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Cerebral Hemodynamic Effects of Morphine and Fentanyl in Patients with Severe Head Injury

Absence of Correlation to Cerebral Autoregulation

Miriam de Nadal, M.D., Francisca Munar, M.D.,* M. Antonia Poca, M.D.,† Joan Sahuquillo, M.D.,‡ Angel Garnacho, M.D.,§ José Rosselló, M.D.‖*

Background: **The current study investigates the effects of morphine and fentanyl upon intracranial pressure and cerebral blood flow estimated by cerebral arteriovenous oxygen content difference and transcranial Doppler sonography in 30 consecutive patients with severe head injury in whom cerebrovascular autoregulation previously had been assessed.**

Methods: **Patients received morphine (0.2 mg/kg) and fentanyl (2 μg/kg) intravenously over 1 min but 24 h apart in a randomized fashion. Before study, carbon dioxide reactivity and autoregulation were assessed. Intracranial pressure, mean arterial blood pressure, and cerebral perfusion pressure were repeatedly monitored for 1 h after the administration of both opioids. Cerebral blood flow was estimated from the reciprocal of arteriovenous oxygen content difference and middle cerebral artery mean flow velocity using transcranial Doppler sonography.**

Results: **Although carbon dioxide reactivity was preserved in all patients, 18 patients (56.7%) showed impaired or abolished autoregulation to hypertensive challenge, and only 12 (43.3%) had preserved autoregulation. Both morphine and fentanyl caused significant increases in intracranial pressure and decreases in mean arterial blood pressure and cerebral perfusion pressure, but estimated cerebral blood flow remain unchanged. In patients with preserved autoregulation, opioid-induced intracranial pressure increases were not different than in those with impaired autoregulation.**

Conclusions: **The authors conclude that both morphine and fentanyl moderately increase intracranial pressure and decrease mean arterial blood pressure and cerebral perfusion pressure but have no significant effect on arteriovenous oxygen content difference and middle cerebral artery mean flow velocity in patients with severe brain injury. No differences on intracranial pressure changes were found between patients with preserved and impaired autoregulation. Our results suggest that other mechanisms, besides the activation of the vasodilatory cascade, also could be implicated in the intracranial pressure increases seen after opioid administration. (Key words: Cerebral blood flow; head trauma; intracranial pressure.)**

MORPHINE and fentanyl are the two most commonly used opioids for the analgesia of critically ill patients and, particularly, of patients suffering head trauma.[1,2] They are routinely used in patients with severe head injury as part of the management of increased intracranial pressure (ICP). However, the cerebrovascular effects of such drugs remain controversial. Studies in laboratory animals and humans have shown increases, decreases. or no change in ICP after opioid administration.[3–14] Most of these studies find a concomitant decrease in systemic arterial pressure and, recently, it has been suggested that reduced mean arterial blood pressure (MABP) could in fact be responsible for the increases in ICP observed after the administration of potent opioids such as sufentanil.[6] In patients with low intracranial compliance and intact autoregulation, reduced MABP would be expected to result in vasodilation, increased blood volume, and thus increased ICP.

The status of cerebrovascular autoregulation could be an important factor in the ICP increases reported after opioid administration. Some authors have suggested that upper and lower thresholds for autoregulation are usually preserved but are shifted to the right in patients after

* Staff Anesthetist, Department of Anesthesiology.

† Staff Neurosurgeon, Department of Neurosurgery.

‡ Associate Professor, Department of Neurosurgery, and Chairman, Neurotraumathology Research Unit.

§ Chairman, Neurotraumathology Intensive Care Unit.

‖ Associate Professor, Department of Preventive Medicine and Epidemiology.

From the Departments of Anesthesiology, Neurosurgery, and Preventive Medicine and Epidemiology and the Neurotraumathology Research Unit, Vall d'Hebron University Hospitals, Barcelona, Spain. Submitted for publication February 11, 1999. Accepted for publication July 19, 1999. Supported by grant no. 98/1385 from the Fondo de Investigaciones Sanitarias de la Seguridad Social, Madrid, Spain; and grant no. 1031/97 from the Marato TV3, Barcelona, Spain. Presented in part at the Tenth International Symposium on Intracranial Pressure and Neuromonitoring in Brain Injury, Williamsburg, Virginia, May 25–29, 1997.

