg\(^{-1}\) [5]) or in elderly postoperative patients (9.3–9.8 ml min\(^{-1}\) kg\(^{-1}\)) [3]. This increase in clearance may be a result of several factors, for example fever, changes in liver blood flow or induction of hepatic mixed function oxidases.

Induction of hepatic enzymes in conjunction with increased liver blood flow in intensive care patients may increase the clearance of methohexitone to 35 (17) ml min\(^{-1}\) kg\(^{-1}\) [8]. Also, the hepatic clearance of hexobarbitone could be enhanced considerably in intensive care patients, in particular in those with infection and fever [7]. Pyrexia may increase the rate of elimination of drugs [7, 15]. However, to our knowledge, conclusive evidence for this has been presented for two drugs only, phenytoin [16] and melphalan [17]. Pyrexia caused by upper respiratory tract infections in children increased the hepatic clearance of phenytoin, while that of phenobarbitone was unchanged. Because of its non-linear elimination kinetics, the clearance of phenytoin is very sensitive to changes in hepatic enzyme activity [16]. Melphalan is eliminated to a large extent by non-enzymic chemical cleavage [17]. Pyrogen-induced fever was shown [18] to increase total liver blood flow markedly in man, both in absolute values and as a percentage of cardiac output. In our patients, the unbound clearance of methohexitone correlated positively with body temperature. The hepatic extraction ratio (E) of methohexitone under “normal” conditions has been estimated to be 0.5 [4] or 0.7 [8]. This implies that clearance of methohexitone is moderately sensitive to changes in hepatic blood flow, and that increased liver blood flow during fever may increase the clearance.

Data from patient No. 3 were excluded from the calculations. The patient was of Philippine origin (the other patients were Caucasians) and had viral hepatitis several years previously. The connection between this and the aberrant pharmacokinetics and -dynamics of methohexitone is not clear. It should be noted, however, that this patient had the highest temperature.

Fever of different aetiology are mediated through a common biochemical pathway, production of interleukin-1, thus causing similar physiological and biochemical changes [19]. Therefore, it is likely that fevers of different origin may have a similar influence on pharmacokinetics.

It is possible that induction of hepatic mixed function oxidases occurred during the 20-h infusions. Enzyme induction by barbiturates is generally thought to take several days, but adequate studies of the time-course and dose-dependency in humans are lacking. There is some evidence that a single large dose of barbiturate can cause substantial auto-induction of metabolizing enzymes [20]. There was no apparent enzyme
induction in the patients treated by Le Normand and colleagues [3]; however, the methohexitone infusion was 6 h shorter than in our study, and in elderly patients the capacity for enzyme induction may be low, as has been shown with antipyrine [21]. In our young patients, enzyme induction might have occurred. It should be noted also that the cigarette smokers showed a significantly greater clearance of methohexitone than the non-smokers, presumably because of prolonged induction of liver enzymes.

There is no obvious reason to suspect that concomitant medication during the study period could have affected the disposition of methohexitone. Cefuroxime, the only other drug given in large doses to all patients, is excreted renally and not metabolized by the liver [22]. The opioid and neuroleptic drugs given during the infusion could not have influenced the disposition of an approximately 100-fold greater molar dose of methohexitone.

No attempt was made to follow the plasma concentration of methohexitone during the initial dose titration phase. The AUC was calculated on the assumption that the plasma concentration increased linearly with time until the first blood sampling at 4 h. With a constant rate infusion, this would be an underestimation of the true AUC. With the gradual escalation of dose in our study, linear approximation becomes fairly plausible. The first trapezoid contributed 7 (3.3) % to the total AUC, and the error involved would be a fraction of this percentage. The portion of the AUC estimated by extrapolation was, in contrast, very small (table II).

The mean $V^{ss}$ and terminal half-life of methohexitone in our patients agree well with values reported previously after prolonged infusions, the greater clearance in our patients giving a shorter half-life. Consequently, there is a clear difference between the results from the two long-term infusion studies and those of the bolus (or short-term infusion) studies. In the latter, the reported mean $V^{ss}$ varied from 1.2 litre kg$^{-1}$ [5] to 2.2 litre kg$^{-1}$ [4], and the mean terminal half-life from 97 min [6] to 3.9 h [4]. After a bolus injection, a major portion of the drug never enters the "deep compartments" of the body, and the late half-life and the volume of distribution of methohexitone at distribution equilibrium can not be characterized adequately. The total pharmacokinetics of the drug, after a bolus injection, are determined to a large extent by slow redistribution [4]. During long-term, high-dose infusions, the "deep compartments" are loaded with drug, and their large volume contributes markedly to the observed $V^{ss}$. This large $V^{ss}$, in turn, prolongs the terminal half-life of the drug.

The mean value for unbound fraction of methohexitone in our patients (21 %) corresponds well with previous data (22 (2) %) [10]. There was no important variation in plasma protein binding between patients. Consequently, the interindividual variations in $V^{ss}$ and clearance could not be explained by variations in plasma protein binding.

As the turnover of the 4'-hydroxy metabolite appears to be formation-rate limited, that is, its elimination half-life equals that of the parent drug, it does not accumulate in the body and probably does not cause late side-effects. Very recently, this metabolite has been shown to have only 10 % the sedative potency of methohexitone in mice [23].

The interindividual variation in clearance and $V^{ss}$ was considerable in our patients. This parallels the large interindividual variation in the disposition of hexobarbitone found in intensive care patients [7], as a result of altered physiology.

Recovery in our patients was rapid and smooth. Post-infusion oversedation reported previously [3] occurred in patients with mean plasma concentrations of methohexitone at the end of infusion of 7.9 or 10.7 mg litre$^{-1}$—approximately twice that of our patients. Postoperative seizures occurred in three of eight neurosurgical patients after a mean plasma concentration of methohexitone, at the end of a 1-h infusion, of 18 mg litre$^{-1}$ [2]. Both these adverse effects were associated with greater plasma concentrations than those attained in our patients.

As far as can be ascertained with postoperative pyrexia as a confounding factor, the infusion of methohexitone during controlled ventilation caused little cardiovascular disturbance. This parallels earlier findings [3]: in surgical patients undergoing controlled ventilation with nitrous oxide in oxygen [1], infusion of methohexitone caused little change in arterial pressure and only a small increase in heart rate. Only during spontaneous ventilation was there marked hypotension [1]. In another study, hypotension was found to occur at a plasma concentration of at least 8 mg litre$^{-1}$ in paralysed patients [2].

Earlier data [1] show that methohexitone is not hepatotoxic. It is not likely that the hepatocellular
damage in patient No. 10 was caused by interaction between enflurane and methohexitone; there was no effect of methohexitone on the kinetics of enflurane in rats when the two drugs were administered almost simultaneously [24]. In addition, enflurane does not cause induction of liver enzymes, at least not those of the mixed function oxidase subtype responsible for the metabolism of antipyrine [25].

In conclusion, methohexitone infusion for sedation of patients undergoing artificial ventilation of the lungs was tolerated well. With individual titration of the dose rate to a predetermined level of sedation, haemodynamic depression and post-infusion oversedation did not occur. The pharmacokinetics of methohexitone were very variable and pyrexia was found to have a marked effect on metabolic clearance.

REFERENCES


