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Endotoxin-induced Fever Increases the Clearance of Methohexitone in Rabbits

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Abstract—We have previously observed that the clearance of methohexitone, given by continuous infusion for sedation in the intensive care unit, was influenced by body temperature in patients with post-operative fever. The aim of the present study was to reproduce this finding in an animal model that can then be used to predict similar influences for other anaesthetic agents. Sixteen rabbits were infused for 2·0 h with methohexitone (8·4 ± 0·5 mg kg^{-1} h^{-1} (mean ± s.d.)) and in eight of them fever was induced with intravenous *Escherichia coli* endotoxin. Arterial blood samples were taken over 6 h and plasma concentrations of methohexitone were assayed by gas chromatography. The mean body temperatures of the rabbits over the periods of measurement varied between 38·5 and 41·8°C, and the total clearance of methohexitone (mean 50·7 mL min^{-1} kg^{-1}) was positively correlated with temperature ($r = 0·545$, $P = 0·029$). No significant correlations with temperature were found for other pharmacokinetic parameters. We conclude that these observations correspond to the findings in the clinical pharmacokinetic study, showing the validity of the animal model.

Methohexitone (Brietal) is an ultra-short-acting barbiturate commonly used for induction or maintenance of anaesthesia and for sedation by intravenous (i.v.) infusion in the intensive care unit. We have previously observed (Redke et al 1991) that the clearance of methohexitone was unexpectedly high and variable in artificially ventilated patients with post-operative fever. In keeping with this, lengthy individual titration of the infusion rate was necessary to achieve the desired degree of sedation. The inter-individual variance in clearance could, in part, be assigned to the post-operative fever, since there was a significant positive correlation of unbound clearance with temperature. Interpretation of pharmacokinetic data obtained in intensive care patients is complicated by factors such as smoking habits, artificial ventilation, concomitant pharmacotherapy and disease. Prospective studies on the influence of fever on pharmacokinetics and pharmacodynamics of anaesthetic agents should ideally be performed under more controlled conditions.

The aim of the present study was therefore to reproduce, if possible, the correlation of methohexitone clearance with temperature in an animal model that can later be used for preclinical studies on other drugs. To simulate post-operative fever in man, a pyrogen response was elicited in rabbits by intravenous injection of *Escherichia coli* endotoxin (Ladefoged 1977, 1978; Thiessen & Poon 1979; Halkin et al 1981; Thiessen et al 1985; Prince et al 1989), and the pharmacokinetics of infused methohexitone was determined.

Materials and Methods

Animals

The study protocol was approved by the Ethics Committee on Animal Studies, University of Lund, Sweden. Sixteen New Zealand White rabbits of both sexes were used. They weighed 2·5 ± 0·24 kg (mean ± s.d.).

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Surgical preparation

The rabbits were anaesthetized using fluanisone, a butyrophenone neuroleptic, (3 mg) with fentanyl (0·1 mg, Hypnorm Vet), and diazepam (2·5 mg). Catheters were inserted into the abdominal aorta and into the inferior vena cava and tunnelled subcutaneously to the neck. The rabbits were allowed to recover until the next day, when their condition and behaviour appeared to be normal.

Drug infusion and blood sampling

Methohexitone sodium solution was freshly prepared by reconstitution of a Brietal (Eli Lilly Sweden AB, Stockholm) vial. The stock solution was diluted with 0·9% NaCl so that the infusion would deliver 18 mg kg^{-1} methohexitone sodium in 19 mL over 120 min. A syringe infusion pump was used, and the syringe was weighed before and after the infusion to determine the volume given. A sample of the solution was frozen for assay.

The rabbit was kept, unrestrained, in a large plastic tray on the bench. A thermistor probe (Ellab Instruments, Copenhagen) was inserted into the rectum, the venous catheter was connected to the syringe pump and the infusion was started. Blood samples were drawn from the arterial catheter before the infusion, at 15, 30, 60, 90 and 120 min during it, and at 5, 10, 15, 25, 40, 60, 90, 120, 180 and 240 min after the end of the infusion. One millilitre of blood was withdrawn into a heparinized syringe, the sample to be analysed was then collected by spontaneous outflow from the catheter and the drawn blood was re-injected followed by 1·5 mL heparin/saline. The sample was centrifuged and the plasma frozen at −20°C until assay. At each sampling time, and additionally at 150 and

210 min post-infusion, the rectal temperature was noted. The haematocrit was checked before and after the experiment.

