Effects of halothane and fentanyl anesthesia on resistance to reabsorption of CSF

ALAN A. ARTRU, M.D.

Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington

Using the technique of ventriculocisternal perfusion, resistance to reabsorption of cerebrospinal fluid (Rₐ) was examined in dogs during anesthesia with halothane (0.8%) or fentanyl (3.0 μg·kg⁻¹·min⁻¹ for 20 minutes, followed by 0.2 μg·kg⁻¹·min⁻¹, intravenously). Compared to normal Rₐ, in dogs (220 to 224 cm H₂O·ml⁻¹·min⁻¹), halothane increased Rₐ to 245 ± 2 cm H₂O·ml⁻¹·min⁻¹ (mean ± standard error of the mean), and fentanyl decreased Rₐ to 114 ± 1 cm H₂O·ml⁻¹·min⁻¹. Changes in Rₐ caused by halothane or fentanyl may contribute, in part, to changes in intracranial pressure (ICP) observed during prolonged anesthesia with these agents. Because decreased Rₐ improves spatial compensation by cerebrospinal fluid volume during increased ICP, fentanyl may be preferred over halothane in patients at risk because of increased ICP.

KEY WORDS: anesthesia · cerebrospinal fluid · intracranial pressure · halothane · fentanyl

Materials and Methods

Twelve unmedicated mongrel dogs (each weighing 10 to 20 kg) were anesthetized with halothane (> 1.0%) and nitrous oxide (N₂O, 60% to 70%) in oxygen. The trachea was intubated, and ventilation was controlled with a Harvard pump and adjusted, along with the inspired oxygen concentration, to maintain initial oxygen tension (PaO₂) and carbon dioxide tension (PaCO₂) (determined by Radiometer BMS MK2 electrodes*) at more than 120 mm Hg and 35 ± 1 mm Hg (mean ± standard error of the mean), respectively. With the animal in the lateral position, a urinary catheter was placed and the right femoral vein was cannulated for fluid and drug administration. Intravenous infusion of succinylcholine, 50 to 120 mg/hr, maintained muscle relaxation. The right femoral artery was cannulated for arterial blood sampling for blood gas analysis and continuous monitoring of systemic arterial blood pressure and heart rate. Mean arterial pressure (MAP) was determined by electronic integration. Expired CO₂ was continuously monitored using a Beckman LB-2 gas analyzer.† Temperature was monitored by an esophag* Harvard pump manufactured by Harvard Apparatus Co., 150 Dover Road, Millis, Massachusetts; and Radiometer BMS MK2 electrodes manufactured by Radiometer A/S, 72 Emdrupvej, DK 2400, Copenhagen, Denmark.
† Beckman LB-2 medical gas analyzer manufactured by Beckman Instruments, Inc., Fullerton, California.

During prolonged halothane anesthesia (for 3½ hours), a late-occurring sustained increase of cerebrospinal fluid (CSF) pressure has been observed in dogs. Unlike the early transient increase of CSF pressure associated with halothane anesthesia, the later, sustained increase could not be explained solely by an increase in cerebral blood volume (CBV). Previously, Van Landingham, et al., reporting on their study in cats, noted that when data on CSF pressure from short-term (several-minute infusions) manometric studies were fit to a nonlinear model, resistance to reabsorption of CSF (Rₐ), as measured in cm H₂O·ml⁻¹·min⁻¹, was greater during anesthesia with halothane (0.7%) than during the control state of pentobarbital anesthesia (achieved by constant intravenous infusion of 10 mg·kg⁻¹·hr⁻¹). Thus, it may be that the late-occurring, sustained increase of CSF pressure observed during prolonged halothane anesthesia in dogs results in part from an increase in CSF volume because of increased Rₐ. However, whether the increase in Rₐ observed during the short-term studies persists during prolonged halothane anesthesia is not known.

