Effects of Sufentanil on Cerebral Hemodynamics and Intracranial Pressure in Patients with Brain Injury

Christian Werner, M.D.,* Eberhard Kochs, M.D.,† Hanswerner Bause, M.D.,† William E. Hoffman, Ph.D.,‡ Jochen Schulte am Esch, M.D.§

Background: The current study investigates the effects of sufentanil on cerebral blood flow velocity and intracranial pressure (ICP) in 30 patients with intracranial hypertension after severe brain trauma (Glasgow coma scale <6).

Methods: Mechanical ventilation (FiO2, 0.25–0.4) was adjusted to maintain arterial carbon dioxide tensions of 28–30 mmHg. Continuous infusion of midazolam (200 µg/kg/h intravenously) and fentanyl (2 µg/kg/h intravenously) was used for sedation. Mean arterial blood pressure (MAP, mmHg) was adjusted using norepinephrine infusion (1–5 µg/min). Mean blood flow velocity (Vmax, cm/s) was measured in the middle cerebral artery using a 2-MHz transcranial Doppler sonography system. ICP (mmHg) was measured using an epidural probe. After baseline measurements, a bolus of 5 µg/kg sufentanil was injected, and all parameters were continuously recorded for 30 min. The patients were assigned retrospectively to the following groups according to their blood pressure responses to sufentanil: group 1, MAP decrease of less than 10 mmHg; and group 2, MAP decrease of more than 10 mmHg.

Results: Heart rate, arterial blood gases, and esophageal temperature did not change over time in all patients. In 18 patients, MAP did not decrease after sufentanil (group 1). In 12 patients, sufentanil decreased MAP > 10 mmHg from baseline despite norepinephrine infusion (group 2). ICP was constant in patients with maintained MAP (group 1) but was significantly increased in patients with decreased MAP. Vmax did not change with sufentanil injection regardless of changes in MAP.

Conclusions: The current data show that sufentanil (3 µg/kg intravenously) has no significant effect on middle cerebral artery blood flow velocity and ICP in patients with brain injury, intracranial hypertension, and controlled MAP. However, transient increases in ICP without changes in middle cerebral artery blood flow may occur concomitant with decreases in MAP. This suggests that increases in ICP seen with sufentanil may be due to autoregulatory decreases in cerebral vascular resistance secondary to systemic hypotension. (Key words: Analgesics opioid; Sufentanil. Measurement technique: cerebral blood flow velocity; intracranial pressure; transcranial Doppler sonography.)

SUFENTANIL has been recommended as a potent and short-acting opioid for use during neuroanesthesia and neurocritical care. However, studies concerning the effects of sufentanil on cerebral blood flow (CBF) have shown inconsistent results in animals and humans. In dogs and rats, CBF may increase or decrease as much as 50% after sufentanil administration (5–200 µg/kg). In awake, unpremedicated patients, sufentanil infusion (1.7 µg/kg) caused a 25% increase in CBF velocity concomitant with decreased electroencephalographic spectral edge frequency. In contrast, CBF was unchanged in healthy volunteers or rabbits with cryogenic brain injury after sufentanil (0.5–2.0 µg/kg). Controversy also persists concerning the effects of sufentanil on intracranial pressure (ICP). In dogs, sufentanil (2–200 µg/kg) did not change ICP. This is consistent with studies in patients with brain injury in whom sufentanil (0.5–2.0 µg/kg) had no impact on ICP. In contrast, studies in patients with brain tumor or brain injury suggest that sufentanil increases ICP by 53%–100% during induction of anesthesia (1.0 µg/kg) or during sedation in intensive care (0.6–1.5 µg/kg). It has been hypothesized that an ICP increase that fol-
lows sufentanil may be related to either increased CBF or decreased cerebral vascular resistance secondary to systemic hypotension. The current study investigates the effects of sufentanil on CBF velocity as an index of CBF and on ICP in patients with head injury with and without decreased arterial blood pressure.

Methods and Materials

Thirty patients with brain injury (Glasgow coma scale <6, m = 21, f = 9) were studied between days 3 and 5 after admission to the intensive care unit after approval from the institutional and National Institutes of Health review boards. The patients presented diffuse bitemporal brain edema on the computed tomography scan. All patients were placed in a 15–20-degree head-up position. Mechanical ventilation (FiO2, 0.25–0.4) was adjusted to maintain arterial carbon dioxide tension at 28–30 mmHg. Continuous infusion of midazolam (150–250 μg·kg·h⁻¹ intravenous) and fentanyl (1–5 μg·kg⁻¹·h⁻¹ intravenously) was used for sedation for a period of 24 h before the investigation. Sedation was titrated according to systemic hemodynamic and clinical parameters. Invasive mean arterial blood pressure (MAP, mmHg) was continuously measured via the radial artery. An attempt was made to maintain MAP constant over time (MAP > 85 mmHg) using a norepinephrine infusion (1–5 μg/min). Monitoring also included measurement of heart rate (beats/min), arterial blood gases, arterial pH, and esophageal temperature. CBF velocity was measured using transcranial Doppler sonography (Transpect, Medasonics, Mountain View, CA). ICP (mmHg) was measured using an epidural probe (Epidyn, Braun), which was inserted under surgical conditions at least 2 days before the investigation. After baseline measurements, a bolus of 3 μg/kg sufentanil was injected over 10 s, and all parameters were continuously recorded for 30 min. The patients were assigned to the following groups according to clinically relevant blood pressure responses: group 1, patients in whom MAP decreased less than 10 mmHg, and group 2, patients in whom MAP decreased more than 10 mmHg.