Of the sixteen rabbits, eight were treated with *E. coli* endotoxin (Whittaker Bioproducts, Walkerville, MD, USA) (36 $\mu g\,kg^{-1}$, i.v.) half an hour before the infusion of methohexitone. This dose, and the time lag for development of fever, was established by titration in rabbits not used in the pharmacokinetic study.

Drug assay

Plasma concentrations of methohexitone were measured by gas-liquid chromatography with nitrogen-selective detection (Heusler et al 1981; Redke et al 1991) using hexobarbitone as internal standard. The within-day coefficient of variation (C.V.) of eight determinations was 1·7% at 12·5 ng/sample and 2·6% at 200 ng/sample. The between-day C.V. was 4·6% at 71 ng/sample (n = 13).

The blood/plasma concentration ratio of methohexitone in normal rabbits was determined on blood samples of which a part was centrifuged to yield plasma. The ratio is consequently defined as total blood concentration divided by corresponding plasma concentration.

The concentrations of methohexitone free acid in the infusion solutions were determined by high-performance liquid chromatography (Björkman & Idvall 1984), by direct injection of the 1:100 diluted solutions and quantitation relative to the standard solutions used in the plasma assay.

Pharmacokinetic analysis

Conventional pharmacokinetic parameters were calculated by nonlinear curve-fitting combined with model-independent methods (Gibaldi & Perrier 1982).

Fitting polyexponential functions to the post-infusion time/concentration data was performed with RSTRIP software (Micro Math, Salt Lake City, Utah, USA). Weighting of the data by 1/(concentration)^2 was used. Bi- and triexponential functions were fitted to the data points, and the best fit was chosen by means of the F-test (Boxenbaum et al 1974) and analysis of the residuals. From the fitted functions, the apparent terminal $t_{\frac{1}{2}}$ was calculated. The area under the curve (AUC) and the area under the first moment curve (AUMC) were calculated by a model-independent procedure using the logarithmic trapezoidal method (MKMODEL software, N. Holford, Auckland, New Zealand). The extrapolated areas after the last datapoint were calculated as:

$$AUC_e = \frac{C_{last}}{k_n} \quad (1)$$

$$AUMC_e = \frac{C_{last}}{k_n}\left(t_{last} + \frac{1}{k_n}\right) \quad (2)$$

where C_{last} is the last measured concentration value, k_n the elimination hybrid rate constant obtained by the polyexponential curve fitting and t_{last} is the sampling time of C_{last}.

The infused dose was calculated from the weight of the infused solution and the measured concentration of methohexitone acid.

The clearance (CL), mean residence time (MRT) and volume of distribution at steady state (Vd_{ss}) were calculated as:

$$CL = \frac{dose}{AUC} \quad (3)$$

$$MRT = \frac{AUMC}{AUC} - \frac{(infusion\ time)}{2} \quad (4)$$

$$Vd_{ss} = MRT \cdot CL \quad (5)$$

The weighted mean temperatures of the rabbits were calculated as the AUC of the time/temperature curves divided by the total time of the experiment (up to the last sampling time at which methohexitone was measurable in the plasma).

Statistics

The putative dependence of a pharmacokinetic parameter on weighted mean body temperature was investigated using linear regression. Comparisons of data from the control and endotoxin-treated groups were performed with an unpaired Student's *t*-test. Results are given as mean ± standard deviation (s.d.) in the text and Table 1, and as mean ± standard error of the mean (s.e.m.) in Figs 1, 2.

Results

The temperature curves of the rabbits are given in Fig. 1. The animals were only lightly sedated by the infused methohexitone, and the effect wore off within 10–15 min after cessation. The haematocrit fell on average from 38 to 33% during the experiment. Fig. 2 illustrates the general shape of the plasma concentration curves. Generally, methohexitone could not be measured in the last (+240 min) sample. Of the total AUC, > 99% always fell under the actually measured curve, only 0·20 ± 0·20% being extrapolated area. For the AUMC, the extrapolated parts were 1·5 ± 2·0%.

