Title : ZERO ORDER PHARMACOKINETICS OF HIGH DOSE THIOPENTAL

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Introduction. In low doses, (5 mg/kg) thiopental (TP) exhibits first order kinetics whereby the rate of elimination (and half-life) is constant at all plasma concentrations (Cp). While evaluating the pharmacokinetics of large doses (300-600 mg/kg) of TP used in the resuscitation of patients with major cerebral ischemic injury, we found that TP exhibits zero order kinetics (dose-dependent or Michaelis-Menton) such that the rate of elimination decreases as the Cp increases.

Methods. Five patients with neurological evidence of severe cerebral ischemia, secondary to cardiac arrest or head trauma were studied. Concurrent intensive care therapy included paralysis, hyperventilation, osmotic agents, steroids and normothermia. TP was administerd as a continuous infusion, the rate of infusion was adjusted to flatten the electroencephalogram as rapidly as possible and maintain it as such for the duration of infusion (Table 1). After termination of the infusion, 20-30 blood samples were drawn at 3-6 hr intervals. TP and pentobarbital plasma concentration were measured with a gas chromatography assay, sensitive to 1 µg/ml.

Data Analysis. Steady state conditions were assumed to be present at the end of the infusion. The TP concentration data was fit to the following zero order, one compartment Michaelis-Menton pharmacokinetic model using nonlinear least squares regression (NONLIN).

$$-dCp/dt = Vm \times Cp/(Km + Cp)$$

where -dCp/dt is the rate of decline of the Cp at time t, Vm is the theoretical maximum rate of drug elimination and Km is a constant equal to the Cp at which the rate of elimination is one-half the theoretical maximum. The data was also fit to a first order one compartment pharmacokinetic model, and the quality of fit statistically compared to the zero order model.

Table 1

| PT. | AGE (yrs) | WT. (kg) | INFUSION DOSE (mg/kg) | DURATION (hrs) | Vm (µg/kg/hr) | Km (µg/ml) |
|---|---|---|---|---|---|---|
| 1 | 21 | 70 | 365 | 89 | .74 | 8.1 |
| 2 | 35 | 80 | 502 | 42 | .71 | 9.7 |
| 3 | 39 | 53 | 477 | 44 | 1.9 | 43.7 |
| 4 | 49 | 82 | 411 | 55 | 1.2 | 52.4 |
| 5 | 58 | 58 | 602 | 71 | 1.6 | 57.6 |

Results. The zero order elimination characteristics of TP can be seen in the data from Pt 2 (Fig 1). The TP concentration does not decline at a constant rate or half-life as would be expected with first order kinetics, rather the rate of decline changes with the Cp. The solid line represents the fitted function from the zero order model. Vm and Km estimates for the 5 patients are in Table 1. All patients had a statistically significant better fit to the zero order model than the first order model. At the end of the TP infusion pentobarbital levels were approximately 10% of the TP concentrations.

Discussion. The change in pharmacokinetics behavior of TP from first order with low doses to zero order with the high doses used in this study may be due to saturation of the hepatic enzymes that metabolize TP. There are important therapeutic consequences of TP exhibiting zero order kinetics when used in high doses for cerebral ischemic resuscitation. As the dose of TP increases, the terminal elimination half life also increases. Thus, after terminating TP administration a longer time is required for the TP concentration to decrease to a low enough level to allow assessment of the level of consciousness. As the duration of infusion and TP concentration increase, the saturation of the hepatic metabolic clearance requires a marked decrease of the infusion rate to prevent excessively high TP concentrations from occurring.

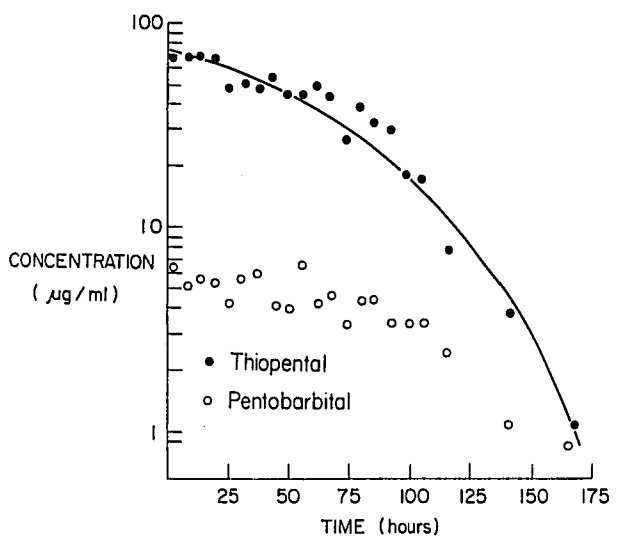


Figure 1.