Address reprint requests to Dr. de Nadal: Unidad de Neurotraumatología, Hospital de Traumatología, Hospitals Vall d'Hebron, Paseo Vall d'Hebron 119-129, 08035 Barcelona, Spain. Address electronic mail to: mdenadal@compuserve.com

severe head trauma.[15] However, others have demonstrated that autoregulation may be impaired or abolished in many of these patients.[16–20] Evaluation of autoregulatory status can be performed using arteriojugular venous oxygen content difference (AVD_{O_2}) as an estimate of cerebral blood flow (CBF).[16,17,21] If we accept the fact that cerebral metabolic rate of oxygen (CMR_{O_2}) is constant during the test, CBF is directly proportional to the reciprocal of AVD_{O_2} ($CBF = CMR_{O_2}/AVD_{O_2}$, $CBF \approx 1/AVD_{O_2}$). Thus, monitoring relative changes in AVD_{O_2} permits the bedside assessment of autoregulation in the acute phase of severe head injury and can be used to monitor CBF changes. To elucidate the role of autoregulation in opioid effect upon ICP, we studied the effect of two commonly used opioids upon ICP in patients with severe head injury in whom we previously assessed the status of autoregulatory mechanisms.

Materials and Methods

Patient Population and Monitoring

After institutional approval, family informed consent was not considered necessary because both morphine and fentanyl were routinely used in the standard management of these patients (protocol number PR-HG143/95). We studied 30 patients with severe closed-head injury (postresuscitation Glasgow coma scale score ≤ 8; 23 men, 7 women) between days 1 and 3 after admission to the intensive care unit. Subjects with history of psychiatric illness, substance abuse, or previous significant systemic illnesses were not included.

Routine monitoring included esophageal temperature, heart rate, arterial oxygen saturation, end-tidal capnometry, and central venous pressure. Invasive MABP and ICP measurements also were made, through a frontal intraparenchymatous Camino transducer (model 110-4B, Camino V420 monitor, Camino Laboratories, San Diego, CA). From these two last variables, cerebral perfusion pressure (CPP = MABP − ICP) was calculated. Continuous jugular venous oxygen saturation (Sj_{O_2}) monitoring through a 5.5-French fiberoptic catheter and an Oximetrix-3 system (Opticath 5.5-French and Oximetrix-3, Abbott Laboratories, Madrid, Spain) was regularly performed in every patient. The fiberoptic catheter was placed on the right side, and radiographic verification was obtained in all patients before obtaining jugular blood samples.

Cerebral AVD_{O_2} was calculated according to the formula, $AVD_{O_2} = Hgb \times 1.34 \times [(\text{arterial oxygen saturation} - Sj_{O_2})/100] \times 0.446$, and expressed in micromoles per milliliter. Jugular blood samples and not the measurements of the oximeter were used to calculate AVD_{O_2}. Blood gases were analyzed on a BGM Instrumentation Laboratory analyzer (model 1,312; Medical Europe, Milan, Italy). All AVD_{O_2} values were corrected for changes in carbon dioxide partial pressure (P_{CO_2}), using the formula AVD_{O_2} (corrected) = AVD_{O_2} (uncorrected) ± (actual P_{CO_2} − basal P_{CO_2}) × CO_2R_{abs}, where CO_2R_{abs} (absolute carbon dioxide reactivity) was calculated as the change in AVD_{O_2} divided by the measured change in P_{CO_2} ($CO_2R_{abs} = \Delta AVD_{O_2} / \Delta P_{CO_2}$). CBF was estimated from the reciprocal of AVD_{O_2} and also by transcranial Doppler (TCD) sonography. The proximal segment (M1) of the right middle cerebral artery was insonated transtemporally using the TCD sonography system (TC 2-64, Eden Medizinische Elektronik, Uberlingen, Germany). Mean flow velocity (V_{mean}, cm/s) was measured at a depth of 45–50 mm and digitally displayed on the monitor. Automatic readings were taken during the end-expiratory phase and also manually calculated from peak systolic ($V_{systolic}$) and diastolic ($V_{diastolic}$) middle cerebral artery flow velocities from the formula: $V_{mean} = (V_{systolic} - V_{diastolic})/3 + V_{diastolic}$.

