A Comparison of the Cerebral Hemodynamic Effects of Sufentanil and Isoflurane in Humans Undergoing Carotid Endarterectomy

William L. Young, M.D., * Isak Prohovnik, Ph.D., † James W. Correll, M.D., ‡ Noeleen Ostapovich, REEGT, § Eugene Ornstein, Ph.D., M.D., ¶ Richard S. Matteo, M.D., ** Kristy Z. Baker, M.D. ††

Prompted by reports of potentially deleterious cerebral vasodilation by the synthetic opioid sufentanil, the authors compared the effects of either isoflurane/N2O and sufentanil/N2O on cerebral blood flow (CBF), arteriovenous difference in oxygen content (AVDO2), and CBF reactivity to changes in PaCO2 during carotid endarterectomy. Cerebral blood flow was measured using the iv method of 133-Xe CBF determination and AVDO2 was measured using systemic arterial-venous venous oxygen content differences. Patients, age 68 ± 1 yr (mean ± SE), received either isoflurane (n = 10), 0.75% in O2 and N2O, 1:1; or sufentanil (n = 10), 1.5–2 μg/kg bolus and then 0.2–0.3 μg·kg⁻¹·h⁻¹ infusion in addition to O2 and N2O, 2:3. Measurements were made immediately before carotid occlusion, and then at two levels of PaCO2 (approximately 92 and 42 mmHg) after insertion of a temporary in-dwelling bypass shunt. Prior to carotid occlusion, there was no significant difference in CBF (ml·100 g⁻¹·min⁻¹) between patients receiving isoflurane (22 ± 3) or sufentanil (20 ± 2). Similarly, there was no difference in AVDO2 (vol-%) between isoflurane (4.5 ± 0.7) and sufentanil (5.4 ± 0.8) groups. Using a two-way ANOVA design with anesthetic as the between-group factor and elevation of PaCO2 as the within-group repeated measure, there was a significant effect of hyperventilation to increase CBF (P < 0.0001) and decrease AVDO2 (P < 0.001). The product of AVDO2 and CBF, which reflects cerebral metabolic oxygen consumption, remained constant (P = 0.364). There was no difference in AVDO2 or CBF between anesthetic groups. CBF reactivity to changes in PaCO2 was similar for both anesthetic regimens. The average slope of the CO2 response (ml·100 g⁻¹·min⁻¹·mmHg⁻¹) was 1.7 ± 0.5 for isoflurane and 1.1 ± 0.2 for sufentanil, respectively, and did not differ significantly. Both sufentanil and isoflurane in combination with N2O, when used in elderly patients with organic cerebrovascular disease, have similar effects on cerebrovascular hemodynamics. (Key words: Brain, cerebral blood flow; metabolism; CO2 reactivity; surgery, cerebrovascular; carotid endarterectomy. Anesthetics, volatile; isoflurane. Anesthetics, intravenous; sufentanil.)

SUFENTANIL HAS BEEN DESCRIBED as offering a greater therapeutic ratio and more hemodynamic stability than that provided by fentanyl. 1 These qualities would render sufentanil a suitable agent for use during neurovascular procedures. The effects of sufentanil on cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO2) and glucose have been investigated in animals2,3 and appear to be qualitatively similar to the cerebrovascular effects of fentanyl. 4 Both agents cause a dose-related depression of CBF and CMRO2. However, two recent reports have suggested that sufentanil may act as a cerebral vasodilator under certain conditions. 5, 6 Cerebral vasodilation may have adverse implications for anesthetic management of ischemic cerebrovascular disease, especially in the presence of focal cerebral ischemia as encountered during carotid endarterectomy. 6 This study was undertaken to compare the cerebral hemodynamic effects of sufentanil with those of isoflurane in the presence of N2O in patients undergoing carotid endarterectomy.

Methods

After institutional approval, informed consent was obtained from patients scheduled to undergo elective carotid endarterectomy. Preanesthetic medication consisted of atropine (0.4 mg/70 kg im) and oral diazepam (10 mg/70 kg). Anesthesia was induced with midazolam (0.04 mg/kg) and thiopental (4 mg/kg), with tracheal intubation facilitated by vecuronium (0.1 mg/kg). Patients received either isoflurane (n = 10), 0.75% (inspired concentration) in 1:1 N2O/O2, or droperidol, 2.5 mg, plus sufentanil (n = 10), 1.5–2 μg/kg followed by a continuous infusion of 0.2–0.3 μg·kg⁻¹·h⁻¹ and 3.2 N2O/O2. Monitoring included the use of a radial arterial catheter for blood pressure measurement and blood gas analysis, temperature probe, a capnograph, and a pulse oximeter. A Neurotrac® Spectral Analyzer (Interspec Medical, Inc., Conshohocken, PA) using a F3-P3 and F4-P4 montage was employed to monitor the EEG. Placement of CBF detectors was done after induction. Blood pressure was maintained within 20% above the preoperative ward level with an

