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Cerebral Protection by Thiopental during Hypoxia

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The effects of thiopental on rates of cerebral ATP depletion and lactate accumulation in dogs anesthetized with N_2O during two different circumstances of impaired oxygen delivery were examined. In ten dogs, five with and five without prior thiopental (15 mg/kg), acute hemorrhagic shock (mean arterial pressure 25–30 mm Hg) was produced and maintained for 9 minutes. The EEG remained active in all these dogs. In the dogs given thiopental, cerebral ATP was sustained at a significantly higher level and cerebral lactate accumulation was significantly less in the initial 5–7 minutes of hypotension. In another ten dogs, five with and five without prior thiopental (15 mg/kg), $F_{I_{O_2}}$ was decreased abruptly to zero and hypoxia, progressing rapidly to anoxia ($Pa_{O_2} < 5$ mm Hg), was maintained for 9 minutes. After 3 minutes, the EEG was flat in all dogs, but activity persisted for a significantly longer period (35 sec) in dogs given thiopental. The rates of ATP depletion and lactate accumulation were greater than with hypotension and were not significantly altered by thiopental. It is concluded that in the circumstance of hypoxia with continued cerebral function (active EEG), thiopental does afford some cerebral protection; in the absence of function (flat EEG), no protection is apparent. The authors suggest that anesthetics such as thiopental diminish energy requirements of the brain only by reducing its function and hence can provide cerebral protection only when the extent of hypoxia is insufficient to abolish function. (Key words: Cerebral protection; Cerebral hypoxia; Cerebral function; Anesthetics; Thiopental.)

IT IS SOMETIMES ASSUMED that any agent or technique that decreases the oxygen requirements of the brain will protect the brain to some extent in the event of impaired oxygen delivery. Such an effect has been established for hypothermia, both experimentally and clinically. A cerebral protective effect for anesthetics has not been clearly established, even though a drug such as thiopental can decrease cerebral oxygen consumption (CMR_{O_2}) by as much as 40 to 50 per cent.[1] We[2] reported previously that in dogs there is no biochemical evidence that thiopental protects the brain during anoxia produced by decapitation. We postulated that the immediate loss of function during anoxia, as evidenced by a flat electroencephalogram (EEG), might account for the lack of protection. We suggested that anesthetics, in contrast to hypothermia, alter CMR_{O_2} only by altering function, and therefore, in the circumstance of hypoxia sufficient to abolish cerebral function, there could be no protective effect provided by anesthetics.

The present study was designed to re-examine this question. In this investigation we considered the question in the context of two different forms of impaired cerebral oxygenation—acute hemorrhagic hypotension and progressive arterial hypoxemia. The circumstances of each were so arranged that cerebral oxygenation was sufficient to maintain function (as indicated by an active EEG) during hypotension, whereas progressive hypoxemia ultimately resulted in cessation of function.

Material and Methods

Twenty unmedicated fasting mongrel dogs were studied. Anesthesia was induced and maintained with N_2O (60–70 per cent) and O_2. Succinylcholine was injected intravenously to facilitate endotracheal intubation (dose, 20 mg) and thereafter to maintain muscle paralysis (rate, 150 mg/hr). Ventilation was controlled with a Harvard pump. Cannulae were inserted in a femoral artery for blood sampling and pressure measurements (strain gauge) and in a femoral vein. A subarachnoid catheter was placed in the cisterna magna through a Tuohy needle.

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After an extensive bilateral frontal–parietal craniectomy had been performed, the dura was excised and the dorsal aspect of the cerebral hemispheres was exposed. During the surgical preparation, serial determinations of blood gases were made (IL electrodes, 37 C) and, by appropriate adjustments in the fractional concentration of inspired oxygen ($F_{I_{O_2}}$), tidal volume, and respiratory rate, Pa_{O_2} was maintained at 130 ± 4 mm Hg (mean ± SE) and Pa_{CO_2} at 39 ± 1 mm Hg. Sodium bicarbonate was administered as required to maintain the buffer base at 48 ± 1 mEq/l. Body (right atrial) and brain (parietal epidural) temperatures were maintained at 37.0 ± 0.1 C by the use of heat lamps and thermal blankets. The EEG was monitored continuously from bifrontal electrodes. The animals then were divided into two groups of ten dogs each for investigation of the effects of acute hemorrhagic hypotension and progressive hypoxemia, respectively.

