TITLE: COMPARATIVE PHARMACOKINETICS OF METHOHEXITAL AND THIOPENTAL

AUTHORS: Robert J. Hudson, M.D., Donald R. Stanski, M.D. and Patrick A. Burch, M.D.

AFFILIATION: Departments of Anesthesia and Medicine (Clinical Pharmacology) Stanford University Medical Center, Stanford, California 94305 and Palo Alto Veteran's Administration Medical Center, Palo Alto, California 94304

Introduction. Methohexital (MHEX) was introduced into clinical anesthesia in 1957. However, there is still no data regarding its disposition in surgical patients. In normal volunteers, Breimer[1] found the clearance of MHEX to be 12.1±2.3(SD) ml/kg/min with a Vdss of 1.13±0.19 L/kg and an elimination half-life ($T_{1/2}\beta$) of 97±22 min. We studied the pharmacokinetics of MHEX in patients free of systemic disease undergoing minor surgery. We also determined the contribution of drug metabolism to the termination of MHEX anesthesia. The results were compared to those obtained from our previous study of patients given thiopental (TP).[2]

Methods. After institutional approval, informed consent was obtained from 9 patients. Anesthesia was induced with a bolus of MHEX and maintained with N2O(50-70%) and enflurane(1-2%) or halothane(0.5-1.5%) Frequent arterial samples were drawn to accurately characterize the distribution phases. Sampling was continued for 12 hours. Serum MHEX was measured with high performance liquid chromatography. Serum concentration(Cp) vs. time(t) data was fit to a bi- or tri-exponential function by nonlinear regression. For each patient, the F ratio test was used to determine the correct model. Pharmacokinetic parameters were calculated using standard formulae. The cumulative loss of drug from the central compartment due to metabolism was calculated using the formula: metabolic loss = clearance x $\int_0^t Cp(t)\,dt$. The total loss of drug (metabolism + redistribution) was calculated using: total loss = $V1 \bullet [Cp(o)-Cp(t)]$ where V1=volume of the central compartment and Cp(o)=initial Cp. The ratio of metabolic to total loss was then determined. The t-test was used to compare results obtained from the two groups.

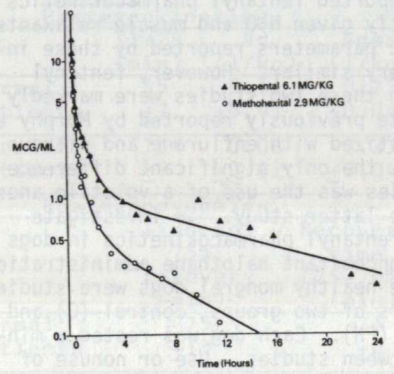
Results. The pharmacokinetic parameters are shown in the table. Fig. 1 shows a representative Cp vs. t curve from each group. Fig. 2 shows the time required for complete metabolic loss (complete elimination) of both drugs. The fraction of MHEX metabolized was greater ($p < 0.05$) than TP from one minute to more than two days.

PHARMACOKINETIC DATA (MEAN ± SD)

	Methohexital	Thiopental
N	9	9
Age (yrs)	30.1 ± 5.4	30.0 ± 4.4
Weight (kg)	76.6 ± 10.6	68.9 ± 11.3
Dose (mg/kg)	2.4 ± 0.4+	6.7 ± 0.7
Distribution $T_{1/2}$ (min)		
Rapid	4.8 ± 1.1	8.5 ± 6.1
Slow	50.0 ± 24.9	62.7 ± 30.4
Elimination $T_{1/2}$ (min)	240 ± 150*	697 ± 362
Clearance (ml/kg/min)	9.9 ± 2.9	3.4 ± 0.5
Vdss (l/kg)	2.1 ± 0.7	2.5 ± 1.0

*$p < 0.005$ +$p < 0.001$

Discussion. This data demonstrates that the elimination half-time ($T_{1/2}\beta$) of MHEX is much shorter than the $T_{1/2}\beta$ for TP (4 vs. 12 hrs.). This is due solely to a three-fold difference in clearance. The $T_{1/2}\beta$ for MHEX in patients is $2\frac{1}{2}$ times greater than the volunteers studied by Breimer.[1] This is probably due to decreased hepatic blood flow caused by anesthesia and surgery. During the time required for recovery from anesthesia, the fraction of drug metabolized is greater for MHEX than TP. After thirty minutes, the ratio of metabolic loss to total loss is 0.36 ± 0.06(SD) for MHEX and 0.22 ± 0.05 for TP ($P < 0.001$). Although MHEX is more rapidly metabolized, redistribution is still the major factor causing termination of anesthesia after one dose of either drug. With large or repeated doses, redistribution is exhausted as tissues become saturated. Under these circumstances, recovery from MHEX would be more rapid than recovery from TP because of the shorter $T_{1/2}\beta$ of MHEX. Based on its pharmacokinetic properties, MHEX may be a better drug whenever rapid recovery from anesthesia is desired, particularly after large or repeated doses.



Figure

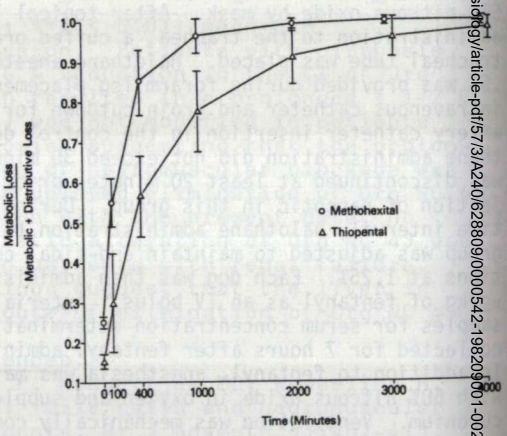


Figure 2

References.

1. Breimer DD: Br J Anaesth 48:643, 1976.
2. Burch PB and Stanski DR: Anesthesiology 55:A175, 1981.