Anesthesiology
V 75, No 3A, Sep 1991

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TITLE: THE CEREBRAL HEMODYNAMIC AND METABOLIC RESPONSE TO ALFENTANIL IN HUMANS

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Alfentanil is reported to increase cerebrospinal fluid pressure in humans.[1] The mechanism may be direct cerebrovasodilation. This has not been documented. We studied the changes in middle cerebral artery velocity (Vmca), intracranial pressure (ICP), cerebral arteriovenous O_2 content difference ($AVDO_2$) and EEG in response to alfentanil. Neurosurgical patients (NS) i.e. patients with either intracranial aneurysms or tumors and non-neurosurgical patients (NN) were studied.

METHODS: Institutional approval and informed consent were obtained. Patients were induced with thiopental 4-6 mg/kg, vecuronium 0.1 mg/kg, lidocaine 1.5 mg/kg and maintained on N_2O 50% and isoflurane 0.4-0.6% (inspired) following intubation. NS patients had an ICP monitor in-situ or placed following induction. The right jugular bulb was catheterized. EEG was recorded and processed using aperiodic analysis (LifeScan /Diatek). During normocapnia patients either received alfentanil 25 μg/kg (LD,n=6) or 50 μg/kg (HD,n=5) intravenously. Right Vmca recorded using a transcranial doppler (Medasonics), ICP, MAP, HR, and processed EEG (activity edge) were recorded every minute for 10 minutes. At 0, 5, and 10 min., arterial and jugular venous blood was sampled. Phenylephrine was administered if the MAP decreased by 30% compared to baseline. NN patients received either the high dose (NN-HD,n=6) or low dose (NN-LD,n=6) alfentanil and Vmca, EEG, MAP, and HR signals were measured. One way ANOVA for repeated measures and Dunnett's test were used for statistical analysis. The table shows the NS groups' results.

RESULTS: A decrease in HR was the only change in the NS-LD group. The NS-HD group showed suppression of EEG, widening of the $AVDO_2$ ($p=0.06$) and a decrease in HR. ICP, $paCO_2$, and Vmca were unchanged. Three NS-HD patients required phenylephrine. In the NN groups the MAP was allowed to decrease. This was significant in both groups and was the only finding in the NN-LD group. The NN-HD group had significant decreases in HR, Vmca, and EEG.

	LOW DOSE(25 μg. Kg^{-1})					
TIME	0 min	1 min	3 min	5 min	7 min	10 min
V_{mca} (cm/s)	55±8	51±9	53±9	53±8	54±7	53±6
$AVDO_2$(vol %)	4.2±.6			4.6±.6		4.6±.6
ICP(mmHg)	17±4	16±4	18±5	18±5	18±5	17±4
EEG(edge-Hz)	7±1	6±1	6±1	6±1	7±1	8±1
	HIGH DOSE(50 μg. Kg^{-1})					
V_{mca} (cm/s)	42±3	40±4	42±3	37±3	37±3	40±4
$AVDO_2$(vol %)	6.1±.8			7.0±.8		7.5±1.2
ICP(mmHg)	18±3	18±3	19±3	19±4	18±4	18±3
EEG(edge-Hz)	9±1	8±1 *	9±1	9±1	10±1	9±1

* $p<0.05$ compared to time 0, all values are mean ± sem

DISCUSSION: Alfentanil transiently suppressed cerebral metabolism as indicated by EEG in the NS-HD group. At 5 minutes the EEG was at baseline but the $AVDO_2$ widened, suggesting an uncoupling of metabolism and flow. Although the decrease in Vmca did not achieve significance by ANOVA ($p=0.18$), the maximum decrease occurred at 5±0.2 min and the values were significantly different from baseline values (paired t test $p<0.05$). This suggests a dual action of alfentanil; an initial indirect vasoconstriction related to depression of cerebral metabolism followed by direct vasoconstriction. The lack of any significant metabolic or Vmca alterations in the LD-NS dose group suggests that these effects may be dose related. We are unable to substantiate any cerebral vasodilatory action of alfentanil. We found that ICP is not increased when alfentanil is used in the above doses and MAP is maintained.

REFERENCE: 1. J Neurosurg Anesthesiology 1:3-7, 1989.

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TITLE: CARBON DIXOIDE AFFECTS MIDDLE CEREBRAL ARTERY BLOOD FLOW VELOCITY DURING GENERAL ANESTHESIA

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Middle cerebral artery blood flow velocity (MCAv) as measured by transcranial Doppler (TCD) decreases and pulsatility index (PI) increases during hypocarbia in awake subjects (1). This study examined the effects of general anesthesia on this relationship.

With institutional review board approval and informed consent, patients between 18 and 41 yr of age, who had no known cardiovascular disease and were scheduled for general anesthesia and surgical operations not involving the brain or its blood supply, were monitored by TCD during the operation. Patients were randomly assigned to undergo anesthesia with nitrous oxide and either halothane, isoflurane, or fentanyl/midazolam (n = 10 for each group). Systolic and diastolic MCAv (measured transtemporally) were measured during normocarbia (end-tidal carbon dioxide [$etCO_2$], 35 mm Hg) and during hypocarbia ($etCO_2$, 25 mm Hg). During MCAv measurement, mean blood pressure varied less than ± 20%; end-tidal isoflurane and end-tidal halothane did not vary significantly ($p < 0.05$); and fentanyl infusion remained constant. Mean MCAv was calculated as [(systolic - diastolic)/3] + diastolic; % change in mean MCA as (MCAv before hypocarbia - MCA during hypocarbia)/MCAv before hypocarbia; and PI as (systolic flow velocity - diastolic flow velocity)/mean MCAv.

During hypocarbia, % change in mean MCAv decreased and PI increased significantly with halothane and isoflurane but not fentanyl/midazolam (table). MCAv was most affected by isoflurane, but the degree of change did not differ significantly from that with the other two anesthetic regimens (Kruskal-Wallis test using Wilcoxon rank sum test for multiple comparisons).

The MCAv changes are similar to those expected in cerebral blood flow in response to hypocarbia. General anesthesia did not obliterate this response, although the finding of less change with fentanyl/midazolam than with either halothane or isoflurane was unexpected. TCD may be useful for monitoring trends in cerebral blood flow patterns during general anesthesia, provided factors that alter diameter of the conducting arteries remain constant during the observation period.

This study was supported by grants from the Florida High Technology and Industry Council and from Medasonics.

Reference
1. J Cereb Blood Flow Metab 4:368-372, 1984.

Table. Effects of General Anesthesia with Nitrous Oxide and Halothane (Hal), Isoflurane (Iso), or Fentanyl/Midazolam (Fent) on Transcranial Doppler Measurements of Middle Cerebral Artery Blood Flow Velocity (MCAv) before and during Hypocarbia (HC)

	MCAv			Pulsatility Index	
	Before HC	During HC	% Change	Before HC	During HC
Hal	76.6 ± 13.3	61.3 ± 11.4	17 ± 22*	0.63 ± 0.13	0.73 ± 0.13*
Iso	71.0 ± 19.2	45.1 ± 15.5	35 ± 17*	0.85 ± 0.19	1.11 ± 0.19*
Fent	66.2 - 21.0	53.1 ± 21.1	15 ± 22	0.84 ± 0.12	0.80 ± 0.11

Values are mean ± SD. *$p < 0.05$ when values before and during HC are compared within each group by Wilcoxon signed rank test.