Accordingly, the present study was designed to examine the effect of prolonged halothane anesthesia on Rₐ in the dog. Also examined was the effect on Rₐ of prolonged administration of fentanyl, an anesthetic that causes no late-occurring increase in CSF pressure (unpublished data).
Intracranial pressure with halothane and fentanyl

gal thermistor probe and maintained at 37.0° ± 0.5°C by heat lamps or ice packs. Depletion of vascular volume was minimized by continuous infusion of saline solution at a rate of 4 to 6 ml·kg⁻¹·hr⁻¹.

With the animal in the prone position and the head slightly elevated and fixed on a stereotaxic frame, cannulas were placed into a lateral cerebral ventricle and into the cisterna magna as described previously.³ The burr hole for the ventricular cannula was sealed and the cannula affixed to the skull using methyl methacrylate resin. A T-connector was attached to the ventricular cannula, and ventricular CSF pressure was measured by connecting one arm of the cannula T-connector to a Statham P23 AA strain gauge transducer, via a short length of fine nylon tubing. The level of the external auditory meatus was used as the zero reference for CSF pressure measurement. A 0.3-ml sample of dog CSF was obtained from the cisternal cannula for measurement of osmolality using a Wescor Model 5100 B vapor pressure osmometer. Mock CSF of matching osmolality was prepared by mixing standard solutions (osmolality 290, 300, or 310 mOsm/kg) labeled with blue dextran (1 mg/ml).

Ventriculocisternal perfusion was begun by infusing through the second arm of the T-connector of the ventricular cannula the labeled mock CSF buffered to a pH of 7.40 by equilibration with 5% CO₂ in O₂. The perfusion rate, controlled with a roller pump, was gradually increased to 0.3 ml/min, while ventricular CSF pressure was continuously monitored. Successful ventriculocisternal perfusion was indicated by outflow of labeled CSF from the cisternal cannula with no increase in CSF pressure above pre-perfusion values. In six of the 12 dogs, the concentration of halothane was decreased to 0.8% (end-expired value determined by gas chromatography) in N₂O (60% to 70%) and O₂. In the other six dogs, halothane was discontinued and anesthesia was maintained with fentanyl (3.0 μg·kg⁻¹·min⁻¹ for 20 minutes, followed by 0.2 μg·kg⁻¹·min⁻¹, administered intravenously) plus N₂O (60% to 70%) in O₂.

For both groups, 2 to 3 hours of ventriculocisternal perfusion was allowed for equilibration of the labeled mock CSF with the dog CSF in the intracerebral CSF spaces of the animals. Steady-state conditions were assumed when tracer concentrations in three consecutive samples of cisternal outflow agreed within 2%. Concentrations of blue dextran in centrifuged cisternal outflow samples and samples of the labeled mock CSF perfused into the ventricle were determined using light absorbance at 610 nm on a Beckman DU-2 spectrophotometer fitted with a Gilford absorbance indicator.⁵ ⁶

Following equilibration of the tracer, Rₘ was determined for each dog as the reciprocal of the slope relating the rate of reabsorption of CSF (Vₐ), measured in milliliters per minute, to CSF pressure. To obtain that slope, Vₐ was determined at four CSF pressures: first at pre-perfusion CSF pressure (control conditions), then at 5, 10, and 15 cm H₂O above control values. The Vₐ was calculated as described previously,⁷ according to the formula of Heisey, et al., by determining tracer clearance. Increases of CSF pressure were achieved by elevating the tip of the cisternal outflow cannula, and the sequence of exposures to the three levels of increased CSF pressure was randomized. At least 45 minutes of perfusion was allowed at each CSF pressure to reestablish near steady-state conditions. Also determined at each of the four CSF pressures was: 1) the rate of CSF production (Vₐ, measured in milliliters per minute, and calculated as previously described⁸); 2) the volume of distribution of the tracer substance (VDₐ, measured in milliliters, and calculated according to the formula of Pappenheimer, et al.); and 3) systemic variables. At the conclusion of all studies, animals were killed by intravenous injection of potassium chloride, the brain was removed for examination, and the choroid plexus dissected free for inspection and weighing.