Table 1 gives the pharmacokinetic parameters of methohexitone in the sixteen animals. Comparisons based on the two groups of animals, normal vs endotoxin pre-treated, yielded no significant difference in any pharmacokinetic parameter. However, a correlation between clearance and

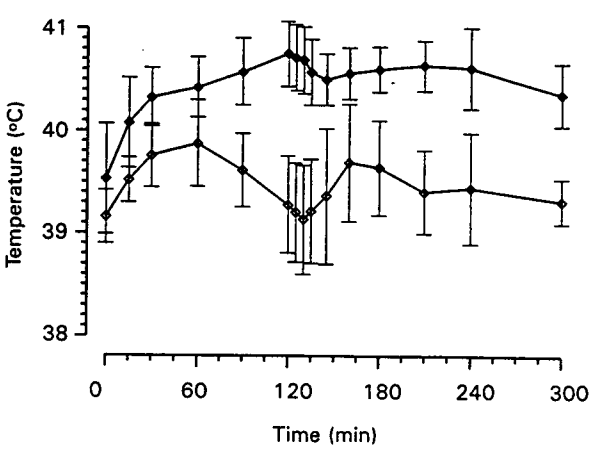

FIG. 1. The mean ± s.e.m. rectal temperatures of the rabbits during the experiment. ◇ Control rabbits (n = 8), ◆ rabbits (n = 8) in which fever had been induced by *E. coli* endotoxin 36 $\mu g\,kg^{-1}$ 30 min earlier.

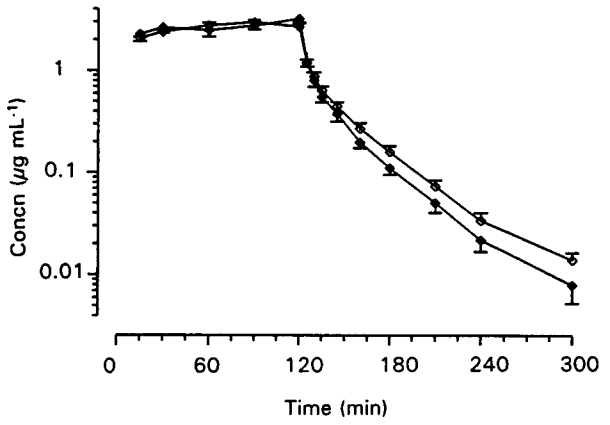

FIG. 2. Plasma concentration curves (mean ± s.e.m.) of methohexitone in control rabbits (◇) and rabbits pre-treated with *E. coli* endotoxin (◆).

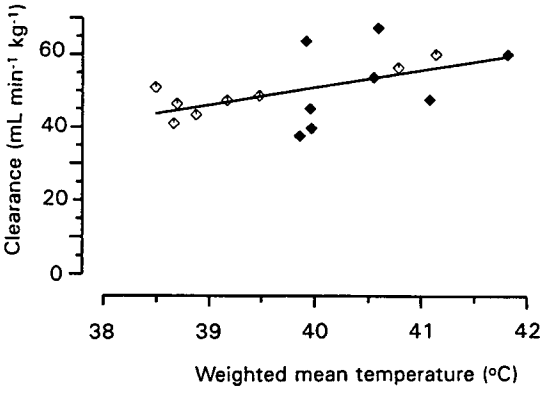

FIG. 3. The correlation of clearance of methohexitone with body temperature, $P = 0{\cdot}029$. Since $r = 0{\cdot}545$, 55% of the inter-individual variance in clearance can be statistically assigned to differences in body temperature. ◇ Control rabbits, ◆ rabbits treated with *E. coli* endotoxin.

temperature was found (Fig. 3). There was no significant correlation between any other pharmacokinetic parameter and temperature. The blood/plasma partition ratio of methohexitone (in normal rabbits) was $0{\cdot}68 \pm 0{\cdot}03$ (n = 9), indicating very little uptake of methohexitone into blood cells.

Discussion

The disposition of drugs in intensive care patients may differ markedly from that in a more normal trial population of healthy volunteers or of patients undergoing elective interventions (Rietbrock et al 1981; Bodenham et al 1988). The influence of fever, either post-operative or due to infectious disease, on the pharmacokinetics of drugs in general and of anaesthetics in particular is largely unexplored. Available data have been summarized in reviews (Farrell 1987; Mackowiak 1989).

Generally, viral infection, influenza immunization or similar types of febrile states induced by endogenous or exogenous pyrogens decrease the metabolic clearance of drugs, which is probably due to suppression of hepatic cytochrome P450-dependent oxidative drug metabolism (Farrell 1987). Decreased clearance of theophylline in children during influenza B infection led to symptoms of toxicity such as headache, nausea and seizures (Kraemer et al 1982). In acutely ill patients with fever due to falciparium malaria, impaired metabolism of quinine may result in toxic plasma levels (Trenholme et al 1976). An exception from the general finding of impaired clearance is that plasma concentrations of phenytoin during chronic treatment decreased after influenza vaccination in adults (Sawchuk et al 1979) and during febrile illness in children (Leppik et al 1986), indicating an increased metabolic clearance. In four of the seven children, this led to loss of seizure control. This parallels our own observation of an increased clearance of

Table 1. The pharmacokinetics of methohexitone in normal and endotoxin pre-treated (e in table) rabbits.

