Title : Hypothermia plus Thiopental: Synergistic EEG Suppression

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Introduction. The effects of hypothermia plus barbiturates on cerebral oxygen consumption ($CMRO_2$) have been demonstrated to be additive.[1] The electroencephalographic (EEG) effect of these two therapies in combination is less clear. We have noted an apparent synergistic effect on duration of EEG suppression induced by hypothermia plus thiopental compared with the sum of effects of each therapy alone.

Methods. Informed written consent, as approved by the institutional Human Studies Committee, was obtained from all patients prior to surgery. Thirteen patients scheduled for elective surgical procedures involving cardiopulmonary bypass (CPB) at 28°C were randomized to one of two treatment protocols. Group I (N=8) patients received a thiopental (8 mg/kg), nitrous oxide, halothane induction followed by halothane/nitrous oxide maintenance of anesthesia. Two additional identical doses of thiopental were given; one immediately following initiation and the other immediately after termination of CPB. Halothane 0.5-1% inspired was administered during and after CPB. $PaCO_2$ was maintained between 35-38 torr. Perfusion pressures during CPB were between 50-100 mmHg, while flow was constant at 2.4 l/min/m^2. Group II (N=5) patients were treated similarly except that anesthetic induction was accomplished with diazepam (.15 mg/kg) in lieu of thiopental, and no thiopental was given at any time. Inspired halothane concentrations were not significantly different at any time period between groups. No other sedatives, narcotics or anesthetics were administered during the study. All patients underwent continuous 16-lead EEG monitoring, starting five minutes prior to induction of anesthesia and terminating one hour after cessation of CPB. The EEG effects of hypothermia (28°C) with or without thiopental as well as thiopental administration during normothermia (36°C) were analyzed and the duration of EEG suppression measured. EEG suppression was defined as the time from the first appearance of total suppression (isoelectricity) or burst suppression pattern to return of continuous activity. Duration of EEG suppression was compared in the two groups in order to examine the EEG effects of hypothermia and thiopental separately and in combination.

Results. (See table) Hypothermia (28°C) alone (Group II-CPB) resulted in EEG suppression in 3 of 5 patients for 5, 9 and 10 minutes respectively (mean = 4.8 min). No patient's EEG became totally isoelectric with hypothermia alone. Burst suppression was the major depressant effect observed. Similarly, 5 of 8 patients induced with thiopental (8 mg/kg) (Group I-induction) underwent a brief (i.e., $\leq$ 2 min) period of burst suppression (mean = 1.3 min) and no patient became cerebrally isoelectric. However, the combination of thiopental and hypothermia (Group I-CPB) resulted in profound EEG suppression, that is, all 8 patients experienced some period of cerebral isoelectricity with a mean duration of EEG suppression of 26.1 minutes. The third dose of thiopental, given to Group I patients after rewarming (36°C) and the discontinuance of CPB (Group I-post-CPB), resulted in a short period of burst suppression in all 8 patients. No patient was cerebrally isoelectric during this period. The mean duration of EEG suppression resulting from the third dose of thiopental was 7.4 minutes.

Discussion. The prolonged cerebral depressant effect seen with the combination of thiopental and hypothermia may in part be accounted for by barbiturate accumulation since the thiopental given during CPB was the second dose. The fact that the third dose of thiopental resulted in significantly ($p < .001$) longer EEG suppression than did the first, although both were administered while the patients were 36°C is also compatible with thiopental accumulation. Still, by adding the durations of EEG suppression for Group II-CPB (4.8 min) and Group I-post-CPB (7.4 min), approximately 12 minutes of EEG suppression would be anticipated for combination therapy (i.e., thiopental plus hypothermia), if the two effects were merely additive. Because 26 minutes of suppression was observed, the combined effects appear to be more than additive with respect to duration of cerebral depression. The administration of thiopental during CPB resulted in a significant increase in duration of EEG suppression compared to hypothermic CPB alone, i.e., 26.1 minutes versus 4.8 minutes ($p < .001$).

EEG suppression is the best available clinical monitor for reduction of $CMRO_2$ and presumably cerebral protection. In man, EEG isoelectricity can only be reliably achieved at 22°C.[2] Cooling to 22°C during CPB would necessitate longer cooling and rewarming times. Hoff et al[3] have demonstrated that to achieve adequate cerebral protection with barbiturates alone requires doses that may result in cardiovascular depression and produce prolonged somnolence. By combining barbiturates and hypothermia in more modest doses, a large reduction in $CMRO_2$, and presumably cerebral protection, can be achieved.

References.

1. Hagerdal M, Keykham M, Perez E, et al: Additive effects of hypothermia and phenobarbital upon cerebral oxygen consumption in the rat. Acta Anaesth Scand 23: 89-92, 1979

2. Smith AL: Barbiturate protection in cerebral hypoxia. Anesthesiology 47:285-293, 1977

3. Hoff JT, Smith AL, Hankinson HL, et al: Barbiturate protection from cerebral infarction in primates. Stroke 6:28-33, 1975

Duration of EEG Suppression (minutes) ($\bar{X} \pm$ SEM)

	Group I (N=8) (thiopental)	Group II (N=5) (no barbiturates)
induction (36°C)	1.3 ± .4[+]	0
CPB (28°C)	26.1 ± 2.2[*]	4.8 ± 2.1[*]
post-CPB (36°C)	7.4 ± 0.9[+]	0

[*] $p < .001$ (Student's unpaired "t" test)

[+] $p < .001$ (Student's paired "t" test)