In both the halothane and fentanyl groups, systemic and CSF variables at increased CSF pressures were compared to their respective control values using Student’s t-test for paired samples. Comparisons between the halothane and fentanyl groups were made using Student’s t-test for unpaired samples. The relationship between CSF pressure and both Vₐ and Vₙ was determined by linear regression analysis and computation of the correlation coefficient. Difference in regression slopes between groups was determined by the F test for homogeneity of regression. For all statistical comparisons, p < 0.05 was considered significant.

Results

During both halothane and fentanyl anesthesia, systemic variables did not change significantly as CSF pressure was increased. Mean values for each of the four levels of CSF pressure (control level, and 5, 10, and 15 cm H₂O above control) were therefore combined (Table 1). Mean values for systemic variables during halothane anesthesia were not significantly different from those during fentanyl anesthesia, except for heart rate which was decreased with fentanyl.

During halothane anesthesia, Vₐ increased as CSF pressure was increased (Fig. 1). The regression line for Vₐ was y = 0.0041 (x) + 0.0158, where x = CSF pressure (cm H₂O), and y = Vₐ (ml/min), with a correlation coefficient of 0.74 (p < 0.05). The Rₙ during halothane anesthesia was 245 ± 2 cm H₂O·ml⁻¹·min⁻¹. By comparison, Vₙ did not change significantly as CSF pressure was increased (Fig. 1). The mean Vₙ value combined from the Vₙ values at each of the four levels of CSF

---

⁴ Statham P23 AA strain gauge transducer manufactured by Statham Laboratories, Inc., Hato Rey, Puerto Rico.

⁵ Wescor Model 5100 B vapor pressure osmometer manufactured by Wescor, Inc., Logan, Utah.

⁶ Spectrophotometer manufactured by Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, California; and absorbance indicator manufactured by Gilford Instrument Laboratories, Inc., Oberlin, Ohio.

---

J. Neurosurg. / Volume 60 / February, 1984

253
TABLE 1
Combined systemic variables from four cerebrospinal fluid (CSF) pressures during halothane or fentanyl anesthesia*

<table>
<thead>
<tr>
<th>Systemic Variables</th>
<th>Halothane Group</th>
<th>Fentanyl Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>157 ± 21</td>
<td>158 ± 30</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>35 ± 1</td>
<td>35 ± 1</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.02</td>
<td>7.39 ± 0.01</td>
</tr>
<tr>
<td>bicarbonate (mEq/liter)</td>
<td>21.1 ± 0.9</td>
<td>20.7 ± 1.1</td>
</tr>
<tr>
<td>hemoglobin (gm/dl)</td>
<td>13.5 ± 1.0</td>
<td>13.2 ± 1.8</td>
</tr>
<tr>
<td>mean arterial pressure (mm Hg)</td>
<td>112 ± 10</td>
<td>129 ± 13</td>
</tr>
<tr>
<td>heart rate (beats/min)</td>
<td>118 ± 11</td>
<td>51 ± 7†</td>
</tr>
<tr>
<td>esophageal temperature (°C)</td>
<td>37.0 ± 0.1</td>
<td>37.1 ± 0.1</td>
</tr>
</tbody>
</table>

* Values are the combined results of determinations made at a control (pre-perfusion) level and at 5, 10, and 15 cm H₂O above control level, and are shown as means ± standard deviations. There were six dogs in each group.

† Significant difference from halothane, p < 0.05.

pressure (control level, and 5, 10, and 15 cm H₂O above control) was 0.036 ± 0.006 ml/min.

During fentanyl anesthesia, Vₜ increased as CSF pressure was increased (Fig. 2). The regression line for Vₜ was y = 0.0088 (x) + 0.0133, where x = CSF pressure (cm H₂O), and y = Vₜ (ml/min), with a correlation coefficient of 0.82 (p < 0.05). The Rₘ during fentanyl anesthesia was 114 ± 1 cm H₂O·ml⁻¹·min⁻¹, significantly less than Rₘ during halothane anesthesia. In contrast, Vₜ did not change significantly as CSF pressure was increased (Fig. 2). The mean Vₜ value averaging the Vₜ values at each of the four levels of CSF pressure was 0.042 ± 0.007 ml/min.

