On recovery from anesthesia, the patient was confused and combative. He was quickly transferred to the recovery room, where six persons were needed to restrain him. Efforts to calm the patient by talking and by reassurance were totally ineffective. Physostigmine, 2.0 mg, iv, had no effect. Naloxone, 0.1 mg, iv, was given 5 min later, and within 30 sec he became markedly less restless. Several minutes later, although he still appeared confused, he was calm, conversant, and did not need restraint. Serum electrolytes and blood glucose values were normal.

The next day, the patient revealed that he had become combative and uncontrollable a year previously when undergoing a similar procedure on the same finger with local anesthesia. Review of that anesthetic record (from another hospital) indicated that his combativeness had seemed to follow the intravenous administration of Innovar® at the start of the surgical procedure.

Discussion

Delirium following anesthesia, frequently a result of pre- or intraoperative cholinergic drug administration, can be treated with physostigmine. We gave physostigmine, 2.0 mg, iv, because of the possibility that physostigmine will reverse the sedative effect of diazepam.[2] When physostigmine had no effect, we administered naloxone, on the chance that the delirium had been induced by fentanyl and could be reversed by a narcotic antagonist. The transition from uncontrollable excitation to calm was almost immediate.

The mechanism responsible for hyperexcitability after morphine administration is uncertain. Berryhill *et al.*[1] outlined the evidence from studies in animals and man to suggest three different possible mechanisms for morphine-induced hyperexcitability: 1) the response may be mediated via central dopaminergic pathways and would be blocked by a dopaminergic inhibitor such as a butyrophenone or a central nervous system catecholamine depletor such as reserpine; 2) endogenous opiate receptors may be involved, and naloxone would be expected to block the response; 3) morphine may have an effect on receptors not responsive to beta-endorphin and not blocked by specific opiate antagonists such as naloxone.

The second mechanism may have been important in the case of our patient, because his delirium was immediately reversed by naloxone. Although stimulation of dopaminergic pathways could have occurred, and would have been reversed by a specific dopaminergic antagonist, the history of a similar episode of delirium after receiving Innovar® suggests that droperidol had not been effective in blocking the response previously.

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Pharmacokinetics of High-dose Thiopental Used in Cerebral Resuscitation

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Administration of large doses of barbiturates has been utilized for various brain injuries: anoxic encephalopathy,[1] Reye's syndrome,[2] and head trauma.[3] During initial clinical trials of large doses of thiopental, we found an alteration in the kinetics of elimination. Thiopental elimination changed from first-order (rate of elimination and elimination half-life are constant regardless of plasma concentration) to nonlinear or Michaelis-Menten elimination (rate of elimination varies with the plasma concentration). This resulted in a decrease of the rate of elimination and an increase in the apparent elimination half-life as the plasma concentration increased.

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Method

Five patients who sustained neurologic evidence of severe cerebral ischemia secondary to cardiac arrest or closed head injury were studied. The protocol has received approval of the Stanford Committee on Human Research, and informed consent was obtained from an available relative. Concurrent intensive

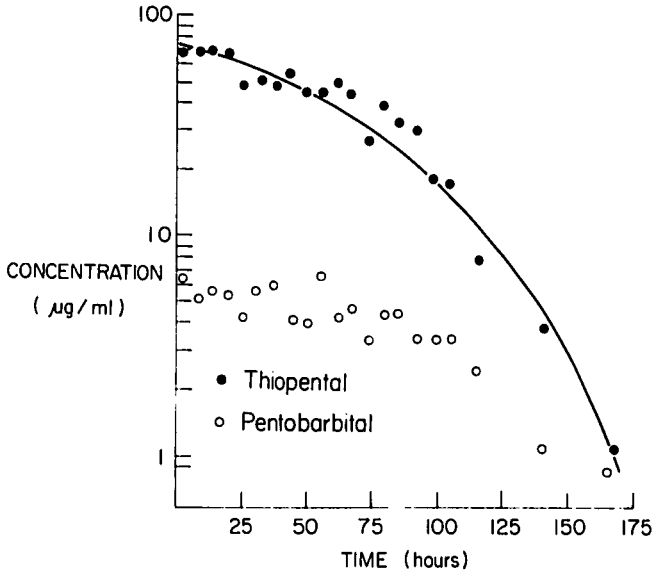

FIG. 1. Postinfusion plasma concentrations of Patient 2, plotted against time. The solid line represents the predicted values of thiopental using the V_m and K_m estimates in table 1.

care therapy included endotracheal intubation, paralysis with neuromuscular blocking agents, hyperventilation, corticosteroids, and mannitol. Normal body temperature was maintained. None of the patients had significant impairment of hepatic or renal function. Two to 18 hours after the acute cerebral ischemic insult, each patient received a bolus (10–15 mg/kg) intravenous injection of thiopental, followed by a continuous infusion, initially at 25 mg/min. An isoelectric electroencephalogram was achived within 1 to 2 hours and maintained for the duration of thiopental infusion. After achievement of an isoelectric encephalogram, the infusion rate was adjusted, using frequent measurements of plasma thiopental concentrations to maintain plasma concentrations between 60 and 100 μg/ml for 42–89 hours (table 1). After termination of the infusion, 20–30 blood samples were drawn at 3–6-hour intervals for pharmacokinetic analysis and comparative assessment of neurologic status with the plasma concentration of thiopental. The plasma concentration of thiopental and one of its metabolites, pentobarbital, were determined by gas chromatography with a sensitivity of 1 μg/ml.[4]