Transcranial Doppler Sonography Measurements

CBF velocity was continuously monitored by trans-temporal approach using a pulsed 2-MHz transcranial Doppler sonography system (Transpect). The system operates with 100 mW ultrasonic intensity and pulse repetition frequencies between 4.96 and 20.52 kHz. A range-gate is used to adjust the ultrasonic focus electronically in steps of 2 mm. The axial extension of the sample volume measures 10 mm according to a burst width of 15 μs. The ultrasonic sample volume was focused on the proximal segment (M1) of the right middle cerebral artery (MCA). To exclude abnormalities of the anatomy of the circle of Willis, the MCA (M1) was identified by insonating the internal carotid bifurcation (biphasic signal). The insonation depth was reduced in decrements of 2 mm until the antegrade flow profile of the MCA (M1) was recorded. The transcranial Doppler sonography probe was fixed in a frame using skin adhesive to maintain the insonation angle and insonation depth constant over time. Signals were computed using spectral analysis by 128-point fast Fourier transformation. After Doppler shift calculation and flow direction discrimination, the instantaneous mean blood flow velocity (Vmean, cm/s) was digitally displayed for each flow spectrum on a video monitor. The recorded waveforms were inspected to verify that the calculated numbers were not due to artifacts.

Statistics

All data are reported as mean ± SD. After two-way analysis of variance, unpaired or paired t-tests were used for post hoc comparisons where appropriate (Bonferroni corrections for multiple comparisons). In all tests, statistical significance was assumed at a P < 0.05.

Results

Table 1 shows systemic hemodynamic variables, MCA mean blood flow velocity, arterial blood gases, arterial pH, and esophageal temperature for group 1 (MAP constant) and group 2 (MAP decrease >10 mmHg). Heart rate, arterial blood gases, and esophageal temperature did not change over time in all patients. In 18 patients, MAP was constant after sufentanil infusion (group 1). In 12 patients, MAP decreased 17% from baseline despite norepinephrine infusion (group 2). Vmean did not change with sufentanil infusion regardless of changes in MAP. Changes in ICP were related to changes in MAP (fig. 1). ICP was constant in patients with maintained MAP (group 1) but was significantly increased in patients in whom MAP decreased. Figure 2 shows the original tracings for arterial blood pressure, ICP, and MCA blood flow velocity in a patient with...
Table 1. Systemic Hemodynamic Data, MCA Mean Blood Flow Velocity, Arterial Blood Gases, Arterial pH, and Esophageal Temperature before and after Sufentanil (3 μg/kg)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>HR (beats/min)</th>
<th>MAP (mmHg)</th>
<th>Vmean (cm/s)</th>
<th>PAO2 (mmHg)</th>
<th>PAVO2 (mmHg)</th>
<th>pH</th>
<th>Temperature (°C)</th>
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HR = heart rate; MAP = mean arterial pressure; Vmean = mean blood flow velocity.
Values are mean ± SD. Group 1, n = 18; Group 2, n = 12.
* P < 0.05 versus baseline within group.

Discussion

The current study shows that sufentanil (3 μg/kg) does not change the MCA mean blood flow velocity and ICP in patients with brain injury and increased intracranial pressure. In addition, sufentanil did not change the blood gases and acid-base balance. There was no change in MAP after sufentanil injection. However, sufentanil caused an increase in cerebral blood flow velocity, which may be due to decreased cerebrovascular resistance. This suggests that increased ICP is not related to increased CBF.

The effects of sufentanil on intracranial hemodynamics and blood gases were not significant. In awake paralyzed dogs, sufentanil increased the MCA mean blood flow velocity and decreased the arterial oxygen content. This suggests that increased CBF is related to decreased cerebrovascular resistance. In addition, sufentanil increased the cerebral blood flow velocity, which may be due to decreased cerebrovascular resistance. This suggests that increased ICP is not related to increased CBF.
The effects of sufentanil on ICP are also controversial. Studies in patients with brain tumor but normal ICP have shown that 1 μg/kg sufentanil may increase ICP during nitrous oxide/oxygen anesthesia.11 Sperri et al.12 and Albanese et al.13 found increased ICP after infusion of 0.6–1.13 μg/kg sufentanil in midazolam- or propofol-sedated patients with brain injury with normal and increased ICP. This is consistent with the increased ICP in halothane-anesthetized rabbits with cryogenic brain injury given 20 μg/kg sufentanil.8 However, MAP decreased significantly with sufentanil in all of these studies. In contrast, ICP did not change in pirritamide-anesthetized dogs with and without increased intracranial elastance after 2 μg/kg intravenous sufentanil.9 This is consistent with studies in anesthetized and sedated patients with normal and increased ICP, in whom sufentanil (0.4–2.0 μg/kg) had no effect on ICP or brain retractor pressure.10,11 During the current study, a dose of 3 μg/kg intravenous sufentanil did not change ICP in fentanyl/midazolam-sedated patients with increased baseline ICP as long as MAP was maintained constant. These data suggest that the ICP/volume responses to sufentanil are probably less a function of different levels of background anesthesia and sedation than of cerebrovascular resistance changes associated with systemic hypotension.