Other cerebral variables, such as CSF pressure at control levels, CSF osmolality, perfusion rate of mock CSF, and VDₛ, were not significantly different during halothane anesthesia from those during fentanyl anesthesia (Table 2). In none of the dogs was there visible evidence of cerebral edema or choroid plexus abnormality. The mean duration of ventriculocisternal perfusion was 324 ± 11 minutes.

Discussion

During both halothane or fentanyl anesthesia Vₜ values for each dog were Vₜ > Vₛ > 0 at control conditions, indicating that the CSF pressures at which control measurements were taken were not significantly increased for any dog, that there were no undetected leaks of blue dextran-labeled mock CSF, and that there were no significant changes in volumes of brain, cerebral blood, or CSF due to non-steady-state conditions during CSF collections. That Vₛ increased directly as CSF pressure was increased agrees with similar observations previously reported in dogs, rabbits, goats, and man.

Intracranial CSF pressure is determined by the volumes of the three compartments of the intracranial space: CBV, CSF volume, and brain tissue volume. Because the structures surrounding these contents (meninges and skull) are poorly distensible, CSF pressure initially will rise with an increase in either CBV or brain tissue volume. If Rₛ and Vₛ are constant, CSF volume contracts so that in time CSF pressure returns to its original value (up to the limits of contraction of the CSF space). If either Rₛ or Vₛ is increased for any reason, ICP stabilizes at a higher than normal level. Thus, within the limits of CSF volume to decrease in response to increases in CBV or brain tissue volume, global (but not necessarily regional) CSF pressure is determined solely by the balance between Rₛ and Vₛ. In the present study, Rₛ during halothane anesthesia (245 ± 2 cm H₂O·ml⁻¹·min⁻¹) was increased compared to values reported as normal for dogs by Bering and Sato (220 cm H₂O·ml⁻¹·min⁻¹) and Oppelt, et al. (224 cm H₂O·ml⁻¹·min⁻¹). These Rₛ values are in contrast to the values reported as normal for dog by Vela, et al. (451 cm H₂O·ml⁻¹·min⁻¹), and by Mann, et al. (40 cm H₂O·ml⁻¹·min⁻¹). Assuming that an Rₛ of 220 to

Definitions of Abbreviations

CBV = cerebral blood volume
CSF = cerebrospinal fluid
ICP = intracranial pressure
MAP = mean arterial pressure
Rₛ = resistance to reabsorption of CSF
Vₛ = rate of reabsorption of CSF
Vₜ = rate of CSF production
VDₛ = volume of distribution of the tracer substance in the perfused mock CSF

A. A. Artru
Intracranial pressure with halothane and fentanyl

![Graph showing the relationship between CSF flow rate and CSF pressure for halothane and fentanyl anesthesia.]

**TABLE 2**

<table>
<thead>
<tr>
<th>Cerebral Variables during halothane and fentanyl anesthesia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Variables</td>
</tr>
<tr>
<td>Vf (ml/min)</td>
</tr>
<tr>
<td>Vr (ml/min)</td>
</tr>
<tr>
<td>Intraventricular CSF pressure (cm H2O)</td>
</tr>
<tr>
<td>CSF osmolality (mOsm/kg)</td>
</tr>
<tr>
<td>Perfusion rate of mock CSF (ml/min)</td>
</tr>
<tr>
<td>VD, (ml)</td>
</tr>
</tbody>
</table>

*See Definitions of Abbreviations table for description of terms. Values are means ± standard deviations. There were six animals in each group.

224 cm H2O·ml⁻¹·min⁻¹ represents "normal" values for dog, then the results of the present study support the idea that increased Rₕ contributes to the prolonged increase of CSF pressure observed during halothane anesthesia.