* Assistant Professor of Anesthesiology.
† Professor of Psychiatry, Neurology and Radiology.
‡ Senior Staff Associate in Anesthesiology.
§ Associate Professor of Clinical Anesthesiology.
¶ Professor of Clinical Anesthesiology.
** Professor of Clinical Anesthesiology.
†† Resident in Anesthesiology.

Received from the Departments of Anesthesiology, Psychiatry, Neurology, Radiology, and Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, New York. Accepted for publication August 1, 1989. Supported in part by a grant from Janssen Pharmaceutica and a Biomedical Research Support Grant, Columbia University College of Physicians and Surgeons. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, California, October 1988. Address reprint requests to: Dr. Young; Department of Anesthesiology, Presbyterian Hospital, Archley Pavilion 9N, 161 Fort Washington Avenue, New York, New York 10032.

infusion of phenylephrine, if necessary. Ventilation was controlled to maintain \(P_{\text{aCO}_2}\) at approximately 35 mmHg.

After neck dissection, a catheter was advanced into the jugular vein approximately 5 cm from the angle of the mandible in a cephalad direction under direct vision by the neurosurgeon into the ipsilateral jugular bulb. Systemic arterial and jugular venous blood were sampled simultaneously during each CBF measurement for determination of arteriovenous difference in oxygen content (AVDO₂). The first CBF measurement was made after dissection and exposure of the carotid artery, after at least 1 h had elapsed from the time of induction of anesthesia. Measurement of CBF began before completion of jugular catheter insertion in several cases, causing a 5–10-min temporal difference between the injection of the CBF tracer and jugular venous sampling. Surgical and anesthetic conditions remained constant during this period.

All patients had a temporary indwelling carotid shunt inserted. When carotid blood flow was re-established after shunt insertion, a second CBF measurement was done. The \(P_{\text{aCO}_2}\) was then increased 10 mmHg by addition of carbon dioxide to the inspired gas mixture and a third CBF was measured. The two measurements at different levels of \(P_{\text{aCO}_2}\) during the period with the temporary bypass shunt in place were used to calculate CBF reactivity.

The CBF device, the Novo Cerebrograph 10a® (Novo Diagnostic Systems, Bagsvaerd, Denmark) is a self-contained data collection system with ten sodium iodide detectors encased in cylindrical lead collimators. The middle cerebral artery territory over each hemisphere was covered by five detectors. The channel analyzer window was set to include the 81 KeV photo peak of 133-Xenon. Approximately 20 mCi of 133-Xenon in sterile saline was injected intravenously for each CBF measurement, resulting in peak count rates between 200 and 600 cps. A small plastic catheter was present in the endotracheal tube for sampling of end-tidal gas to determine tracer activity. The resultant air activity curve was used in deconvolution of the head curves and to correct for recirculation of tracer. Clearance was recorded for 11 min. Data were transferred to a PDP 11/73 computer for visual inspection of the individual detector head curves and their corresponding curve fits. The technical reliability of this methodology and equipment has been previously described.

The CBF data are expressed as the Initial Slope Index (ISI). This index reflects flow in both fast and slow compartments of the brain, but is weighted towards the fast compartment. It is inherently more stable than pure gray matter flow (Fg) during low-flow conditions.

In our experience, the ISI reliably describes hemodynamic changes in both awake and anesthetized patients.

The \(P_{\text{aO}_2}\) and \(P_{\text{vO}_2}\) were determined using a standard blood gas analyzer (Instrumentation Laboratory 1303).

Oxygen content was calculated as: \((1.34)(\text{Hb})(\% \text{ Saturation}) + (0.003)(P_{\text{aO}_2}) + (1.34)(\text{Hb})(\% \text{ Saturation}) + (0.003)(P_{\text{vO}_2})\). Oxygen saturation was derived from the nomograms described by Kelman and Nunn.

Patients were categorized into four preoperative risk groups using the grading system described by Sundt et al. based upon angiographic findings, neurological status, and general health. For the purpose of analysis, patients were grouped into lower risk (groups 1 and 2) and higher risk (groups 3 and 4) categories.

