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Hypothermia Plus Thiopental:

Prolonged Electroencephalographic Suppression

Arthur L. Quasha, M.D., John H. Tinker, M.D.,† Frank W. Sharbrough, M.D.‡*

Duration of EEG suppression was compared in three groups of patients undergoing hypothermic cardiopulmonary bypass (CPB) at 25–30° C under halothane–nitrous oxide anesthesia. Group I (n = 8) received three doses of thiopental (8 mg/kg, iv): 1) for induction of anesthesia, 2) immediately after the institution of CPB, and 3) just after emergence from CPB. Group II (n = 5) received no thiopental. Group III (n = 4) received thiopental, 8 mg/kg administered intravenously, during CPB only. An unexpectedly prolonged duration of EEG suppression (26.1 min) was noticed in Group I patients with thiopental and hypothermia in combination, as compared with 4.8 min of suppression in Group II patients during hypothermic CPB without thiopental. To rule out a possible cumulative effect of thiopental administration, Group III patients were studied. With only a single dose of thiopental, administered during CPB, 29.3 min of EEG suppression was noticed. Mild cardiovascular depression occurred with thiopental administration during induction of anesthesia, whereas mild-to-moderate depression was associated with thiopental administration following emergence from CPB.

It appears that thiopental and hypothermia, when administered in combination in modest doses during CPB, result in profound depression of cerebral electrical activity and presumably cerebral metabolism. (Key words: Anesthetics, intravenous: thiopental. Brain: electroencephalography; protection. Hypothermia. Hypnotics: barbiturates. Monitoring: encephalography.)

WHILE ENGAGED in a prospective, randomized clinical trial of barbiturate-induced cerebral protection during cardiac surgery, an unexpectedly profound depressant effect on electroencephalographic activity was noticed when thiopental and hypothermia were administered concomitantly. This interaction has not been previously reported in man. The study design permitted analysis of the electroencephalographic effects of thiopental and hypothermia separately and in combination. The electroencephalographic suppression associated with combination therapy was unexpectedly prolonged.

* Assistant Professor, Department of Anesthesia, University of California, San Francisco, California 94143.

† Associate Professor of Anesthesiology, Department of Anesthesiology, Mayo Clinic.

‡ Associate Professor of Neurology, Department of Neurology, Mayo Clinic.

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Address reprints to Dr. Quasha: Department of Anesthesia, University of California, San Francisco, Room S436, Third and Parnassus Avenues, San Francisco, California 94143.

Methods

Thirteen adult patients scheduled for elective cardiac surgery under hypothermic (25–30° C) cardiopulmonary bypass (CPB) were studied. Approval was received from the institutional human studies committee, and informed written consent was obtained from patients the evening before surgery. Patients were randomly assigned to one of two groups. Group I (n = 8) received thiopental, 8 mg/kg administered intravenously, over 60 s for induction of anesthesia, followed by inhalation of nitrous oxide (60 per cent inspired) and halothane (0.5–1.0 per cent inspired) in oxygen. Muscle relaxation was attained with pancuronium, 0.1 mg/kg administered intravenously. After endotracheal intubation, anesthesia was maintained with nitrous oxide (60 per cent inspired) and halothane (0.5–1.0 per cent inspired). Two additional doses of thiopental (8 mg/kg) were administered intravenously, one immediately after initiation of CPB, and one within 5 min of the termination of CPB, after hemodynamic stability was achieved. Hemodynamic stability was defined as a systolic blood pressure of 100 torr or greater with a normal sinus rhythm. Halothane (0.5–1.0 per cent inspired) in oxygen was administered during and after CPB.

Patients in Group II (n = 5) were treated similarly, except that no patient received thiopental at any time. Anesthesia was induced with diazepam, 0.15 mg/kg administered intravenously, instead of thiopental. No other sedatives, narcotics, tranquilizers, or anesthetics were administered to any patient during the study period.

Subsequently, a third group of patients was studied. Patients in Group III (n = 4) were treated similarly to those in Group II, except that a single dose of thiopental, 8 mg/kg, was administered intravenously when CPB was begun. Group III was added to study the electroencephalographic effects of a single dose of thiopental in combination with hypothermia.

Arterial blood pressure and heart rate were closely monitored before, during, and for 15 min after administration of thiopental. A decrease in systolic blood pressure of 20 torr or more was treated with administration of a rapid infusion of crystalloid (200–400 ml, iv) over 3 to 5 min, and, if necessary, intravenous administration of calcium chloride (5 mg/kg). A decrease in perfusion pressure was not treated if it occurred after the administration of thiopental while the patient was on CPB.