Acute Hemorrhagic Hypotension

In each of the ten dogs in the first group, a large cannula was placed in a femoral artery, then cross-clamped, and connected to the bottom of a reservoir containing heparin (50 mg). The top of the reservoir was connected to an aneroid manometric device that permitted control of the pressure within the reservoir. Blood samples were then taken for baseline determinations of blood gases, hemoglobin concentration (IL CO-Oximeter), and lactate and pyruvate concentrations (enzymatic techniques [3]). A sample of cerebrospinal fluid (CSF) was obtained for determination of lactate concentration.

Five of the ten dogs were then given sodium thiopental (15 mg/kg, intravenously) over a 60-second period; the other five dogs received no thiopental (untreated). Thereafter, in each dog the femoral-artery cannula was opened to the reservoir and the mean arterial pressure (MAP) was lowered rapidly (within 30 seconds) to between 25 and 30 mm Hg in all dogs. Arterial blood pressure and EEG were recorded continuously, starting just before the administration of thiopental or the commencement of bleeding, or both. Then, 30 seconds after the desired decrease in MAP had been achieved, a biopsy (200 to 400 mg) was taken from the exposed cerebral hemispheres, according to the method of Kramer and associates [4] in which tissue is obtained and deposited in liquid nitrogen within 1 second of penetration of the brain. Subsequent biopsies were taken at 1.5, 3, 5, 7, and 9 minutes. Blood and CSF sampling was repeated at 9 minutes. The animals then were killed. Thereafter, the cerebral tissue was prepared in a manner previously described [5] and assayed for ATP concentration (firefly bioluminescent technique [6]) and lactate concentration (enzymatic technique [3]).

Progressive Arterial Hypoxemia

In each of the ten dogs in the second group, baseline blood and CSF samples first were obtained in a manner identical to that described for the first group of dogs. Then, five of the ten dogs were given thiopental (15 mg/kg) over a 60-second period; the other five dogs received no thiopental (untreated). Thereafter, the O_2 in the inspired gases was replaced abruptly by nitrogen. During a subsequent 9-minute period of continuous anoxic ventilation ($F_{I_{O_2}} = 0$), blood and CSF samples were drawn, brain biopsies were obtained and assayed according to the method already described, and the arterial blood pressure and EEG were recorded continuously.

Within the two groups of ten animals, significant differences in mean values between untreated animals and animals given thiopental were determined by Student's t test for unpaired data, $P < 0.05$ being considered statistically significant.

Results

Acute Hemorrhagic Hypotension

In the animals made hypotensive, MAP's during the 9-minute period of hypotension (calculated from measurements made at 1-minute intervals) were 27 ±1 (mean ± SE) and 28 ± 1 mm Hg in the untreated and thiopental-treated dogs, respectively.

The EEG's generally remained active in all dogs throughout the period of hypotension. In the five untreated dogs, the EEG changed abruptly after the onset of hypotension (within 30 seconds) from a desynchronized pattern of low-amplitude (10–60 μV), rapid (16–24 Hz) waves superimposed on higher-amplitude (100–

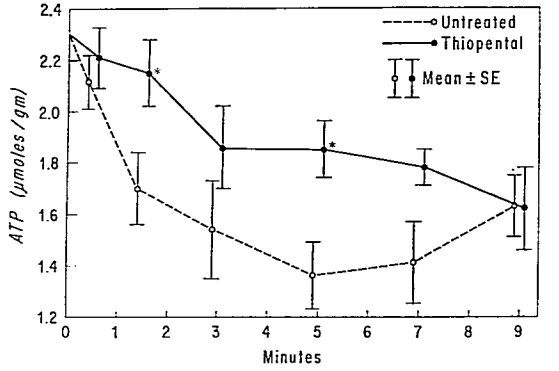

FIG. 1. Effect of thiopental on cerebral ATP concentrations during hypotension. In the initial 5–7 minutes, ATP levels were consistently greater in dogs given thiopental. Differences were significant at 1.5 and 5 min; the lack of difference at 9 min can be explained in part by the progressively diminishing effect of thiopental on the brain. The possibility of unknown compensatory mechanisms in untreated dogs after 5 min cannot be ruled out.