During the current study, the response of ICP was related to changes in MAP. We found a clinically relevant increase in ICP only in patients with concomitant decrease in MAP (12 of 50 patients). These patients did not differ in Glasgow coma scale, Pao₂, or other clinical variables from the patients in whom MAP and ICP did not change. Although the changes in ICP and MAP in these patients may be coincidental, this is consistent with all the previous studies showing increased ICP only with decreased MAP after sufentanil.9,10,11 Several studies have shown that decreasing ICP stimulates cerebral vasodilation to maintain CBF constant (i.e., CBF autoregulation).15–17 This supports the current data, whereby CBF (as measured using transcranial Doppler sonography) remained unchanged regardless of the status of MAP. However, autoregulatory decreases in cerebral vascular resistance are associated with concomitant increases in cerebral blood volume and ICP.15,16 This is consistent with the view that increased ICP seen with sufentanil is due to autoregulatory increases in cerebral blood volume secondary to systemic hypotension.

Sufentanil may decrease reabsorption of cerebral spinal fluid, thus increasing cerebral spinal fluid volume.18 Therefore, sufentanil may increase ICP, particularly if the individual ICP/volume curve has reached the limit of compensatory potential. However, the turnover of production and reabsorption dynamics of cerebral spinal fluid is too slow to make this mechanism likely to be responsible for the immediate ICP increase in our patients. Opioids may induce seizure activity, cerebral hypermetabolism, and neuronal necrosis.19,20 This may increase CBF and ICP during high intracranial elastance. However, studies in humans have shown that infusion of a large dose of sufentanil (50–100 μg/min) decreases the electroencephalogram to lower frequencies without evidence of seizure activity.

References:


Fig. 1. Changes in mean arterial blood pressure (Δ MAP, mmHg) and intracranial pressure (Δ ICP, mmHg) during baseline and after sufentanil (3.0 μg/kg) in groups 1 and 2 (mean ± SD, *P < 0.05 vs. group 1).
SUFENTANIL, INTRACRANIAL HEMODYNAMICS, AND ICP

Fig. 2. Original tracings of arterial blood pressure (AP, mmHg), intracranial pressure (ICP, mmHg), and transcranial Doppler sonography flow velocity (cm/s) before and after sufentanil in one patient of group 2. Mean arterial blood pressure decreased from 95 to 72 mmHg, and ICP increased from 19 to 28 mmHg.

without evidence of seizure activity. This is consistent with a constant MCA blood flow velocity during the current study. These data suggest that decreases in reabsorption of cerebral spinal fluid or seizure activity in response to 3 μg/kg sufentanil did not occur.

A confounding factor during the current study may be the presence of sedation with midazolam and fentanyl. Midazolam22-25 and fentanyl24-26 produce dose-dependent cerebral vasoconstriction in animals and humans. The presence of these drugs as a clinically required background sedation may have obscured potential increases in CBF and/or ICP during sufentanil administration. However, previous studies have shown sufentanil-induced increases in CBF or ICP in paralyzed, awake dogs, in midazolam- or propofol-sedated, patients with brain injury, and in patients anesthetized with thiopental/nitrous oxide.5,11-13 This indicates that sufentanil may produce increases in CBF and ICP even in the presence of stress- or drug-induced cerebral vasoconstriction, and it seems unlikely that alterations in CBF and/or ICP were blunted by background sedation.

Norepinephrine infusion was used to control MAP before and after sufentanil. Studies in humans and baboons have shown that intracarotid infusion of norepinephrine in doses that caused a minor increase in MAP did not change CBF.27,28 In contrast, experiments in rabbits suggest that norepinephrine may produce cerebral vasodilation.29 The impact of norepinephrine infusion on the current findings is unclear. It is possible that norepinephrine produced cerebral vasoconstriction in our patients. This may antagonize the potential cerebral vasodilation induced by sufentanil. It is also possible that norepinephrine-induced cerebral vasodilation resulted in a high baseline CBF. This may have masked an increase in CBF after sufentanil.

In conclusion, sufentanil does not change MCA blood flow velocity and ICP in patients with brain injury with intracranial hypertension and controlled MAP. However, increased ICP may occur concomitant with a decreased MAP after sufentanil. This increased ICP is not connected to increased CBF and appears to be related to an autoregulatory decrease in cerebral vascular resistance secondary to systemic hypotension.15-17 The current results show that sufentanil can be used in hypoxic patients with increased intracranial clausole and high ICP as long as arterial blood pressure is maintained constant.

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References


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