Desflurane and Isoflurane Increase Lumbar Cerebrospinal Fluid Pressure in Normocapnic Patients Undergoing Transsphenoidal Hypophysectomy

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Background: Rapid emergence from anesthesia makes desflurane an attractive choice as an anesthetic for patients having neurosurgery. However, the data on the effect of desflurane on intracranial pressure in humans are still limited and inconclusive. The authors hypothesized that desflurane and desflurane increase intracranial pressure compared with propofol.

Methods: Desflurane was induced with intravenous fentanyl and propofol in 30 patients having transsphenoidal hypophysectomy with no evidence of mass effect, and it was maintained with 70% nitrous oxide in oxygen and a continuous 100 µg·kg⁻¹·min⁻¹ infusion of propofol. Patients were assigned to three groups randomized to receive only continuous propofol infusion (n = 10), desflurane (n = 10), or isoflurane (n = 10) for 20 min. During the 20-min study period, each patient in the desflurane and isoflurane groups received, in random order, two concentrations (0.5 minimum alveolar concentration [MAC] and 1.0 MAC end-tidal) of desflurane or isoflurane for 10 min each. Lumbar cerebrospinal fluid (CSF) pressure, blood pressure, heart rate, and anesthetic concentrations were monitored continuously.

Results: Lumbar CSF pressure increased significantly in all patients receiving desflurane or isoflurane. Lumbar CSF pressure increased by 5 ± 3 mmHg at 1-MAC concentrations of desflurane and by 4 ± 2 mmHg at 1-MAC concentrations of isoflurane. Cerebral perfusion pressure decreased by 12 ± 10 mmHg at 1-MAC concentrations of desflurane and by 15 ± 10 mmHg at 1-MAC concentrations of isoflurane. Heart rate increased by 7 ± 9 bpm with 0.5 MAC desflurane and by 8 ± 7 bpm with 1.0 MAC desflurane, and by 5 ± 11 bpm with 1.0 MAC isoflurane. Systolic blood pressure decreased in all but the patients receiving 1.0 MAC desflurane. To maintain blood pressure within predetermined limits, phenylephrine was administered to six of 10 patients in the isoflurane group (range, 25 to 600 µg), two of 10 patients in the desflurane group (range, 200 to 500 µg), and in no patients in the propofol group. Lumbar CSF pressure, heart rate, and systolic blood pressure did not change in the propofol group.

Conclusion: Desflurane and isoflurane, at 0.5 and 1.0 MAC, increase lumbar CSF pressure. (Key words: Anesthetics, volatile; desflurane; isoflurane. Intracranial pressure. Cerebrospinal fluid pressure. Blood pressure. Heart: heart rate. Surgery: neurosurgery; transsphenoidal.)

Desflurane is a volatile anesthetic with a relatively low blood/gas solubility ratio (blood/gas partition coefficient, 0.42), which permits a more rapid emergence from anesthesia than is possible with other volatile anesthetics. Desflurane is thus an attractive choice for anesthesia in patients having neurosurgery when rapid emergence is desirable because it facilitates neurologic evaluation of the patient soon after surgery. However, the feasibility of desflurane for neuroanesthesia relies, in part, on whether it increases intracranial pressure, and whether this effect differs from that of the other commonly used potent inhalation anesthetics. Thus far the data are limited and inconclusive.

Animal studies indicate that desflurane is a potent cerebral vasodilator. Similar findings were recently reported by Muzi and colleagues, who found that desflurane, but not isoflurane, increased intracranial pressure in hypapnic patients with supratentorial mass lesions having neurosurgery. However, these investigators studied only a single anesthetic concentration (1.0 MAC). In our study, we investigated the effects of two different doses of desflurane on intracranial pressure, comparing these with two equipotent doses of isoflurane in patients receiving a continuous propofol infusion and 70% nitrous oxide.

Methods

Study Population

With approval from our human research committee and written informed consent, we studied 30 patients...
undergoing transphenoidal pituitary surgery at the University of California, San Francisco Medical Center. Study entry criteria included patients who were between 18 and 60 y old and required a lumbar intrathecal catheter during operation. Excluded from the study were patients with clinical evidence of elevated intracranial pressure.

**Experimental Protocol**

On the morning of surgery, patients were premedicated with intravenous 2 mg midazolam; then they breathed 100% oxygen while anesthesia was induced with intravenous fentanyl (up to 3 μg/kg) and propofol (up to 2.5 mg/kg). Vecuronium (0.1 mg/kg given intravenously) was administered to achieve muscle relaxation before tracheal intubation and as necessary (in 1- to 2-mg boluses) to maintain zero twitch tension (train-of-four monitoring). After tracheal intubation, anesthesia was maintained with 70% nitrous oxide in oxygen and an intravenous propofol infusion (100 μg·kg⁻¹·min⁻¹). Ventilation was adjusted to maintain end-tidal carbon dioxide between 35 and 40 mmHg.

