TITLE: ISOFLURANE INFLUENCES THE EFFECTS OF BARBITURATES ON CBF

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INTRODUCTION: Barbiturates are generally regarded as cerebral vasoconstrictors. However, the reduction in cerebral blood flow(CBF) seen with barbiturates may well occur as a secondary response to a reduction in $CMRO_2$ rather than as a result of direct cerebral vasoconstriction (1). This raises the possibility that if $CMRO_2$ were already greatly reduced, the administration of barbiturates might no longer produce reductions in CBF. In order to examine this hypothesis, we measured CBF before and after the administration of pentobarbital(PB) to animals anesthetized with either the potent cerebral metabolic depressant isoflurane(I) (Low CMRO Group) or morphine sulfate and nitrous oxide (MS/N_2O) (High $CMRO_2$ Group).

METHODS: 14 New Zealand white rabbits were anesthetized with either halothane(H) (n=7) or I(n=7) in a plexiglass box. Animals were paralyzed with pancuronium(P) 1mg, intubated, placed in a stereotactic head frame and ventilated with oxygen. In those animals induced with I, anesthesia was maintained with 0.75% MAC end tidal(ET) I(1.51%). In the other group, H was discontinued and a bolus dose of morphine sulfate 10mg/kg followed by an infusion of 2mg/kg/hr was administered IV and these animals were then ventilated with 70% nitrous oxide(N_2O) in oxygen. All animals were kept paralyzed with an infusion of P 0.5 mg/hr. Following 0.25% bupivacaine local anesthesia, catheters were placed through the groin into the femoral vessels and the head was incised longitudinally to bare the skull. After placement of the vascular catheters, 30 cc of hetastarch in normal saline(Hespan) was administered slowly followed by an infusion of normal saline at 5cc/kg/hr. Platinum needle electrodes were placed in the parietal cortex bilaterally through burr holes to measure CBF via the hydrogen clearance method. A bipolar fronto-occipital electroencephalogram (EEG) was recorded continuously. Following the surgical preparation, the animals were left undisturbed for 30 minutes at normocapnia with either 0.75 MAC end tidal(ET) I anesthesia or MS/N_2O anesthesia. Control(pre-PB) CBF was then measured. Pentobarbital(PB) was then introduced as a bolus of 45mg/kg(over 20 minutes) followed by an infusion of 30mg/kg/hr, a dose sufficient to produce an isoelectric EEG in most animals. MAP was supported at pre-PB levels with angiotensin II. One hour following the loading dose of PB, CBF was measured a second time. Measured variables included mean arterial pressure(MAP), EEG, ET CO_2, ET volatile agent and arterial blood gases(ABGs). Statistical analysis was accomplished by applying a paired t-test to the before and after PB CBF within groups. ABGs and cardiovascular variables were compared between groups with unpaired t-tests. $p < 0.05$ was considered statistically significant.

RESULTS: There were no differences in pH, $PaCO_2$, or MAP between groups either before or after the administration of PB. PaO_2 was higher at all times in animals anesthetized with I (TABLE 1). Initial EEG in the I group demonstrated burst suppression while the EEGs of the animals in the MS/N_2O group remained active. Following PB, the EEG became isoelectric in all of the I anesthetized animals and in all but two of the MS/N_2O anesthetized animals. The EEGs of these latter two animals demonstrated a burst suppression pattern. Pre-PB CBF was 46 ± 15 $ml \cdot 100g^{-1} \cdot min^{-1}$ in those animals anesthetized with MS/N_2O. Following PB, CBF decreased significantly in the MS/N_2O animals to 36 ± 9 $ml \cdot 100g^{-1} \cdot min^{-1}$ but increased significantly in the I anesthetized animals to 73 ± 33 $ml \cdot 100g^{-1} \cdot min^{-1}$ (TABLE 1).

DISCUSSION: These data suggest that the effects of barbiturates on CBF may depend on the existing anesthetic or metabolic state of the brain. Although $CMRO_2$ was not measured directly, the pattern of burst suppression in the I anesthetized animals suggests that $CMRO_2$ was lower in those animals than in those animals anesthetized with MS/N_2O. Therefore we speculate that antecedent $CMRO_2$ may be responsible for these differences, although the data cannot exclude direct drug interactions.

TABLE 1 CBF, ABG and MAP DATA

	I	I+PB	MS/N_2O	MS/N_2O+PB
CBF	46±15	74±33#	57±13	36±9#
$PaCO_2$	39±1	38±1	37±1	39±2
pH	7.41±.05	7.39±.06	7.42±.03	7.39±.03
PaO_2	408±44*	373±51*	143±20	136±24
MAP	75±11	73±9	79±10	78±10

*Denotes significant difference from MS/N_2O Group($p<0.05$)
#Denotes significant difference from pre PB CBF($p<0.05$)
CBF expressed as $ml.100g^{-1} \cdot min^{-1}$
$PaCO_2$, PaO_2, MAP units=mm Hg

References 1. Smith AL, Wollman H: Cerebral blood flow and metabolism: effects of anesthetic drugs and techniques. Aneshthesiology 36: 378-400, 1972.
2. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane. Anesthesiology 60:276-282, 1984.