Patient Treatment

All patients were treated with standard protocols that emphasized prompt evacuation of intracranial mass lesions and prevention of secondary ischemic events. Paralysis using vecuronium ($0.08 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and sedation and analgesia using midazolam ($0.2–0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and morphine (1–3 mg/h) were induced in all patients; the last drug was withdrawn at least 4 h before the study and replaced by nonsteroidal antiinflammatory drugs, as necessary, to maintain analgesia. Further treatment included optimized hyperventilation (with continuous monitoring of Sj_{O_2}) and intermittent boluses of mannitol. Strict control of intravascular volume was performed to maintain adequate MABP and CPP above 60 mmHg. In addition, phenylephrine ($0.15–0.3 \ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) was used as vasoactive drug to increase MABP, and every effort was made to maintain hemoglobin > 10 g/dl.

Carbon Dioxide Reactivity and Autoregulation Studies

Carbon dioxide reactivity and autoregulation were tested on each day before opioid administration. The methodology used to test both autoregulation and carbon dioxide reactivity has been previously de-

scribed.[16,17] Briefly, percentage carbon dioxide reactivity ($CO_2R\%$) was calculated as the percentage increase or decrease of estimated CBF ($1/AVD_{O_2}$) per 1 mmHg change in P_{CO_2} after ventilator manipulations. In those patients with a basal P_{CO_2} less than 40 mmHg, the ventilator settings were manipulated to increase arterial P_{CO_2}; in those with P_{CO_2} above or equal to 40 mmHg, the manipulations were directed to reduce arterial P_{CO_2}. The mean absolute change in arterial P_{CO_2} in the entire group was 4.3 ± 2.4 mmHg (mean ± SD). Patients with $CO_2R\%$ above 1% were considered to have intact carbon dioxide reactivity, and patients in whom $CO_2R\%$ was below or equal to 1% were classified as having impaired or abolished carbon dioxide reactivity.

For autoregulation testing only the AVD_{O_2} response to induced hypertension was studied. In hemodynamic stable patients, phenylephrine was used to increase MABP by about 25% from baseline over at least 10 min. Mean increase in MABP in the entire group was 27 ± 9 mmHg (mean ± SD). Autoregulation was evaluated by calculating AVD_{O_2} before and after a steady state of hypertension was achieved. The percentage change of $1/AVD_{O_2}$ relative to the resting value (corrected for P_{CO_2}) was calculated according to the following equation: $\%(1/AVD_{O_2}) = [(1/AVD_{O_2}B - 1/AVD_{O_2}H)/1/AVD_{O_2}B] \times 100$, where $AVD_{O_2}B$ is the basal arteriovenous differences of oxygen and $AVD_{O_2}H$ the arteriovenous differences of oxygen after raising MABP with phenylephrine. In those patients in whom ICP did not change after increasing MABP (Δ ICP $\leq$ 2 mmHg), we used the criteria of Enevoldsen and Jensen[19] to classify autoregulation; that is, patients with changes in $1/AVD_{O_2}$ less than or equal to 20% from baseline were included in the intact autoregulation group, and patients with estimated CBF changes above 20% were classified as having impaired or abolished autoregulation. Patients in whom ICP changed after increasing MABP (Δ ICP $>$ 2 mmHg) were classified into four different patterns: pattern 1, decreased ICP and increased CBF; pattern 2, increased ICP and increased CBF; pattern 3, increased ICP and no change or decrease in CBF; and pattern 4, decreased ICP and unchanged or decreased CBF. Patients included in patterns 1 and 4 were considered to have preserved autoregulation; patients in groups 2 and 3 were considered to have impaired or abolished autoregulation.[17]

Opioid Administration

The first day of study (mean time after injury 17.8 ± 11.5 h), patients were randomized to receive either 0.2 mg/kg morphine (Morfina, Laboratories Serra Pamies, Barcelona, Spain) or 2 μg/kg fentanyl (Fentanest, Roche, Madrid, Spain) intravenously over 1 min. Although precise evaluation of an opioid's potency ratio is difficult, these dosages are considered to be clinically equipotent doses.[22] A syringe containing the assigned study drug was prepared by the nurse so as to provide the dose in a volume of 10 ml, keeping investigators blinded as to which opioid was being given. Each patient received the second drug in the same manner 24 h later. Before infusion, heart rate, esophageal temperature, MABP, ICP, end-tidal capnometry, arterial oxygen saturation, and Sj_{O_2} (as measured with an Oximetrix system) were recorded and CPP calculated. At time 0 min (T_0), the study drug was infused, and all the measurements were repeated at T_2, T_5, T_{10}, T_{15}, T_{20}, T_{25}, T_{30}, T_{40}, T_{50}, and T_{60}. Arterial and jugular blood samples were collected at T_0, T_5, and T_{60} for measurement of AVD_{O_2}. CBF velocity was measured using TCD sonography at the same times.