A radial arterial cannula was placed to measure arterial blood pressure. An 18 G polyamide epidural catheter (Burrn Medical, Bethlehem, PA) was placed intrathecally at the L3–4 or L4–5 interspace and threaded cephalad approximately 20 cm to allow measurement of lumbar cerebrospinal fluid (CSF) pressure. The patency of the pathway between the lumbar CSF space and the cranium was confirmed by observing the change in lumbar CSF pressure during gentle manual compression of the internal jugular veins. The study was conducted and completed before the surgical procedure while patients were unstimulated and supine. Baseline blood pressure and heart rate were defined as the median values obtained during the minute before the 20-min study period. Blood pressure was maintained within ±20% of this baseline value throughout the study by administering phenylephrine as necessary.

We assigned the patients randomly to three groups. After baseline measurements, patients received either only the continuous intravenous propofol maintenance infusion (n = 10) or the addition of desflurane (n = 10) or isoflurane (n = 10) for 20 min. During the 20-min study period, each patient in the desflurane and isoflurane groups received, in random order, two concentrations (0.5 MAC and 1.0 MAC end-tidal) for 10 min each. One MAC for desflurane was defined as 7.25 vol% for patients ages 18 to 30 y and 6.0 vol% for those ages 31 to 60 y. One MAC for isoflurane was defined as 1.28 vol% for patients ages 18 to 30 y and 1.15 vol% for those ages 31 to 60 y. The transition between test concentrations (0.5 and 1.0 MAC) was achieved by a rapid change of the inspired concentration to the target end-tidal test concentration during a period of 1 min. A fresh gas flow of 10 L/min was used throughout the study to facilitate rapid adjustment of the end-tidal anesthetic concentration.

**Clinical Data Collection**

Lumbar CSF pressure was measured via an intrathecal catheter connected to a Transpac II transducer (Abbott Laboratories, North Chicago, IL) inserted during operation; arterial blood pressure was measured using a radial arterial cannula connected to a second Transpac II transducer also inserted during operation; and heart rate was measured via three-lead electrocardiography using a portable hemodynamic monitor (ProspaQ 106; Protocol Systems, Beaverton, OR). The transducers were set at the zero level of the micromanometer. Hemoglobin oxygen saturation (SpO₂) was measured noninvasively using a pulse oximeter (ProspaQ 106) with the probe placed on a distal phalanx. Anesthetic concentration was measured continuously at the proximal orifice of the endotracheal tube using an infrared anesthetic gas monitor (Datec Ultima, Helsinki, Finland). Hemodynamic, lumbar CSF pressure, SpO₂, and anesthetic gas data were recorded at 10-s intervals from the monitors through an automated data-acquisition system.

**Data Analysis**

For analysis, the blood pressure, heart rate, and lumbar CSF pressure data (recorded every 10 s) were reduced to 1-min median values. Cerebral perfusion pressure (CPP) was calculated as mean arterial pressure – lumbar CSF pressure. For continuously measured variables (systolic blood pressure, heart rate, lumbar CSF pressure, and CPP), baseline values were defined as the median value obtained during 1 min before the 20-min study period. The peak, lowest, and 10-min values were calculated for each study period for 0.5 and 1.0 MAC.

Demographic data were analyzed using analysis of variance. Values for peak and lowest systolic blood pressure, heart rate, lumbar CSF pressure, and CPP after each change in anesthetic concentration and the last values obtained during each 10-min study interval were compared with baseline values in each group using repeated-measures testing, and between the study and propofol groups by analysis of variance. Carbon dioxide...
Table 1. Demographic and Clinical Characteristics of Study Patients (n = 30)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Propofol (n = 10)</th>
<th>Isoflurane (n = 10)</th>
<th>Desflurane (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38 ± 10</td>
<td>39 ± 10</td>
<td>33 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85 ± 22</td>
<td>88 ± 30</td>
<td>75 ± 16</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171 ± 11</td>
<td>172 ± 9</td>
<td>170 ± 13</td>
</tr>
<tr>
<td>Propofol (mg/kg)</td>
<td>2.2 ± 0.6</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>Fentanyl (μg/kg)</td>
<td>1.6 ± 0.8</td>
<td>1.7 ± 0.6</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>35 ± 4</td>
<td>35 ± 3</td>
<td>36 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

data were compared using repeated-measures analysis of variance. Data are reported as the mean ± SD. P < 0.05 identified statistical significance. Statistical calculations were performed using StatView 4.02 software (Abacus Concepts, Berkeley, CA).