To maximize statistical reliability and power in the testing of the overall effects of anesthetics, the mean of the ten CBF detectors covering both MCA supply territories was taken as an index of global CBF. The global CBF reactivity to carbon dioxide was calculated as the absolute increase in CBF in per mmHg change in \(P_{\text{aCO}_2}\) (ml·100 g⁻¹·min⁻¹·mmHg⁻¹) and as the percent increase in CBF per mmHg increase in \(P_{\text{aCO}_2}\). Hemispheric CBF and CO₂ reactivity were also examined. Data were analyzed using ANOVA. If there were significant differences, post hoc testing was done using the Fisher progressive least significant differences test. Nonparametric data were compared using contingency analysis (chi-square). The threshold for significance was taken as \(P < 0.05\). All results are expressed as mean ± SE.

**Results**

Clinical characteristics of the study population are shown in table 1. There were no differences between anesthetic groups with respect to preoperative diagnosis groups, risk grouping, preoperative medications, gender, site of operation, or intraoperative use of phenylephrine.

Physiological results are summarized in table 2 for the baseline measurement prior to carotid occlusion. Global

<table>
<thead>
<tr>
<th>Table 1. Study Population Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Gender (female/male)</td>
</tr>
<tr>
<td>Site (left/right)</td>
</tr>
<tr>
<td>Risk group (high/low)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Prior cerebrovascular accident</td>
</tr>
<tr>
<td>Nitrates</td>
</tr>
<tr>
<td>3-adrenergic blocking drugs</td>
</tr>
<tr>
<td>Calcium channel blocking drugs</td>
</tr>
<tr>
<td>Other antihypertensive drugs</td>
</tr>
<tr>
<td>% Ipsilateral carotid stenosis</td>
</tr>
<tr>
<td>% Contralateral carotid stenosis</td>
</tr>
</tbody>
</table>

All differences are NS. Age and % stenosis are expressed as mean ± SE. Risk groups refer to the system described by Sundt et al. High-risk patients were in the Sundt et al. groups 3 and 4 and low-risk patients were in Sundt et al. groups 1 and 2.
CEREBRAL EFFECTS OF SUFENTANIL VERSUS ISOFLURANE

<table>
<thead>
<tr>
<th>TABLE 2. Cerebral Blood Flow (CBF), Arteriovenous Oxygen Content Difference (AVDO₂), Mean Arterial Blood Pressure (MABP), and Other Physiological Variables Immediately Prior to Carotid Occlusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
</tr>
<tr>
<td>CBF (ml·100 g⁻¹·min⁻¹)</td>
</tr>
<tr>
<td>AVDO₂ (vol-%)*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. No significant differences between groups.

* n = 9 for both groups.

CBF and AVDO₂, as well as other measured variables, were similar in both groups. In one patient in each of the two anesthetic groups, it was not possible to obtain jugular venous blood for AVDO₂ calculation because of technical problems. The AVDO₂ values given are for the remaining nine patients in each group. When hemispheric mean CBF values were compared, there were no significant differences.

Measurements carried out during the period of temporary bypass shunting are summarized in table 3. Individual patient CBF responses to changes in PaCO₂ are shown in figures 1 and 2. Eight patients were excluded from this portion of the study as data were lost in two and surgical time constraints precluded increasing PaCO₂ in six. Using a two-way ANOVA design with anesthetic as the between-group factor and elevation of PaCO₂ as the within-group repeated measure, there was a significant effect of hypercarbia to increase CBF (P < 0.0001) and decrease AVDO₂ (P < 0.001) (fig. 3). The product of AVDO₂ and CBF, which reflects cerebral metabolic oxygen consumption, remained constant (P = 0.564). There was no difference in AVDO₂ or CBF between anesthetic groups. There was a similar CBF reactivity to changes in PaCO₂ for both anesthetic regimens. The average slope of the CO₂ response (ml·100 g⁻¹·min⁻¹·mmHg⁻¹) was 1.7 ± 0.2 for isoflurane and 1.1 ± 0.2 for sufentanil (NS), corresponding to a relative percentage change (% change/mmHg) from the baseline lower PaCO₂ of 5.4 ± 0.6 and 3.4 ± 0.4 (P < 0.05), respectively. There was no difference in mean hemispheric CO₂ reactivity.

In the sufentanil group of patients, the EEG pattern prior to carotid occlusion demonstrated predominant peaks in the 2–4 Hz frequency range with amplitudes of 40–60 µV. In the patients receiving isoflurane, the baseline EEG demonstrated frequencies in the 1–10 Hz range symmetrically with a more prominent peak in the 8–9 Hz range, with amplitudes ranging from 40–80 V. There were no dramatic EEG changes with carotid occlusion. One patient receiving sufentanil had an increase in the 2–4 Hz range and two patients receiving isoflurane had slight loss of higher frequencies and decrease in total power with application of the carotid cross-clamp. The EEG showed improvement immediately following shunt insertion in all three cases. There was no apparent relationship between the occurrence of EEG change and any physiological variables, percent carotid stenosis, or risk grouping.