Data Analysis

The postinfusion thiopental plasma concentrations were fit to the following nonlinear, one-compartment Michaelis-Menten pharmacokinetic model with a nonlinear least-squares regression computer program:[5]

$$-dC_p/dt = V_m \times C_p/(K_m + C_p)$$

where $-dC_p/dt$ is the rate of decline of the plasma concentration (C_p) at time t, V_m (μg/ml/hr) is the theoretical maximum rate of drug elimination, and K_m (μg/ml), the Michaelis constant, is the plasma concentration at which the rate of elimination is half of the theoretical maximum. Plasma concentration values were weighted to the inverse square. The same data were also fit to a first-order one-compartment pharmacokinetic model and the quality of fit statistically compared with that of the nonlinear model using the general linear test.[6]

Results

The nonlinear pharmacokinetic behavior of thiopental is illustrated in figure 1. In a one-compartment model with first-order elimination, the rate of decline of thiopental should be constant, with the log concentration *vs.* time relationship forming a straight line. The rate of thiopental decline was not constant; rather, it slowly increased with time, indicating the presence of nonlinear elimination kinetics. For thiopental elimination in all five patients, a significant ($P < 0.05$) better fit was obtained with the Michaelis-Menten model relative to the first-order model. V_m and K_m estimates are given in table 1. At lower thiopental concentrations, when saturation is not occurring, the ratio V_m/K_m should yield an estimate of the rate constant and half-life of elimination. Patients 1 and 2 showed the most pronounced nonlinear kinetics, having V_m and K_m values that predicted terminal elimination half-lives of 7.6 and 9.5 hours. Patients 3, 4 and 5 had less pronounced nonlinear kinetics, with calculated terminal elimination half-lives of 15.9, 30.3 and 25.0 hours. The latter elimination half-lives are longer than the six to seven hours previously seen with thiopental at lower doses.[7] Since the patient population studied is small, it is not possible to determine from our data whether the true first-order elimination half-life of thiopental changes with increasing dose.

Patients 2, 3, and 5 survived and began to show

TABLE 1. Patient Characteristics, Doses of Thiopental, Durations of Infusion, and Pharmacokinetic Estimates

	Age (Years)	Weight (kg)	Total Dose of Thiopental (mg/kg)	Duration of Infusion (Hours)	V_m* (μg/ml/hr)	K_m† (μg/ml)
Patient 1	21	70	365	89	0.74	8.1
Patient 2	35	80	502	42	0.71	9.7
Patient 3	39	53	477	44	1.9	43.7
Patient 4	49	82	411	55	1.2	52.4
Patient 5	58	58	602	71	1.6	67.5

* Theoretical maximum rate of drug elimination.
† The Michaelis constant.

evidence of cerebral activity (movement in response to noxious stimuli) at plasma thiopental concentrations of 31, 19, and 24 μg/ml, 92, 88, and 86 hours, respectively, after termination of the infusion. Patients 1 and 5 sustained brain death and showed no evidence of cerebral activity with thiopental plasma concentrations below a hypnotic concentration. At the end of the thiopental infusion, plasma pentobarbital concentrations were approximately 10 per cent of thiopental concentrations.

Discussion

When used in low doses (5 mg/kg bolus) for the induction of anesthesia, thiopental shows first-order kinetics.[7] When used in higher doses for more prolonged periods, the drug shows nonlinear kinetics. Nonlinear kinetics have also been reported to occur with ethyl alcohol, salicylate, and phenytoin.[8] The nonlinearity is probably due to progressively increasing saturation of the hepatic enzyme systems that oxidize thiopental to an inactive carboxylic acid metabolite or remove a sulfur molecule to form pentobarbital.[9]

There are several important clinical implications of nonlinear kinetics when thiopental is used in high doses as a therapeutic modality. As the infusion dose increases, progressive saturation of the hepatic clearance mechanisms results in rapidly increasing plasma concentrations; the rate of thiopental administration then should be decreased to avoid excessively high plasma concentrations. As the plasma thiopental concentration increases, so will the apparent elimination half-life increase. For example, the half-life of thiopental under first-order kinetics is six hours,[7] whereas the apparent half-life at a plasma concentration of 60–70 μg/ml is approximately 60 hours (fig. 1). Thus, when the infusion is terminated, the plasma concentration of thiopental will decline at a slower rate and will increase the time required for the plasma concentration to fall to a level low enough to allow assessment of neurologic status. This phenomenon was seen in the present study, in which 80–90 hours were needed for the plasma thiopental concentration to fall low enough to allow evidence of cerebral activity in surviving patients.

The optimal plasma concentration of thiopental for cerebral resuscitation is unknown. The plasma thiopental concentration of 60–100 μg/ml was chosen in our study to assure maximal decrease of cerebral metabolic activity and oxygen demand. Had lower thiopental levels been used, cerebral recovery from the thiopental effect could have been assessed earlier. From the data of our three surviving patients, we believe that when the plasma thiopental concentration falls to 20–30 μg/ml, assessment of neurologic function is possible. Finally, pentobarbital is a metabolic product of prolonged thiopental infusion. The pentobarbital formed will probably have a pharmacologic effect on the brain similar to that of thiopental.

While the exact role of high-dose thiopental in cerebral resuscitation has not been established, it is currently being used as a therapeutic modality. Until the nonlinear kinetics are more fully characterized, we suggest that the plasma concentrations of thiopental be measured frequently during thiopental infusion and be used to adjust the infusion rate. This will help to avoid the occurrence of excessively high plasma concentrations, which prolong the time necessary for recovery of cerebral function.

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