Discussion

Our results show that lumbar CSF pressure increases with desflurane and isoflurane administration in unstimulated normocapnic patients undergoing transsphenoidal hypophysectomy. At both 0.5 and 1.0 MAC, desflurane and isoflurane increased lumbar CSF pressure, with no difference in effect between anesthetics or anesthetic concentration. In contrast, continuous propofol anesthesia did not alter lumbar CSF pressure.

Comparison with Other Studies

The existing data on the effects of desflurane on intracranial pressure in patients having neurosurgery are limited. Muzzi and colleagues compared a single dose (1 MAC) of desflurane and isoflurane during operation in hypocapnic patients with supratentorial mass lesions and reported a gradual increase of lumbar CSF pressure (from 11 ± 4 mmHg to 18 ± 6 mmHg) during administration of desflurane but not isoflurane. Beginning 20 min after the institution of desflurane, lumbar CSF pressure was significantly greater than baseline. We also found that desflurane increased lumbar CSF pressure, but within only a few minutes of beginning desflurane administration (fig. 1). Unlike Muzzi and colleagues, we found a similar increase in lumbar CSF pressure with isoflurane. In addition, we found that this pressure increased significantly at both 0.5 MAC and 1.0 MAC of both isoflurane and desflurane. However, we studied the effect of desflurane and isoflurane on lumbar CSF pressure for 20 min compared with their 45 min. Thus it is possible that our results reflect acute short-term effects and that further changes in lumbar CSF pressure may occur over time.

Ornstein and associates examined the effect of 1.0 and 1.5 MAC desflurane and isoflurane on cerebral blood flow in patients with intracranial mass lesions. They found that desflurane and isoflurane had similar effects on absolute cerebral blood flow, lack of change in cerebral blood flow in response to increasing concentration of either agent, and preservation of carbon dioxide reactivity at 1.25 MAC of either agent. However, they did not measure cerebral blood flow before administration of the inhalation anesthetic or study patients without an inhalation anesthetic agent. Lacking such controls, the possibility that 1.0 MAC of either desflurane or isoflurane may cause a significant and maximal change in cerebral blood flow cannot be excluded. The relatively short time course of the increase in lumbar CSF pressure in our patients (fig. 1) suggests that it is
Table 2. Lumbar Cerebrospinal Fluid Pressure (LCSFP), Cerebral Perfusion Pressure (CPP), and Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Propofol</th>
<th>Desflurane</th>
<th>Isoflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>0.5 MAC</td>
<td>1.0 MAC</td>
</tr>
<tr>
<td>LCSFP Last</td>
<td>9 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>Maximum</td>
<td>9 ± 2</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>CPP Last</td>
<td>56 ± 11</td>
<td>57 ± 12</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>Minimum</td>
<td>54 ± 11</td>
<td>54 ± 12</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>HR Last</td>
<td>64 ± 8</td>
<td>61 ± 8</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Maximum</td>
<td>64 ± 8</td>
<td>62 ± 9</td>
<td>62 ± 9</td>
</tr>
<tr>
<td>SBP Last</td>
<td>104 ± 15</td>
<td>103 ± 15</td>
<td>99 ± 14</td>
</tr>
<tr>
<td>Minimum</td>
<td>101 ± 15</td>
<td>98 ± 14</td>
<td>98 ± 14</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
Baseline = value (1 min median) immediately prior to the 20-min study period; HR = heart rate; SBP = systolic blood pressure; Maximum = peak value (1 min median); Last = last value (1 min median) during a 10-min study period; Minimum = lowest value (1 min median); MAC = minimum alveolar concentration.

Fig. 1. Data from a representative study, panel illustrates changes in cerebral blood pressure.

Secondary to changes in cerebral blood volume rather than changes in CSF production and reabsorption, however, we did not measure cerebral blood flow or cerebral blood volume and thus we cannot comment further on the potential relation of these factors and lumbar CSF pressure.

Several studies in animals, primarily dogs, have examined the effects of desflurane on cerebral physiologic characteristics.2-7 Desflurane is a potent cerebral vasodilator in dogs, producing dose-dependent (0.5 to 2.0 MAC) decreases in cerebral vascular resistance that, during induced hypotension, result in significant decreases in cerebral perfusion pressure and cerebral blood flow.2 When mean arterial pressure is maintained, concomitant increases in cerebral blood flow are induced. In addition, 0.5 MAC desflurane increases intracranial pressure significantly over baseline,2 whereas higher concentrations produced no further increases. Consistent with these results, we found an increase in CPP pressure with 0.5 MAC desflurane, with no additional increase at 1.0 MAC, suggesting a maximal effect at the lower dose. The time course of the increase in CPP pressure in our study also is consistent with the cerebral vasodilatory effects of desflurane in dogs.