Statistical Analysis

Data were analyzed using statistical software (release 6.1 for Windows, SPSS, Chicago, IL). Two models of analysis of variance for repeated measures (T_0, T_5, and T_{60}) were used, one to asses to assess the effects of the drug (morphine/fentanyl) and the second to asses the effect of autoregulation (preserved/impaired). In both of them, within-groups effects (ICP, MABP, CPP, AVD_{O_2}, V_{mean}) at T_5 *versus* baseline values and at T_{60} *versus* the means of both T_0 and T_5 were determined. Also, *t* tests for paired samples were used to assess differences in percent changes of estimated CBF ($1/AVD_{O_2}$) at 5 and 60 min. All values are mean ± SD. For all analysis, statistical significance was inferred if $P < 0.05$.

Results

The age and weight of the patients (mean ± SD) was 30 ± 13 yr and 74 ± 12 kg, respectively. The initial Glasgow coma scale scores for the 30 patients ranged from 3 to 8; two patients with initial scores of 9 to 12 deteriorated into coma within the 1st day after injury and were also included in the study. According to the Traumatic Coma Data Bank classification, 10 patients (33%) were included in the diffuse injury II category, 12 cases in diffuse injury III (40%), one patient in diffuse injury IV (3%), four in the evacuated mass lesion category (13%), and three in the nonevacuated mass lesion subgroup (10%). Traumatic subarachnoid hemorrhage was present in six patients (20%), but none of them met TCD sono-

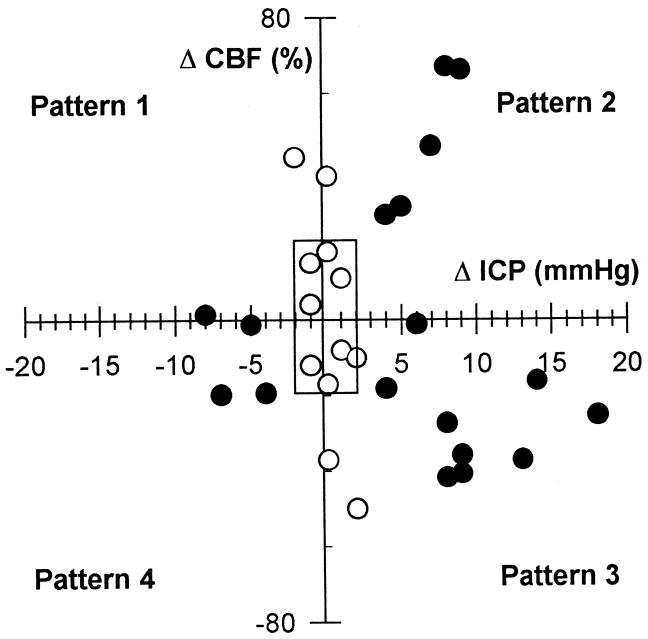

Fig. 1. Induced intracranial pressure changes (ΔICP) plotted against changes in estimated cerebral blood flow (ΔCBF) during the autoregulation tests. The open circles represent the 12 patients in whom ΔICP ≤ 2 mmHg after increasing mean arterial blood pressure (MABP); eight of them had estimated CBF changes less than 20% (enclosed in the central box) and were considered to have preserved autoregulation, and only four presented with ΔCBF > 20% (impaired or abolished autoregulation). The closed circles represent the 18 patients in whom ICP changed after increasing MABP (ΔICP > 2 mmHg). In this subgroup, the most common pattern was pattern 3 (increased ICP and decreased CBF) (n = 9). Patients included in patterns 1 and 4 were considered to have preserved autoregulation; patients in patterns 2 and 3 were considered to have an impaired or abolished autoregulation. Thus, the total number considered to have preserved autoregulation was of 12 patients (43.3%) and impaired or abolished autoregulation of 18 patients (56.7%).

graphic criteria of cerebral vasospasm during the study period. At 6 months eight patients had died, one was in a persistent vegetative state, and five were severely disabled. A bad outcome (severe disability/vegetative state/death) was therefore the final result for 46.7% of patients in the series. Hemodynamic instability forced the exclusion of two patients during the second day of study, one in the morphine group and the other in the fentanyl group. Thus, the hemodynamic data reflect 29 morphine and 29 fentanyl cases.