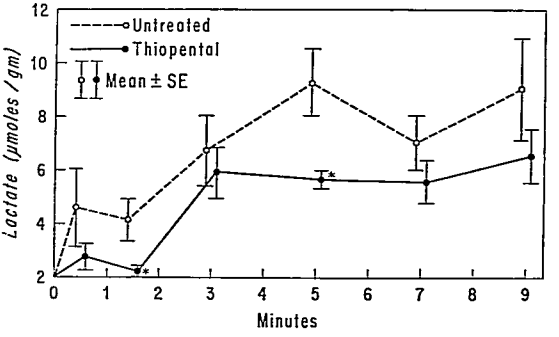

FIG. 2. Effect of thiopental on cerebral lactate concentrations during hypotension. Differences between two groups were significant at 1.5 and 5 min.

200 μV), slower (4–8 Hz) waves to a more synchronized pattern of high-amplitude (300–700 μV), slow (2–4 Hz) waves with intermittent bursts of low-amplitude (20–80 μV), more rapid (6–10 Hz) waves. In the dogs given thiopental, EEG changes were less striking. Thiopental *per se* produced a pattern of synchronized, high-amplitude (600–800 μV), low-frequency (2–4 Hz) waves superimposed on lower-amplitude (75–100 μV) more rapid (4–6 Hz) waves and was, in general, little altered during hypotension.

Cerebral ATP concentrations decreased and cerebral lactate concentrations increased in all dogs during hypotension (figs. 1 and 2). In dogs given thiopental, however, the ATP concentrations were generally sustained at a level greater than that observed in the untreated dogs; this difference was statistically significant at both 1.5- and 5-minute intervals. Lactate accumulation similarly was less in dogs given thiopental and was significantly different at the 1.5- and 5-minute intervals. After 5 minutes, significant differences were not observed. At 9 minutes, cerebral ATP concentrations were similar.

Arterial lactate concentrations (and L/P ratio) increased in all dogs, but the increase was significantly less in dogs given thiopental (table 1). The mean CSF lactate concentra-

TABLE 1. Arterial Blood and CSF Values before and after Arterial Hypotension

	Prior to Hypotension				After 9 Minutes of Hypotension			
	Untreated Dogs		Thiopental-treated Dogs		Untreated Dogs		Thiopental-treated Dogs	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Po_2, mm Hg	124	4	130	6	125	8	131	8
Pco_2, mm Hg	38	2	38	1	27	1	31	1
*p*H	7.41	0.01	7.40	0.01	7.40	0.02	7.39	0.02
BB^+, mEq/l	48	1	47	1	43	1	43	1
Hb, g/100 ml	17.1	0.9	17.3	1.1	14.5	1.4	15.0	1.1
Lactate, mEq/l	2.89	0.17	2.71	0.48	8.85	1.02	5.61*	0.89
Pyruvate, mEq/l	0.26	0.03	0.27	0.05	0.27	0.05	0.23	0.02
L/P ratio	12	2	11	1	38	6	24	3
CSF lactate, mEq/l	2.65	0.29	2.10	0.21	3.07	0.34	2.14*	0.20

* Significantly different from the value in untreated dogs ($P < 0.05$).

tion changed little in the dogs given thiopental and was significantly less than that observed in the untreated dogs (table 1).

Blood-gas concentrations (table 1) changed similarly in all dogs following 9 minutes of hypotension; they were characterized by decreases in both Pa_{CO_2} and buffer base, with no resultant change in *p*H.

PROGRESSIVE ARTERIAL HYPOXEMIA

In the animals made hypoxemic, Pa_{O_2} decreased to <5 mm Hg within 3 minutes.