Rabbit no.	Weight (kg)	Dose (mg)	Mean temperature (°C)	CL		MRT (min)	Vd_{ss}		$t_{\frac{1}{2}}$ (min)
				(mL min^{-1})	(mL min^{-1} kg^{-1})		(L)	(L kg^{-1})	
1	2·5	42·4	38·66	103	41·1	20·0	2·05	0·82	35·8
2	2·7	48·3	38·69	126	46·5	21·9	2·75	1·02	27·5
7	2·6	44·1	39·17	123	47·5	17·8	2·19	0·84	44·7
8	2·3	37·5	38·87	100	43·5	15·4	1·54	0·67	41·9
10	2·4	39·3	39·48	117	48·8	13·7	1·60	0·67	23·2
14	1·9	30·5	41·14	114	60·3	15·9	1·83	0·96	45·1
15	2·5	43·2	40·78	142	56·6	21·3	3·01	1·20	63·8
16	2·7	42·1	38·49	138	51·0	22·2	3·06	1·13	(150)[a]
Mean	2·5	40·9	39·41	120	49·4	18·5	2·25	0·92	40·3
s.d.	0·3	5·3	1·01	14·9	6·43	3·29	0·61	0·20	13·4
3e	2·6	41·9	40·59	175	67·5	17·1	3·00	1·15	27·5
4e	2·5	44·8	41·08	120	47·8	23·6	2·82	1·13	54·9
5e	2·7	49·1	41·82	163	60·4	20·4	3·32	1·23	27·5
6e	2·8	46·8	40·55	151	53·9	15·8	2·38	0·85	19·1
9e	2·8	41·8	39·92	179	63·8	15·2	2·72	0·97	27·6
11e	2·5	43·8	39·86	94	37·7	15·2	1·44	0·57	28·0
12e	2·4	36·3	39·97	96	39·8	8·4	0·81	0·34	21·4
13e	2·1	35·9	39·96	95	45·2	16·3	1·55	0·74	52·3
Mean	2·6	42·6	40·47*	134	52·0	16·5	2·26	0·87	32·3
s.d.	0·2	4·6	0·70	37·1	11·1	4·38	0·89	0·31	11·7

[a]Inaccurate due to missing datapoints. Not included in mean. *$P < 0{\cdot}05$ vs normal.

methohexitone in patients with post-operative fever (Redke et al 1991). Phenytoin and methohexitone are both lipophilic weak acids, in which the heterocyclic rings, hydantoin in phenytoin and barbiturate in methohexitone, show considerable structural similarity.

We chose to investigate endotoxin-induced fever in rabbits (Ladefoged 1977, 1978; Thiessen & Poon 1979; Halkin et al 1981; Thiessen et al 1985; Prince et al 1989) as a putative model for post-operative fever in man. The dose of endotoxin, usually *E. coli* lipopolysaccharide, used to produce fever varies considerably between studies. Peak temperature rises of approximately 2°C have been obtained using 0·1 (Ladefoged 1977), 1–2 (Thiessen et al 1985), 10 (Thiessen & Poon 1979) or 35 (Halkin et al 1981) $\mu g\,kg^{-1}$ or 20–40 μg per rabbit (Prince et al 1989) of *E. coli* endotoxin. In a dose-effect study on this endotoxin (Wolff et al 1965), a plateau in the fever response was reached with doses exceeding 100 μg per rabbit (approx. 50 $\mu g\,kg^{-1}$). Different makes and batches of *E.coli* endotoxin show considerable differences in biological activity, and any study must entail a preliminary dose titration of this agent. The dose ($36\,\mu g\,kg^{-1}$) used in the present study was found to produce sustained fever without marked behavioural changes, hypothermia or other symptoms of endotoxin shock.

As in our clinical study (Redke et al 1991), we used an infusion rather than a bolus injection of methohexitone. In this way a major part of the AUC is determined by concentration data obtained during the infusion, and the extrapolated AUC (and AUMC) is small in comparison; thus accurate estimates of the pharmacokinetic parameters are obtained. In addition, loading of the deep tissue compartments with drug during the infusion gives better conditions for determination of the terminal half-life and the Vd_{ss}. Since the disposition of a drug is considerably faster in a small animal than in man (Mordenti 1986), it was feasible to scale down the 20-h infusions used in the clinical study to more convenient 2-h infusions in the rabbits.