Although cerebrovascular response to carbon dioxide was preserved in all cases ($CO_2R\% > 1\%$) on both days of the study, autoregulation was impaired or abolished in 18 patients (56.7%) and preserved in only 12 patients (43.3%) (fig. 1); the autoregulation status did not differ on the second day of the study. In 18 patients, ICP significantly changed (Δ ICP > 2 mmHg) after increasing MABP; in those the most common pattern of ICP *versus* estimated CBF changes after phenylephrine infusion was pattern 3 (increase in ICP with no change or decrease in estimated CBF), which was seen in nine cases (30%), followed by pattern 2 (increased ICP and increased CBF) in five patients (16.7%).

Table 1 summarizes physiologic measurements for the morphine and fentanyl groups. Before and after administration of the opioids no significant differences were found in P_{CO_2}, oxygen partial pressure, *p*H, temperature, or central venous pressure. The effects of morphine and fentanyl on estimated CBF ($1/AVD_{O_2}$) and middle cerebral artery V_{mean} in the entire group and after autoregulation status are presented in table 2. Changes in $1/AVD_{O_2}$ after both morphine and fentanyl were not statistically significant. Estimated CBF (percentage changes in $1/AVD_{O_2}$) increased 14% after fentanyl and 7% after morphine at 5 min ($P = 0.56$ and 0.41, respectively), returning at 1 h to baseline levels. TCD sonographic data were similar between the groups, and there were no differences in V_{mean} baseline values nor in the relative changes in these values.

Changes in MABP, ICP, and CPP are presented in figure 2. Both morphine and fentanyl induced significant decreases in MABP at 5 min ($P = 0.002$ and 0.016, respectively) and persisted significantly lower at 60 min after

Table 1. Arterial Blood Gases, Esophageal Temperature, and Central Venous Pressure before (T_0) and after (T_{60}) Morphine and Fentanyl Administration

	Morphine (2 mg/kg)	Fentanyl (0.2 μg/kg)
pH		
T_0	7.4 ± 0.1	7.4 ± 0.1
T_{60}	7.4 ± 0.1	7.4 ± 0.1
Pa_{O_2} (mmHg)		
T_0	129 ± 34	123 ± 35
T_{60}	139 ± 43	131 ± 43
Pa_{CO_2} (mmHg)		
T_0	29 ± 5	31 ± 5
T_5	28 ± 6	29 ± 5
T_{60}	29 ± 5	31 ± 5
Temperature (°C)		
T_0	37.4 ± 1	37.5 ± 1
T_{60}	37.4 ± 1	37.5 ± 1
CVP (cm H_2O)		
T_0	10 ± 3	10 ± 3
T_{60}	10 ± 4	10 ± 4

Data are mean ± SD. There were no significant differences between groups.

Pa_{O_2} = arterial partial pressure of oxygen; Pa_{CO_2} = arterial partial pressure of carbon dioxide; CVP = central venous pressure.

Table 2. Effects of Morphine and Fentanyl on Estimated Cerebral Blood Flow ($1/AVD_{O_2}$) and Middle Cerebral Artery Mean Flow Velocity in the Entire Group and after Autoregulation Status

	Morphine			Fentanyl		
	Total (n = 29)	Intact Autoregulation (n = 12)	Impaired Autoregulation (n = 17)	Total (n = 29)	Intact Autoregulation (n = 12)	Impaired Autoregulation (n = 17)
$1/AVD_{O_2}$ (μmol/ml)						
Baseline	0.66 ± 0.5	0.71 ± 0.4	0.62 ± 0.6	0.66 ± 0.5	0.66 ± 0.6	0.66 ± 0.4
5 min*	0.77 ± 0.5	0.83 ± 0.5	0.66 ± 0.5	0.71 ± 0.6	0.71 ± 0.5	0.71 ± 0.8
60 min*	0.62 ± 0.5	0.66 ± 0.5	0.62 ± 0.5	0.62 ± 0.5	0.66 ± 0.5	0.62 ± 0.6
V_{mean} (cm/s)						
Baseline	48 ± 4	49 ± 3	48 ± 4	54 ± 4	53 ± 3	55 ± 4
5 min	47 ± 4	48 ± 4	49 ± 4	49 ± 5	51 ± 4	52 ± 3
60 min	50 ± 4	49 ± 4	49 ± 4	48 ± 4	47 ± 4	50 ± 5

Data are mean ± SD. There were no differences within and between groups (morphine and fentanyl) or between patients with preserved or impaired autoregulation.