Cerebral ATP concentration decreased rapidly (to 35 per cent of normal in 5 minutes) in both untreated dogs and those given thiopental (fig. 3). Cerebral lactate concentrations accumulated in a reciprocal fashion (fig. 4). Overall, the changes in both ATP and lactate concentrations were greater in this group of dogs than in the dogs made hypotensive. After 5 minutes, the rates of ATP depletion and lactate accumulation appeared to decrease.

Changes in MAP were similar in both groups of dogs such that there was an initial increase which peaked at 3 minutes (at approximately 50 per cent above control), followed by a progressive decrease to near zero pressure at 9 minutes.

Changes in blood gases and also blood and CSF lactate concentrations were similar in both groups of dogs (table 2).

The only statistically significant difference between the two groups of dogs was the time at which the EEG became flat after the initiation of arterial hypoxemia. In dogs given thiopental, the average duration of electrical activity was 35 seconds longer than in untreated dogs (2 minutes, 58 seconds vs. 2 minutes, 23 seconds).

Discussion

In a previous study,[2] we found no evidence that thiopental protected the brains of dogs (at 37 C) during cerebral anoxia produced by decapitation. The EEG became flat within 15 seconds of decapitation, cerebral ATP was depleted to 25 per cent of normal within 4 minutes, and cerebral lactate accumulated in a reciprocal fashion. Different anesthetic circumstances, known to be associated with as much as a twofold difference in CMR_{O_2}, were associated with virtually identical changes in ATP and lactate concentrations; these changes are summarized in table 3. Cooling of the brain to 30 C—a temperature that is known to decrease CMR_{O_2} to an extent similar to that caused by thiopental—did, however, significantly decrease the post-decapitation rates of ATP depletion and lactate accumulation. We concluded that anesthetics and hypothermia alter CMR_{O_2} by dissimilar mechanisms and that anesthetics therefore cannot be expected to provide similar cerebral protection in the event of anoxia. We suggested that anesthetics alter CMR_{O_2} only by altering cellular (neuronal) function; accordingly, in the absence of function (flat EEG), anesthetics

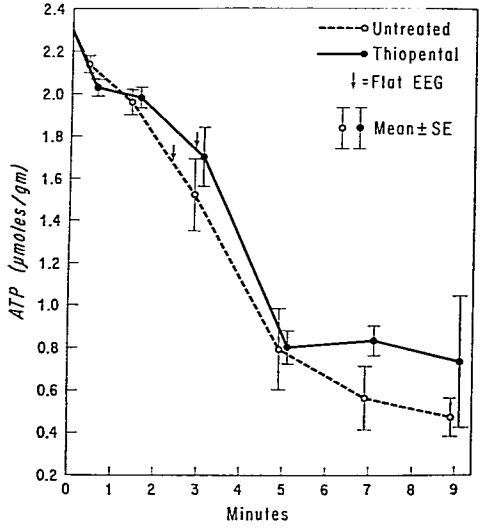

FIG. 3. Effect of thiopental on cerebral ATP concentrations during progressive arterial hypoxemia. Although there was no significant difference in ATP values at any time, at 3 min (approximate time of onset of flat EEG in dogs given thiopental) the mean ATP concentration was higher in dogs given thiopental (1.7 *vs.* 1.5 μmol/g); and onset of flat EEG averaged 35 sec earlier in untreated dogs—a significant difference.

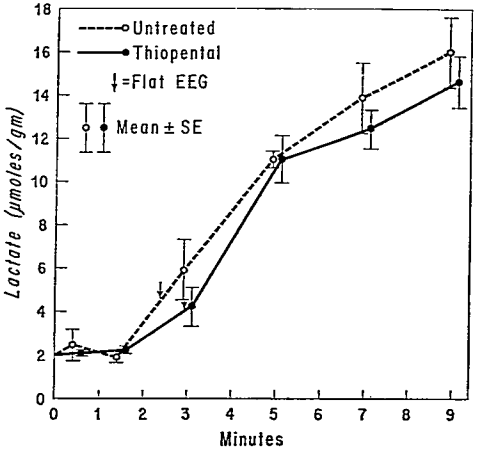

FIG. 4. Effect of thiopental on cerebral lactate concentrations during progressive arterial hypoxemia. Although there was no significant difference in lactate values at any time, at 3 min the mean cerebral lactate concentration was lower in dogs given thiopental (4.2 *vs.* 5.9 μmol/g).