Three patients receiving sufentanil required the use of naloxone (0.04, 0.12, and 0.4 mg iv) to obtain a satisfactory respiratory rate (greater than 8/min) at the conclusion of surgery before extubation of the trachea. No patients emerged from anesthesia with a new neurological deficit.

**Discussion**

This study demonstrates that two different anesthetic techniques yielded no difference in global CBF or AVDO₂ in the period immediately prior to carotid occlusion or

<table>
<thead>
<tr>
<th>TABLE 3. Cerebral Blood Flow (CBF), Arteriovenous Oxygen Content Difference (AVDO₂), Mean Arterial Blood Pressure (MABP), CO₂ Reactivity and Other Physiological Variables during Baseline (A) and CO₂ Challenge (B).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>MABP (mmHg)</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
</tr>
<tr>
<td>CBF (ml·100 g⁻¹·min⁻¹)</td>
</tr>
<tr>
<td>AVDO₂ (vol-%)</td>
</tr>
<tr>
<td>SLOPE of CBF response (ml·100 g⁻¹·min⁻¹·mmHg⁻¹)</td>
</tr>
<tr>
<td>% change in CBF (%/mmHg)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE.
* Significantly different from baseline.
† Significantly different from isoflurane.
during the period of temporary bypass shunting at two different levels of \( \text{PaCO}_2 \). Furthermore, CBF reactivity to changes in \( \text{PaCO}_2 \) is qualitatively similar for both anesthetic regimens.

In this study, we studied the cerebrovascular effects of two clinically acceptable regimens of isoflurane or sufentanil, in combination with \( \text{N}_2\text{O} \). Although the two regimens chosen afforded a smooth induction, similar degrees of autonomic stability, rapid emergence, and appeared to be clinically comparable, the doses used for each agent may not be strictly equivalent in terms of MAC.

The values for CBF are comparable to values we have previously reported from a comparison of isoflurane, halothane, and fentanyl under similar conditions.\(^{18} \) Compared to other descriptions of CBF during carotid endarterectomy,\(^{19,21} \) our relatively low values for CBF are in part due to the slightly reduced body temperature in our population (about 35.5\(^\circ\)C), mild hypocarbia, and the methodology employed. Despite mathematical correction for the contribution of the extracerebral compartments,\(^{10} \) the iv method of CBF determination and weighted mean blood flow values such as the ISI underestimate true brain flow.\(^{22} \) This effect may be exaggerated in patients that already have decreased CBF secondary to cerebrovascular disease, as may be expected in the patient population studied.\(^{19} \) However, the influence of tracer washout from the external carotid artery distribution of scalp and muscle has been found to be negligible during general anesthesia for carotid endarterectomy.\(^{23} \) There is good agreement between CBF values obtained during steady-state conditions from direct intracarotid injection and from iv injection of tracer.\(^{24,25} \)

The jugular blood sampled for determination of arteriovenous oxygen content difference represents venous drainage from a somewhat different mixture of cortical and deep brain structures than that seen by the cortical CBF detector array, which primarily covered the territory of the middle cerebral artery (MCA). Therefore, the product of global cortical CBF and AVDO\(_2\) does not, strictly speaking, reflect true CMRO\(_2\). Using weighted CBF indices such as the ISI that underestimate CBF further complicate the issue. However, despite these caveats, the product of CBF and AVDO\(_2\) serves as a relative measure of cerebral oxygen consumption. Using similar methodology, Todd and Drummond\(^{26} \) demonstrated dose-related differences in the effect of halothane and isoflurane on feline CMRO\(_2\) and Obrist et al.\(^{27} \) identified a stratification of head injury patients based on the coupling of CBF to CMRO\(_2\). In this study, we observed that increasing \( \text{PaCO}_2 \) significantly increased CBF and decreased AVDO\(_2\); their product remained constant. There was no effect of anesthetic group on this response. The lack of a demonstrable relative difference between anesthesia groups with respect to the product of CBF and AVDO\(_2\) should be valid. Given the limitations of the methodology, this strongly implies that the effect of isoflurane/\( \text{N}_2\text{O} \) and sufentanil/\( \text{N}_2\text{O} \) on CMRO\(_2\) is similar.
CEREBRAL EFFECTS OF SUFENTANIL VERSUS ISOFLURANE

Figure 3. Comparison of cerebral blood flow (CBF) and arteriovenous difference in oxygen content (AVDO₂) values for sufentanil (open circles) and isoflurane (closed circles) groups during the period of temporary bypass shunting. The X axis is PaCO₂ for both the upper and lower panels. There was a significant effect of PaCO₂ level to increase CBF (P < 0.0001) and decrease AVDO₂ (P < 0.001); the product of CBF and AVDO₂, which reflects cerebral metabolic oxygen consumption, remained constant (P = 0.364). There was no significant effect of anesthesia group.