AVD_{O_2} = arteriojugular oxygen content difference; V_{mean} = middle cerebral artery mean flow velocity.

* Corrected for changes in carbon dioxide partial pressure.

fentanyl ($P = 0.016$). ICP increased after the administration of both drugs, at 5 min ($P = 0.008$ with morphine and $P = 0.044$ with fentanyl) and at 60 min ($P = 0.008$ and 0.044, respectively). Maximum ICP values were reached at 2 min after bolus administration and were of 21 ± 13 mmHg after morphine and 20 ± 10 mmHg with fentanyl (mean ± SD). The decrease in MABP and the increase of ICP resulted in a transient decrease in CPP after the administration of both drugs, reaching at 5 min a minimum value of 64 ± 15 mmHg after morphine ($P = 0.001$) and 65 ± 18 mmHg after fentanyl ($P < 0.0001$; mean ± SD). No differences were found between the opioids in the amount of change of these variables.

Figure 3 shows ICP changes if patients were classified by their autoregulation status. Although patients with preserved autoregulation seemed to experience a greater rise in ICP than the group with impaired or abolished autoregulation, no significant changes in ICP were detected between the group with preserved autoregulation (n = 12; ICP maximum increase of 3.6 mmHg after morphine and 4.8 mmHg after fentanyl; $P = 0.40$) and the group with impaired or abolished autoregulation (n = 18; ICP maximum increase of 2.9 mmHg after morphine and 2.3 mmHg after fentanyl; $P = 0.42$). Estimation of CBF, whether through AVD_{O_2} ($1/AVD_{O_2}$) or TCD sonography (V_{mean}), did not show differences between patients with preserved or impaired autoregulation (table 2). With regard to all studied parameters, no significant difference was observed after the use of either opioid.

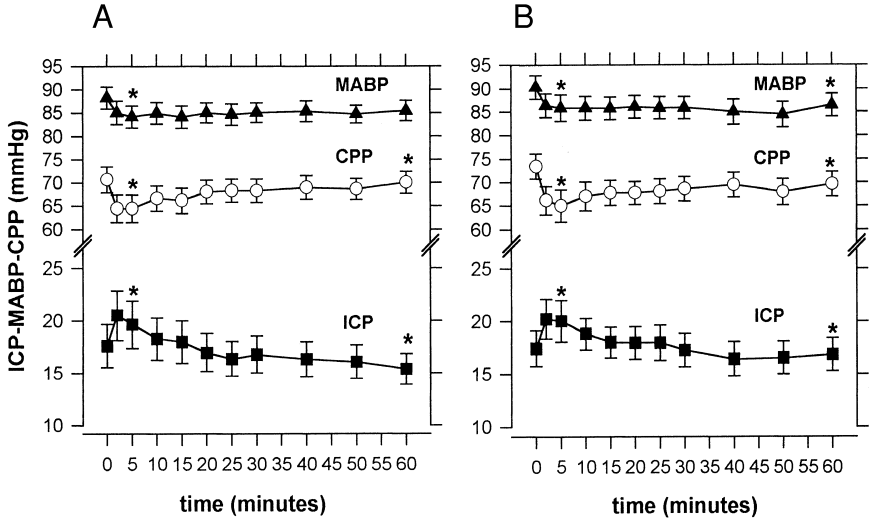

Fig. 2. Morphine- and fentanyl-induced changes in intracranial pressure (ICP), mean arterial blood pressure (MABP), and cerebral perfusion pressure (CPP). (*A*) Morphine: MABP and CPP at 5 min and CPP at 60 min were significantly lower than baseline values; ICP was significantly higher at 5 and 60 min. (*B*) Fentanyl: MABP and CPP at 5 and 60 min were significantly lower than baseline values; ICP was significantly higher at the same times (*$P < 0.05$). All values are mean ± SD. No differences were found between both opioids in the amount of change of these variables.