Critique of Method
The intracranial disease of our patients was limited to the pituitary gland. No patient had clinical signs of increased intracranial pressure. Therefore we did not study patients with increased intracranial pressure. However, we predict that desflurane and isoflurane also will increase lumbar CSF pressure in such patients. If the mechanism for the increase in lumbar CSF pressure in humans proves to be cerebral vasodilation, as has been observed in dogs,8 increases in lumbar CSF pressure might be even more profound in patients with decreased intracranial elastance.

We measured lumbar CSF pressure instead of intracranial pressure. Lumbar CSF pressure measurements correlate well with intracranial pressure measurements when no disease obstructs the CSF space.9 Therefore we selected patients with no known intracranial disease that might interfere with lumbar CSF pressure measurements. In addition, before our study, we confirmed continuity in the CSF between the cranium and our site of measurement by manually compressing the internal jugular veins while observing for changes in lumbar CSF pressure.

All patients received a propofol infusion throughout our study. Although propofol has been reported to have no effect on intracranial pressure, we cannot exclude the possibility of some effect in our patients.10,11 That is, propofol-induced cerebral metabolic suppression has been suggested to interfere with cerebral flow-metabolism coupling, making the brain more prone to vasodilation by volatile agents.12 However, this hypothesized uncoupling is unlikely to be consequential in our study given the relatively low dose of propofol used. That is, although 100 µg·kg⁻¹·min⁻¹ propofol, a sedative dose, increases beta activity, it is approximately one-third the dose needed to induce burst suppression.13 Furthermore, cerebral autoregulation appears to remain intact at 200 µg·kg⁻¹·min⁻¹ propofol.14 We chose to use a propofol infusion to enable us to collect data before administering an inhalation anesthetic and in the absence of an inhalation anesthetic. Without this infusion,
DESFLURANE, ISOFURANE, AND CSF PRESSURE

Fig. 1. Data collected at 10-s intervals from a patient receiving propofol (left) and a patient receiving desflurane (right). The first panel illustrates the end-tidal desflurane concentration during each of the two consecutive 10-min study periods. The second panel illustrates the heart rate. The third panel shows the lumbar cerebrospinal fluid pressure. The fourth panel shows the blood pressure (systolic, mean, and diastolic). The vertical lines mark the beginning of each of the 10-min study periods.

We would have lacked a control group and been unable to obtain baseline measurements before administering desflurane or isoflurane.

We chose to conduct our study under conditions of normocarbia (P_{aCO_2}, 55 to 40 mmHg) because there were no preoperative clinical indications for hyperventilation; that is, none of our study patients had signs of increased intracranial pressure or computed tomographic evidence of intracranial disease outside of the pituitary gland.

We included 70% nitrous oxide as part of our baseline anesthetic to reflect our usual clinical practice. Other investigators have reported similar increases in CSF pressure in response to 0.5 MAC of either isoflurane and desflurane in the presence of 50% nitrous oxide. It is unlikely that the increases in lumbar CSF pressure in our patients were induced by nitrous oxide alone. Nitrous oxide has been shown to increase cerebral blood flow and cerebral metabolic oxygen consumption, which may increase intracranial pressure or lumbar CSF pressure, but we do not believe that it was responsible for the acute changes in lumbar CSF pressure that we observed. We administered nitrous oxide to all patients, including those in the propofol group; consequently, any nitrous oxide–induced changes in lumbar CSF pressure should be reflected equally.

The increases in lumbar CSF pressure may be gradual over time, rapid in onset followed by a sustained plateau, or have a temporary but clinically significant increase that may not be evident at the end of a 10-min study period. Therefore, for the continuously measured variables (lumbar CSF pressure, heart rate, and blood pressure), we reported peak or lowest values in addition to the values at the end of the 10-min study intervals.

We administered the volatile anesthetics for only 20 min while measuring lumbar CSF pressure. Although...
the end-tidal anesthetic concentrations (MAC values) were similar, with different blood-gas solubilities, the brain concentrations may not have had sufficient time to reach similar concentrations.

When comparing desflurane and isoflurane to the propofol group, we found statistically significant differences, and so by definition our power was sufficient. However, to detect a 10% difference between the desflurane and isoflurane groups with an alpha value of 0.05, 80% power, and assuming a standard deviation of 30% of the mean, we should have studied at least 150 patients per group. Thus, our study does not have enough power to detect a potential difference between desflurane and isoflurane.

We found that desflurane and isoflurane, at 0.5 and 1.0 MAC, increase lumbar CSF pressure in normocapnic patients with normal intracranial pressure undergoing transphenoidal hypophysectomy, and that neither the two inhalation anesthetics nor the two anesthetic concentrations of each differed significantly in their effects.

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