TITLE: ANESTHETICS PRODUCE PROLONGED ALTERATIONS OF CSF DYNAMICS

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Introduction. In short-term manometric studies (several 8 min infusions), both enflurane (ENF) and halothane (HAL) were reported to increase the rate of cerebrospinal fluid (CSF) production in rats. It was speculated that increases in CSF volume caused by ENF or HAL may contribute to the increased intracranial pressure (ICP) observed with these anesthetics. However, because the above studies were short-term, it was not known whether anesthetic-induced changes in the rate of CSF production ($\dot{V}_f$) produced by ENF or HAL were of sufficient magnitude and duration to influence CSF volume and ICP. We recently examined the effect on $\dot{V}_f$ of prolonged anesthesia with ENF in dogs (1). We found that ENF increased $\dot{V}_f$ by 50% and that $\dot{V}_f$ remained increased for 5 - 5.5 hr. The present study examined the effect of prolonged anesthesia with HAL, isoflurane (ISO), or fentanyl (FEN) on $\dot{V}_f$.

Methods. Twenty-seven dogs (weights 12-20 kg) were studied. Anesthesia was induced, the trachea was intubated, and ventilation was controlled. A femoral artery was cannulated for blood sampling for blood gas analysis, and for continuous measurement of mean arterial pressure and heart rate. A femoral vein was cannulated for fluid and drug administration. Intravenous infusion of succinylcholine 50-120 mg/hr maintained muscle relaxation. With the head fixed in a stereotaxic frame, an infusion cannula was placed in the lateral ventricle and a collecting cannula placed in the cisterna magna. Nine dogs were assigned to each of three anesthetic groups, HAL (0.8%, end-tidal), ISO (1.4%), or FEN 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 20 min followed by 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, intravenously. For each group $\dot{V}_f$ was determined over 5.5 hr during both anesthesia and control conditions (nitrous oxide, 60 - 70%). $\dot{V}_f$ was determined by ventriculocisternal perfusion, a technique whereby tracer labelled mock dog CSF is perfused through the cerebral CSF space and $\dot{V}_f$ calculated from dilution of the perfusate by freshly formed CSF. Variables within groups were compared using Student's t-test for paired samples, and between groups using Student's t-test for unpaired samples. A P-value of < 0.05 was considered significant. The effect of time on $\dot{V}_f$ during anesthesia or in controls was determined by linear regression analysis and computation of the correlation coefficient.

Results. Compared to control values, ISO and HAL decreased heart rate and mean arterial pressure and FEN decreased heart rate. Otherwise there were no significant differences in systemic variables between groups. HAL decreased $\dot{V}_f$ by 30% while ISO and FEN caused no change in $\dot{V}_f$ (Table). There were no significant changes in $\dot{V}_f$ with time either during anesthesia or in controls. In controls the regression slope for $\dot{V}_f$ was - 4.5 $\mu l \cdot min^{-1} \cdot h^{-1}$.

Discussion. Control values for both $\dot{V}_f$ and the regression slope for $\dot{V}_f$ were in excellent agreement with values previously reported using ventriculocisternal perfusion (1,2). That in the present study HAL decreased $\dot{V}_f$, but increased $\dot{V}_f$ in short-term studies in rats, may be explained by species differences, differences in methodology, or a change in the effect of HAL with time. During prolonged anesthesia an increase in $\dot{V}_f$ with ENF and decrease with HAL parallel the effects on choroid plexus metabolism reported for these anesthetics (3). The effects of ISO or FEN on choroid plexus metabolism are not known.

The results of this study are of particular interest to patients at risk for increased ICP. In such patients hypocapnia, barbiturates, and FEN commonly are used to minimize increases in ICP produced by inhalational anesthetics. However, it was previously reported that neither hypocapnia nor barbiturates decrease $\dot{V}_f$. The present study indicates that FEN also does not decrease $\dot{V}_f$. Thus when anesthetics which increase $\dot{V}_f$ (e.g., ENF) are employed, commonly used "protective" treatments may not prevent increase in ICP. By comparison, HAL, ISO, or FEN do not increase $\dot{V}_f$, and there should occur no increase in CSF volume that would limit usefulness of ICP "protective" treatments.

Table. $\dot{V}_f$ **and** $\dot{V}_a$**, ml/min (mean ± SEM)**

	N_2O Controls	Anesthetic
	$\dot{V}_f$	$\dot{V}_f$
(a)	.047±.008	
ENF(a)	.050±.005	.074±.007*
HAL	.047±.006	.033±.005*
FEN	.054±.010	.058±.007
ISO	.039±.008	.042±.004

* = Significantly different from N_2O controls, $P < 0.05$

(a) = Values from a previous study (1)

References.

1. Artru A, Nugent M, Michenfelder JD: Enflurane causes a prolonged and reversible increase in the rate of CSF production in the dog. Anesthesiology (in press)
2. Martins AN, Doyle TF, Newby N: P_{CO_2} and rate of formation of cerebrospinal fluid in the monkey. Am J Physiol, 231:127-136, 1976
3. Myers RR, Shapiro HM: Paradoxical effect of enflurane on choroid plexus metabolism: Clinical implications (Abstr). Am Soc Anesth, 489-490, 1978