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In all patients, Pa_{CO_2} was maintained between 35 and 45 torr. Carbon dioxide was added to the perfusate during CPB to maintain this level of normocarbia, while pH_a remained between 7.27 and 7.42 at 37° C. Blood gas tensions were always measured at 37° C in order to provide a constant frame of reference when comparing data. Radial or femoral arterial perfusion pressure ranged from 30 to 100 torr during CPB, while flow was held constant at 2.4 $l \cdot min^{-1} \cdot m^{-2}$. Nasopharyngeal temperatures ranged from 25 to 30° C during hypothermic CPB.

In addition to standard monitoring (V_5 lead electrocardiogram, esophageal stethoscope, arterial and central venous pressures), all patients were continuously monitored with a 16-lead electroencephalogram (EEG) beginning 5 min before anesthetic induction and ending one hour after emergence from CPB. We analyzed the electroencephalographic effects of hypothermia and thiopental separately and in combination, and measured the duration of electroencephalographic suppression. Suppression was defined as a period during which the amplitude of all electroencephalographic activity was less than 5 μV. This level was chosen as the cutoff because it is the lowest voltage that can be easily seen using the short-distance bipolar derivations (with a sensitivity of 3 μV/mm) employed (fig. 1). Four levels of electroencephalographic suppression were then defined by quantitating the percentage of time during which the EEG amplitude was less than 5 μV (fig. 1, table 1). The total duration of electroencephalographic suppression was measured as the time from the first appearance of periods of suppression lasting at least one second to the return of a continuous electroencephalographic pattern. The duration of suppression was then compared among the groups to examine the electroencephalographic effects of hypothermia and thiopental separately and in combination. Paired Student *t* tests were used to compare data within a patient group. Data between groups were analyzed using a one-way analysis of variance plus multiple range testing. A *P* value of less than 0.05 was considered significant.

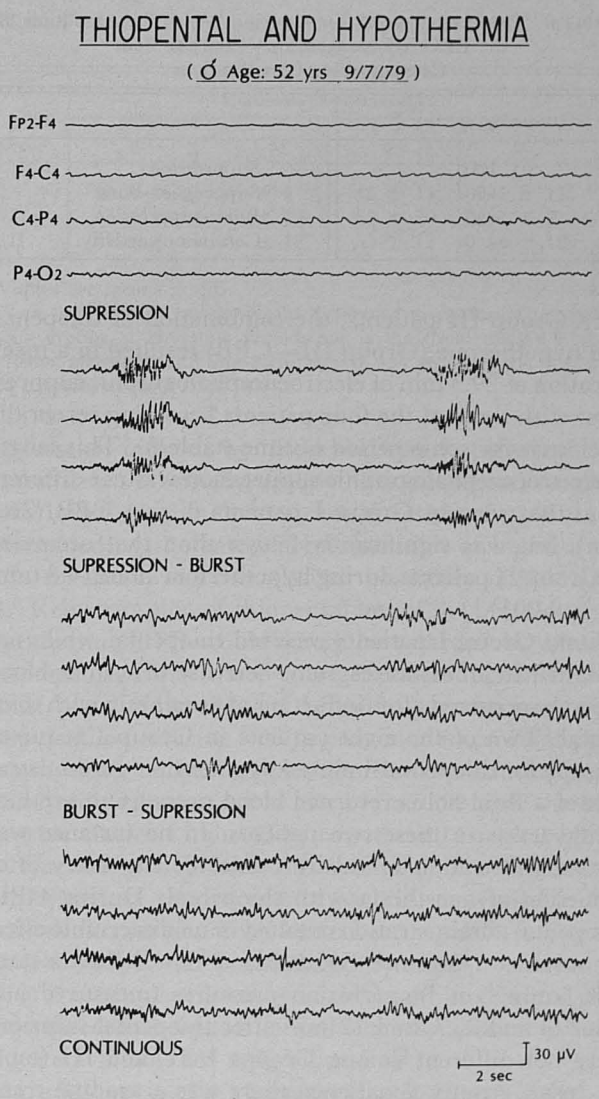

FIG. 1. The EEG of a patient who received thiopental upon institution of CPB at 28° C. All four electroencephalographic categories defined in table 1 are represented.