The measurement of cerebrovascular CO₂ reactivity during temporary bypass shunting minimized the difference between the two patient populations, i.e., after the shunt was in place, both groups of patients had an identical degree of ipsilateral “stenosis.” The CO₂ reactivity values are similar to ones reported previously during carotid endarterectomy.²⁸,²⁹ One possible reason for the observed difference between anesthetic groups in relative CO₂ reactivity may have been the slight difference in the PaCO₂ range. An intriguing question that deserves further study is whether or not inhalational anesthesia increases sensitivity to changes in PaCO₂ compared with that in the presence of opioids. Although this may be of minimal importance in the control of increased intracranial pressure, such a difference may have some importance concerning the relative ability of different anesthetic regimens to influence the outcome from cerebral ischemia by hemodynamic mechanisms, i.e., inverse or “Robin Hood” steal.³⁰,³¹

The effects of most anesthetic agents on quantitative CBF responses of the human cerebral circulation to changes in PaCO₂ have not been well characterized, other than during cardiopulmonary bypass³² and younger patients with brain tumors.³³ The sensitivity of CBF to PaCO₂ changes has been reported to be similar for awake and anesthetized subjects, but halothane causes a somewhat steeper response to similar increases in PaCO₂.³⁴,³⁵ In the cat and the rabbit, isoflurane appears to enhance CO₂ responsiveness compared with halothane.³⁶,³⁷ In the dog, fentanyl/droperidol/N₂O anesthesia resulted in a
similar CBF response between a Paco2 of 40 and 60 mmHg compared with halothane/N2O. However, the CBF response between a Paco2 of 20 and 40 mmHg was greater for halothane/N2O. In a similar preparation by the same group, there was no difference in CO2 reactivity between halothane and isoflurane. During halothane anesthesia, hypercapnia with a Paco2 in the range of 50 mmHg may result in decreased flow to ischemic areas, and this has been attributed to “cerebral steal.” Relative CO2 reactivity in patients with cerebrovascular disease has not been adequately compared for different anesthetic regimens.

The influence of N2O in this investigation deserves some comment. Attention has been called recently to the influence of N2O on the interpretation of results of studies that include N2O as part of the anesthetic or its use as a “control” state. As argued by Michenfelder, studies that employ N2O as a control state generally tend to show opioids to be cerebral vasoconstrictors. Conversely, those investigations without N2O generally show opioids to have minimal effect, or in a few cases, tended to cause increased CBF. There are at least two possible speculations in this regard as concerns our results. One may view our results as indirect evidence that isoflurane and sufentanil, in the doses employed in this study, have similar effects on cerebrovascular resistance. This also implies that sufentanil is similar to fentanyl in its cerebrovascular effects in man, based on a comparison to our previously reported data. On the other hand, one could argue that the presence of N2O obscures the true vasoactive nature of either drug.

We conclude that during maintenance of anesthesia in patients undergoing carotid endarterectomy with clinically comparable regimens of either sufentanil or isoflurane in nitrous oxide, there is remarkably little difference in their effects on cerebral hemodynamics. It remains to be demonstrated whether sufentanil may cause transient cerebral vasodilation when given rapidly as a bolus. Further work is needed to prospectively define the influence of narcotic versus inhalational anesthetic techniques on electrophysiological or clinical outcome from cerebral ischemia.

The authors wish to thank Angela Wang, Ayelet Barkai, and Grace Park for expert technical assistance; Joyce Ouchi for assistance in preparation of the manuscript; Darin Gitelman, M.D. and Clarence Williams, B.A. for computer assistance; T. S. T. Wang, Ph.D. and Philip O. Alderson, M.D. for assistance with radiopharmaceuticals; and Donald O. Quest, M.D. for helpful suggestions.

References


37. Scheller MS, Todd MM, Drummond JC: Isoflurane, halothane, and regional cerebral blood flow at various levels of P CO2 in rabbits. ANESTHESIOLOGY 64:558–604, 1986