The crucial issue is whether the animal model gives data that are consistent with findings in man. *E. coli* endotoxin-induced fever was found to reduce the clearance of antipyrine in rabbits by 30% (Thiessen & Poon 1979), which confirms the modest reductions during fever found in man (Elin et al 1975; Forsyth et al 1982; Sonne et al 1985; Williams & Farrell 1986). Also in rabbits, pretreatment with *E. coli* endotoxin increased the volume of distribution of trimethoprim while the elimination rate constant was not changed (Ladefoged 1977), and likewise the volume of distribution of gentamicin was doubled, with unchanged total plasma clearance (Halkin et al 1981). Similar effects may apply in man (Mackowiak 1989). Another study in rabbits (Prince et al 1989) failed to find any significant influence of fever on the disposition of theophylline. However, the effect of endotoxin on hepatic metabolism may not have had time to develop during the study period (see below).

In the present study, the effect of endotoxin-induced fever on the pharmacokinetics of methohexitone was quite modest and could not be demonstrated by comparison of data from the normal and treated groups of rabbits. When, however, as in the clinical study (Redke et al 1991), the data were evaluated by linear regression, a significant correlation of clearance with temperature was found.

Methohexitone is eliminated almost exclusively by hepatic metabolism (Murphy 1974). A change in hepatic clearance may, for a drug with a high hepatic extraction ratio (E), be due to a change in hepatic blood flow or, for a drug with a low E, to a change in the metabolic capacity of the liver. The E of methohexitone in man has been estimated at 0·5 (Hudson et al 1983) or 0·87 (Lange et al 1992). Dividing the mean CL value of $49{\cdot}4\,mL\,min^{-1}\,kg^{-1}$ in our control rabbits by an estimated total hepatic plasma flow of $76\,mL\,min^{-1}\,kg^{-1}$ (Mordenti 1986), gives E = 0·65 (the direct comparison of plasma clearance and hepatic plasma flow is correct since the blood/plasma partition coefficient of 0·68 implies that very little methohexitone is distributed to the blood cells). If the plasma flow is calculated from data (haematocrit, cardiac output and total liver blood flow as % of cardiac output) given by another source (Wyler et al 1970), it may be estimated as $44\,mL\,min^{-1}\,kg^{-1}$, in which case the calculated E will be greater than one. Although the estimates of E are uncertain, it is obvious that methohexitone has a high hepatic extraction and that the clearance will be sensitive to changes in hepatic blood flow.

In rabbits, a bolus dose of $4\,\mu g\,kg^{-1}$ of *E. coli* endotoxin did not significantly affect total liver blood flow (Riedel & Hales 1983), while a $5\,mg\,kg^{-1}$ dose, eliciting endotoxin shock and death within 7 h, caused a progressive decrease (Wyler et al 1970). This severe impairment of total liver blood flow is also reflected as a gross perturbation in the pharmacokinetics of warfarin in rabbits (Ladefoged 1978). Although fever has been shown to raise total liver blood flow in man (Bradley 1949; Hamrick et al 1955) and sheep (Kisauzi & Leek 1991), this has not been proved in rabbits. However, the increased clearance of methohexitone indirectly suggests such an effect.

The impairment of cytochrome P450-dependent drug metabolism by endotoxin is well established (Farrell 1987). It should be noted, however, that a significant impairment occurs with a time-lag of at least 6 h after the injection, as shown in the rat (Sonawane et al 1982; Morgan 1989). This effect should, therefore, not be important in our study. This observation could also explain why the clearance of theophylline in rabbits was not significantly affected by immediate pretreatment with endotoxin (Prince et al 1989) (the found clearance of approx. $1\,mL\,min^{-1}\,kg^{-1}$ implies $E < 0{\cdot}02$, which makes the clearance independent of liver blood flow). In the only pharmacokinetic study using chronic treatment of rabbits with endotoxin (Thiessen et al 1985), no change in the mean clearance of valproic acid was found. However, in animals that developed tolerance to the febrile response, an increased clearance was found, whereas nontolerant animals showed decreased clearance of valproic acid. This difference may be due to increased cytochrome P450 activity in tolerant and decreased activity in nontolerant animals. These findings emphasize the need to distinguish between acute and late effects of endotoxin.

In conclusion, the present results show that the influence of fever on the metabolic clearance of methohexitone found in our clinical study can be reproduced in an animal model. The pharmacokinetic characteristics of methohexitone suggest that the effect of fever is due to a change in hepatic blood flow. The model should be useful for predictive studies on other anaesthetic agents.

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