Results

Patients in Groups I, II, and III did not differ significantly with respect to age, weight, duration of CPB, or nasopharyngeal temperature before, during, or after CPB (table 2). The data are summarized in table 3. Thiopental alone (Group I—Induction) produced some degree of electroencephalographic suppression in five of eight patients. No patient developed an isoelectric pattern (total suppression) with thiopental (8 mg/kg) at normothermia; the predominant pattern was burst-suppression. The mean duration of electroencephalographic suppression (burst-suppression or greater) with thiopental alone was 1.3 min per patient. Hypothermia without thiopental (Group II—CPB) resulted in an average of 4.8 min of electroencephalographic suppression. Again, no patient was rendered cerebrally isoelectric, and burst-suppression was the most common pattern. The combination of thiopental and hypothermia (Group I—CPB) resulted in a markedly different pattern, namely total electroencephalographic suppression, *i.e.*, isoelectricity for varying periods in all eight patients. The average duration of overall electroencephalographic suppression in these patients was 26.1 min ($P < 0.001$ as compared with Group II during CPB, *i.e.*, hypothermia without thiopental). No detectable suppression was observed in Group II patients with induction of anesthesia (Group II—Induction) or after CPB (Group II—Post CPB).

TABLE 1. The Percentage of Time during Which the Amplitude of the EEG is Less than 5 μV, and the Four Corresponding Classifications

Percentage of Time	Classification
100	Suppression
>50	Suppression-burst
<50	Burst-suppression
0	Continuous activity

In Group III patients, the combination of thiopental and hypothermia (Group III—CPB) resulted in a mean duration of 29.3 min of electroencephalographic suppression, with three of the four patients becoming cerebrally isoelectric for some period of time (table 3). This length of electroencephalographic suppression was not different from that seen in Group I patients during CPB (26.1 min), but was significantly longer than that occurring in Group II patients during hypothermia alone (4.8 min) ($P < 0.001$).

Only Group I patients received thiopental while not on CPB. In all instances, some decrease in systolic blood pressure occurred after induction of anesthesia with thiopental. Two of the eight patients in Group I required therapy for thiopental-induced hypotension. Administration of a fluid bolus returned blood pressure to prethiopental levels in these two patients. In no instance was the administration of calcium chloride necessary after induction of anesthesia with thiopental. During CPB, thiopental administration resulted in no discernible effect on vascular resistance. With blood flow held constant ($2.4\ l \cdot min^{-1} \cdot m^{-2}$), perfusion pressures (measured just prior to and 2, 7, and 12 min after thiopental infusion) were not different among Groups I, II, and III (table 4). In all groups of patients, there was a gradual trend towards higher perfusion pressures with time; however, these changes were not significant in the small number of patients in this series. However, during emergence from CPB, thiopental-induced cardiovascular depression appeared to be more pronounced. All patients required rapid fluid administration following emergence from CPB. Five of eight patients in Group I also received calcium chloride, and two patients in Group I required dopamine after administration of thiopental following CPB. The first patient required only transient (10 min) inotropic support, while the second required dopamine and nitroprusside for more than one hour after termination of CPB. The latter had a cardiac arrest 93 min after emergence from CPB and exsanguinated in the operating room after receiving 18 units of blood. This patient underwent a combined procedure of aortic valve replacement and aortic root replacement with a vascular prosthesis. Massive hemorrhage occurred through the pores of the graft, and the patient exsanguinated when the bleeding could not be controlled.

Of the five patients in Group II, two received calcium chloride for cardiovascular support during emergence from CPB. One of these two patients received dopamine for several hours following CPB. One patient in Group III received calcium chloride after CPB, and no other inotrope was required. There were no intraoperative deaths in Groups II or III.

The authors did not prospectively compare the patient groups with respect to postoperative complications, such as myocardial infarction or prolonged endotracheal intubation. However, all patients were extubated successfully within 18 h of surgery.