In contrast to halothane, fentanyl anesthesia decreased Rₚ (114 ± 1 cm H2O·ml⁻¹·min⁻¹). This reduced Rₚ may contribute to the sustained decrease of CSF pressure that has been observed during administration of fentanyl.¹,¹² Because decreased Rₚ improves spatial compensation by CSF volume, decreased Rₚ also may minimize increases in CSF pressure caused by increases in CBV during prolonged fentanyl anesthesia. Artru² reported that a 5-minute trial of increased CBV (produced by hypercapnia) caused a significantly greater increase in CSF pressure in dogs anesthetized for 2½ hours with halothane or in control animals (N₂O anesthesia) than in dogs anesthetized for 2½ hours with fentanyl.

A number of systemic variables, such as MAP,¹⁸ pH,¹⁷,₂⁰ temperature,¹¹,₂³ and PaO₂,¹⁵ have previously been reported to significantly affect Vₚ, and consequently Vₚ. In the present studies, these variables were controlled and thus had minimal effects on CSF dynamics. During both halothane or fentanyl anesthesia, Vₚ values were similar to values reported previously for halothane and fentanyl.³ That Vₚ did not change significantly as CSF pressure was increased agrees with previous studies that examined the relationship between Vₚ and CSF pressure.⁶,⁹,¹⁰,¹³

For both halothane and fentanyl anesthesia, the intersection of the slopes of Vₚ versus CSF pressure and Vr versus CSF pressure (Figs. 1 and 2) calculates for each anesthetic an "equilibrium" CSF pressure; that is, the CSF pressure at which production and absorption in this experimental situation are balanced.⁹ In the open-skull preparation used in this study, the "equilibrium" CSF pressure calculated for halothane was about 11 cm H2O. This value agrees with the intraventricular CSF pressure of 10 ± 1 cm H₂O observed during a 3½-hour period of anesthesia with halothane (0.8%) in a closed-skull dog preparation.⁴ In the present study, the "equilibrium" CSF pressure calculated for fentanyl was about 8 cm H₂O, which is also close to the CSF pressure of 7 ± 3 cm H₂O measured from an intraventricular cannula during 3½ hours of anesthesia with fentanyl (administered by continuous intravenous infusion, using the same protocol as in this study) in a closed-skull dog preparation in this laboratory (unpublished data).

That halothane increases Rₚ and fentanyl decreases Rₚ may be of particular interest for patients at risk because of increased ICP. Controlled hyperventilation has been recommended for use during halothane anesthesia for such patients to decrease CBV and hence intracranial CSF pressure.⁷ Previously, it was reported in dogs that controlled hyperventilation to a PaCO₂ of 20 mm kg during halothane anesthesia decreased cerebral blood flow, and presumably CBV, to values similar to those observed during administration of fentanyl at a normal PaCO₂.¹⁹ Based on these results, neither anesthetic appears to offer an advantage over the other as regards CSF pressure, providing that controlled hyperventilation was employed when halothane was used. However, the results of this study suggest that fentanyl anesthesia may be preferable to halothane for patients with increased intracranial CSF pressure, because Rₚ is decreased with fentanyl compared to halothane. Decreased Rₚ offers the advantage that, if CBV or brain tissue volume increases, a compensatory decrease of CSF volume will occur (due to reabsorption of CSF) at a lower intracranial CSF pressure than if Rₚ were unchanged.
References

4. Artru AA: Relationship between cerebral blood volume and CSF pressure during anesthesia with halothane or enfurane in dogs. Anesthesiology 58:533-539, 1983
5. Artru AA, Nugent M, Michenfelder JD: Enflurane causes a prolonged and reversible increase in the rate of CSF production in the dog. Anesthesiology 57:255-260, 1982

Manuscript received June 20, 1983.
This work was supported in part by a grant from Ohio Medical Anesthesists, Madison, Wisconsin.
Address reprint requests to: Alan A. Artru, M.D., Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington 98195.