TABLE 2. Arterial Blood and CSF Values before and after Arterial Hypoxemia

	Prior to Arterial Hypoxemia				After 9 Minutes of Arterial Hypoxemia			
	Untreated Dogs		Thiopental-treated Dogs		Untreated Dogs		Thiopental-treated Dogs	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
P_{O_2}, mm Hg	128	5	131	2	4	1	4	1
P_{CO_2}, mm Hg	41	1	40	1	24	5	25	1
*p*H	7.40	0.01	7.40	0.01	7.49	0.03	7.43	0.02
BB^+, mEq/l	49	1	49	1	45	1	43	1
Hb, g/100 ml	14.9	0.3	14.9	0.2	15.2	0.3	15.8	0.3
Lactate, mEq/l	2.54	0.65	2.54	0.55	9.67	1.38	10.94	0.79
Pyruvate, mEq/l	0.25	0.06	0.22	0.05	0.22	0.03	0.17	0.02
L/P ratio	10	1	12	1	44	8	64	7
CSF lactate, mEq/l	1.72	0.15	1.89	0.08	3.40	0.26	3.56	0.23

would have no effect on energy requirements for the basic maintenance of cellular integrity. Hypothermia, in contrast, decreases the rates of all enzymatic reactions to a similar extent, and so decreases the energy requirements for both the maintenance of function and cellular integrity. Accordingly, hypothermia will prolong cerebral viability even in the absence of function, whereas anesthetics will not. These concepts are graphically represented in figure 5.

The present study was designed to explore these concepts further. As a means of restricting oxygen delivery to the brain without abolishing function we induced acute hemorrhagic hypotension. As a means of producing gradual cerebral anoxia (as compared with decapitation) and hence of prolonging the period of continued cerebral function, we induced progressive arterial hypoxemia. We selected thiopental as the test anesthetic since it can decrease CMR_{O_2} both abruptly and substantially—15 mg/kg of thiopental in a single dose producing an almost immediate decrease in CMR_{O_2} of 40 per cent, with a return toward control after 5 minutes.[7]

In the hypotensive animals, thiopental did afford some cerebral protection, at least during the initial 5 to 7 minutes of hypotension. In the absence of thiopental, cerebral function (EEG) was grossly altered, cerebral ATP concentration decreased progressively to 60 per cent of control within 5 minutes, and lactate concentration increased more than fourfold. Oxygen delivery clearly was impaired, the balance between energy available and energy required for maintenance of function was disturbed, and function accordingly was grossly altered in relation to the decrease in energy stores. After the administration of thiopental, less energy was required for maintenance of function—hence the decreases in oxygen delivery and energy production were less deleterious to the brain and were reflected by better maintenance of ATP concentrations, smaller accumulation of lactate, and, grossly, less alteration in function.

TABLE 3. Effects of Different Anesthetic Circumstances and Hypothermia on CMR_{O_2} and Cerebral ATP and Lactate Concentrations 4 Minutes after Decapitation*

Anesthetic Circumstances (Agent, Body Temp.)	CMR_{O_2} (ml/100 g/min)	Concentrations of	
		ATP (μmol/g)	Lactate (μmol/g)
At body temperature of 37 C			
Halothane, 0.8 per cent	4.65	0.69	11.6
N_2O, 70 per cent	5.88	0.60	11.3
Thiopental, 23 mg/kg/hr	2.89	0.60	11.8
At body temperature of 30 C			
Halothane, 0.8 per cent	2.80	1.42	7.7

* Data from Michenfelder JD, Theye RA.[2]