Discussion

The first 13 patients studied (Groups I and II) were part of a prospective, randomized clinical trial to evaluate the effect of barbiturate administration on neurologic complications during cardiac surgery. After evaluating these patients, the authors were surprised by the total duration of electroencephalographic suppression that occurred in hypothermic patients receiving thiopental (Group I—CPB, 26.1 min) as compared with those not receiving barbiturate (Group II—CPB, 4.8 min). It was questioned as to whether the profound cerebral depression induced by this combination of thiopental and hypothermia was in part due to accumulation of thiopental in the brain, since Group I patients received their second dose of thiopental during CPB. Support for this hypothesis lay in the fact that the third dose of thiopental administered to Group I patients (Group I—Post CPB) resulted in 7.4 min of electroencephalographic suppression, a significantly ($P < 0.001$) longer period than that resulting from the initial dose of thiopental (Group I—Induction), *i.e.*, 1.3 min (table 4). To test this hypothesis, four additional patients were studied (Group III). In Group III patients, no possibility of thiopental accumulation existed, since only one dose was administered. This single dose of thiopental, combined with a similar degree of hypothermia (Group III—CPB) resulted in the same profound electroencephalographic suppression, 29.3 min, as seen in Group I patients during CPB

TABLE 2. Patient Profile (Mean + SD)

	Group I (Thiopental × 3) (n = 8)	Group II (No Thiopental) (n = 5)	Group III (Thiopental × 1) (n = 4)
Age (yr)	54 ± 9	59 ± 15	45 ± 19
Weight (kg)	79 ± 8	77 ± 8	70 ± 14
Duration of CPB (min)	87 ± 31	104 ± 47	88 ± 66
Temperature (°C)			
induction	36.1 ± 0.5	36.1 ± 0.7	35.6 ± 0.3
during CPB	27.1 ± 1.9	26.2 ± 1.6	26.3 ± 2.5
after CPB	36.4 ± 1.0	36.3 ± 0.6	36.3 ± 0.3

(Group I—CPB), *i.e.*, 26.1 min, but was significantly ($P < 0.001$) more prolonged than that which occurred without administration of thiopental during hypothermia (Group II—CPB), *i.e.*, 4.8 min.

Diazepam, 0.15 mg/kg, administered intravenously to patients in Groups II and III for anesthetic induction, had minimal effects on the EEG. Some patients exhibited slight generalized fast activity, consistent with previous reports.[1] No burst-suppression was noticed in any patient following diazepam administration.

Although more suppressed by barbiturates than hypothermia at equivalent levels of cerebral hypometabolism,[2] the EEG remains the best available clinical monitor for reduction of cerebral oxygen consumption (CMR_{O_2}) and, possibly, cerebral protection from hypoxia. The depressant effects of hypothermia plus barbiturates on CMR_{O_2} have been demonstrated to be additive in animal models.[2,3] Yet, once cerebral isoelectricity occurs, deeper hypothermia, but not additional barbiturate, should reduce CMR_{O_2} further.[4] Barbiturate administration sufficient to result in cerebral isoelectricity in dogs produces severe cardiovascular depression and prolonged somnolence, and results in only a 40 per cent reduction in CMR_{O_2}.[5] Hypothermia of 28° C in dogs results in a 50 per cent reduction of CMR_{O_2},[6] but cerebral isoelectricity can only be reliably achieved at temperatures less than 22° C.[7] Hypothermia of this degree would necessitate longer times for both cooling and rewarming during CPB. The combination of moderate hypothermia and modest doses of barbiturates apparently achieves a similar degree of cerebral depression, although CMR_{O_2} was not measured in these patients.

We can only speculate as to the mechanism responsible for the observed prolonged electroencephalographic suppression induced by thiopental and hypothermia in combination. Normally, following a single intravenous bolus injection of thiopental, the duration of narcosis is determined by the rate of redistribution of barbiturate from the brain to other tissues, primarily muscle and fat.[8] Redistribution of thiopental out of the brain during hypothermic CPB would likely be retarded by several mechanisms. First, there is a general reduction in cerebral blood flow induced by both hypothermia[9] and nonpulsatile perfusion.[10] This reduction in cerebral perfusion would tend to increase the time constant for thiopental redistribution out of the brain.[11] Second, the hypocarbic alkalosis induced by hypothermia might reduce the fraction of nonionized thiopental in the brain and thereby reduce the fraction of barbiturate available for transport across the blood-brain barrier, also tending to slow redistribution.[8] Finally, slightly more protein binding of thiopental will occur in the brain as cerebral *p*H is increased, thereby further reducing the amount of barbiturate available for redistribution.[12]

In addition to the pharmacokinetic effects of hypothermia and CPB on barbiturate redistribution, a pharmacodynamic mechanism is possible. Above some unknown threshold concentration of thiopental in the brain, the EEG will become isoelectric. Alternatively, at zero cerebral levels of thiopental, some degree of hypothermia will also induce electroencephalographic isoelectricity. It is easy to imagine that hypothermia could therefore substantially decrease the threshold brain barbiturate concentration necessary to suppress the EEG. By reducing this threshold concentration of brain barbiturate, hypothermia would result in a prolonged duration of electroencephalographic suppression. This prolongation of electroencephalographic isoelectricity would occur as a consequence of the exponential elimination phase of brain barbiturate washout.[8]

Finally, reduced hepatic metabolism secondary to hypothermia and reduced hepatic blood flow during CPB may account for some slight prolongation of thiopental narcosis. In man, hepatic extraction of thiopental varies from 0–50 per cent, and decreases in hepatic blood flow

TABLE 3. Minutes (Mean ± SD) of Electroencephalographic Suppression for Groups I, II, and II with Corresponding Study Period

	Group I (Thiopental × 3) (n = 8)	Group II (No Thiopental) (n = 5)	Group III (Thiopental × 1) (n = 4)
Induction (36°C)	(0/8) 1.3 ± 1.11*	0	0
CPB	(8/8) 26.1 ± 6.2†	(0/5) 4.8 ± 4.7	(3/4) 29.3 ± 20.0†
Post CPB (36°C)	(0/8) 7.4 ± 2.5*	0	0

Numbers in parentheses are the number of patients whose EEG was isoelectric. Note that Groups I and III had significantly ($P < 0.001$) longer periods of electroencephalographic suppression than did Group II patients during CPB. Also, the EEG's of Group I patients were suppressed for a longer period of time ($P < 0.001$) after the third, as compared with the first, dose of thiopental.

* $P < 0.001$ (paired Student t test).

† $P < 0.001$ (ANOVA plus multiple range testing), as compared with Group II-CPB.

TABLE 4. Perfusion Pressures (Torr) During the First 13 Min of Cardiopulmonary Bypass

Group	Minutes after Institution of CPB 0	1–3	6–8	11–13
I	37 ± 7	41 ± 9	46 ± 11	47 ± 12
II	47 ± 14	45 ± 19	51 ± 20	57 ± 23
III	41 ± 8	46 ± 12	53 ± 12	54 ± 10

Values are means ± SE.

Note that there is no significant difference in perfusion pressures among groups at any time period, nor is the trend toward higher perfusion pressures with time significant in any group. Blood flow was held constant at 2.4 $l \cdot min^{-1} \cdot m^{-2}$.

or metabolism will only have significant effects on thiopental half-life if hepatic extraction is initially high.[13] From our data, we cannot ascertain which, if any, of these mechanisms is responsible for the observed prolonged effect on electroencephalographic suppression.

Induction of anesthesia with intravenous thiopental 8 mg/kg resulted in little or no cardiovascular depression. Recently, it has been shown that the administration of thiopental, 15 mg/kg, has no significant hemodynamic effects when used as an anesthetic induction agent in normovolemic patients without cardiac disease.[14] Similarly, the 8 mg/kg dose of thiopental, administered following the initiation of CPB, resulted in no alteration of vascular resistance or perfusion pressures. During emergence from CPB, thiopental administration was associated with rapid fluctuations in blood pressure and heart rate. This period, however, was unstable in all patients, irrespective of whether they received thiopental. Hemodynamic instability during this period may have been related to the administration of protamine and large volumes of blood, as well as to the residual effects of cardioplegia. Therefore, thiopental cannot be incriminated as being responsible for post-CPB hemodynamic instability. The one death in Group I patients was not related to barbiturate administration, but was secondary to hemorrhage.

Since perfusion pressures were not different among Groups I, II, and III during CPB, it is not likely that the large differences in duration and degree of cerebral electrical suppression were secondary to varying cerebral perfusion pressures. The effect of nonpulsatile perfusion on the prolonged electroencephalographic suppression observed with barbiturates and hypothermia in combination may be very significant. However, in our clinical study, we could not evaluate the electroencephalographic effects of hypothermia and barbiturate administration without CPB.

In summary, the administration of a moderate dose of thiopental during hypothermic (25–30° C) CPB profoundly depressed cerebral metabolism, as reflected by the EEG. This dose of thiopental resulted in mild cardiovascular depression prior to CPB, and in mild-to-moderate depression after emergence from CPB. Whether or not barbiturates should be administered during CPB for cerebral protection is controversial. Clearly, however, the combination of hypothermia plus barbiturates results in considerable cerebral depression. The effect, if any, of profound cerebral depression on the incidence or extent of post-CPB neurologic deficit is not known. Based on the prolonged cerebral depression noticed herein with the two modalities used in combination, controlled clinical trials seem warranted.

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