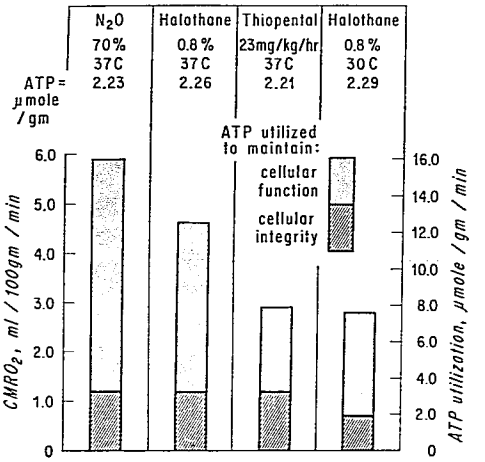

FIG. 5. Effects of three anesthetics, at normothermia and hypothermia (30 C), on cerebral ATP concentration, CMR_{O_2}, rate of ATP utilization, and differences in energy requirements for maintenance of cellular (neuronal) function (active EEG) and cellular integrity. ATP utilization rates were calculated from previous CMR_{O_2} determinations, assuming 100 per cent aerobic glycolysis and a P:O ratio of 3:0. ATP utilization rates for maintenance of cellular integrity were calculated from previous measurements of rates of ATP depletion and lactate accumulation during anoxia, as previously described in detail.[2] In all four circumstances, the energy stores (ATP) are the same. The three normothermic anesthetic circumstances alter energy utilization rates only by altering the energy required for maintenance of function; the energy utilization rates required for maintenance of cellular integrity are identical in all circumstances. Hypothermia, however, decreases both components by a direct effect of temperature on the rates of all enzymatic reactions. Hence, in the absence of function, only hypothermia would prolong cerebral viability, whereas in the presence of function, thiopental and, to a lesser degree, halothane should provide some cerebral protection during hypoxia.

During progressive arterial hypoxemia, the cerebral protective effect provided by thiopental was less apparent; it was not demonstrated convincingly by the biochemical determinations used in this study. Presumably, as is the case following decapitation, the period of continued cerebral function is too brief to permit statistically significant differences to be detected at the time intervals selected and by the relatively insensitive methods used. However, in the initial 3 minutes of progressive hypoxemia, the mean decrease in cerebral ATP concentration and the mean increase in cerebral lactate concentration were less in the dogs given thiopental than in the controls; these observations are compatible with a protective effect during the period of continued function. At 5 minutes (after function had been abolished for 2 to 3 minutes), there were no differences in mean ATP and lactate concentrations; these observations are compatible with lack of a protective effect in the absence of function. Perhaps more convincing was the significant difference in time of onset of a flat EEG between the dogs that received thiopental and those that did not. Assuming that there is a critical energy level below which function is not possible, this level was reached later in dogs given thiopental than it was in untreated dogs. This observation also is compatible with a protective effect provided by thiopental during the period of continued function.

From the observations of our initial study,[2] we concluded that anesthetics do not protect the brain during anoxia and suggested that it was the absence of function *per se* which negated any possible protective effect. If this hypothesis is correct, then it follows that anesthetics could protect the brain during hypoxia if cerebral function continues. The results of the present study completely support such a hypothesis. Further, our observations and conclusions are compatible with the results of other studies. Wilhjelm and Arnfred[8] reported prolongation of survival following barbiturate administration in mice breathing 5 per cent oxygen. Presumably some cerebral function would continue for a time in these circumstances, and therefore protection would be expected. Nilsson[9] found evidence of cerebral protection provided by barbiturates during hemorrhagic shock in rats but no evidence of protection following abrupt onset of asphyxia. These circumstances might be compared with those of the present study, in that function probably continued during hypotension but probably was rapidly abolished following asphyxia, thus explaining his apparently conflicting observations regarding the cerebral protective effect of barbiturates.

The clinical significance of the limited cerebral protection that might be provided by certain anesthetics is difficult to assess. Certainly one should be skeptical of any technique that relies on deep anesthesia to provide significant cerebral protection. Deep anesthesia cannot be equated with hypothermia in terms of cerebral protection. It is possible that when cerebral function may be borderline and oxygen delivery is impaired (*e.g.*, during carotid endarterectomy or induced hypotension), a relatively large dose of an intravenous barbiturate given at that time might afford some protection. It is questionable, however, whether the extent of protection achieved would warrant the undesirable systemic effects that would be likely to follow a large dose of a barbiturate.

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