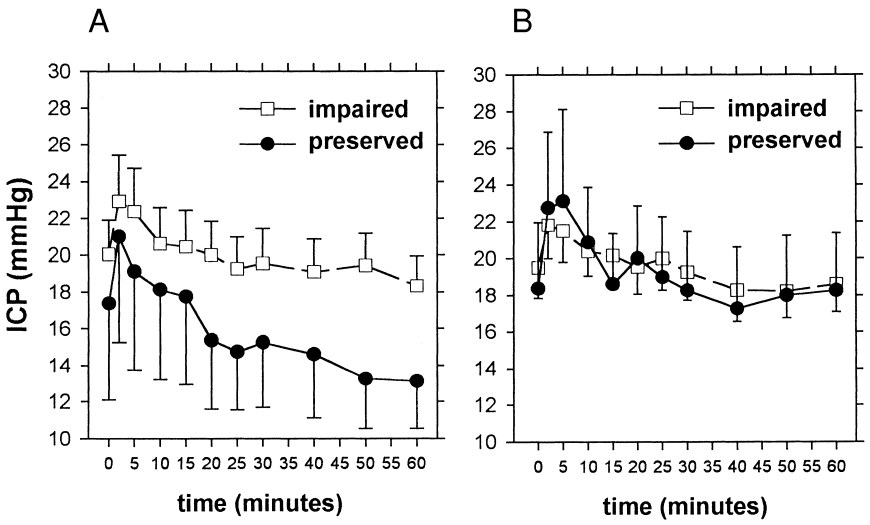

Fig. 3. Intracranial pressure (ICP) measurements after autoregulation status (impaired or preserved) after the administration of morphine (*A*) and fentanyl (*B*). All values are mean ± SD (overlapping bars removed for clarity). No differences were found between the impaired (open squares) and preserved (closed circles) autoregulation groups, although ICP increases were slightly greater in patients with impaired autoregulation, both after morphine (3.6 *vs.* 2.9 mmHg) and with fentanyl (4.8 *vs.* 2.3 mmHg).

Discussion

This study shows that, in patients with severe head injury and raised ICP, morphine and fentanyl significantly increase ICP and decrease MABP both in patients with preserved and impaired cerebrovascular autoregulation and induce no significant variations in CBF estimated by AVD_{O_2} and TCD sonography. Similar or greater ICP increases, with concomitant decreases in MABP, have been reported in the literature after boluses of potent opioids given to patients with head trauma.[3,5,14] However, in a recent study in which decreases in MABP were rapidly corrected,[9] no increases of cerebrospinal fluid pressure were found after fentanyl (4.5 μg/kg) and sufentanil (0.8 μg/kg) were administered. In addition, it has been demonstrated that in patients with brain injury in whom MABP was controlled, a bolus of sufentanil (3 μg/kg) did not change ICP values, but transient increases in ICP were described concomitant with decreases in MABP.[6] In contrast, another study in neurosurgical patients comparing the hemodynamic effects of remifentanil (0.5–1 μg/kg) *versus* alfentanil (10–20 μg/kg) showed that neither opioid caused a significant increase in ICP, although both drugs were associated with a dosage-dependent decrease in MABP.[10] Regarding the opioid effects upon CBF, only one study in nonintracranial surgical patients has reported increases in CBF velocity after the infusion of fentanyl (150 μg/min) and sufentanil (15 μg/min).[4] Other studies based on flow velocity as an index of CBF and also on metabolic data found no differences on CBF after the administration of sufentanil (3 μg/kg) and alfentanil (25–50 μg/kg), respectively.[6,7] Albanèse *et al.*[14] have recently showed that alfentanil, sufentanil, and fentanyl induced no significant variations in AVD_{O_2} and in lactate–oxygen index in patients with severe head injury. Another study with fentanyl and remifentanil showed that absolute CBF values were similar if they were measured by the intravenous xenon-133 technique.[23] Therefore, despite some inconsistent data, it can be concluded that ICP elevations in patients with low intracranial compliance but preserved autoregulation could be related to autoregulatory vasodilation secondary to systemic hypotension rather than increases in CBF.[6–9]

One of the most controversial issues in the management of severe head injuries concerns whether or not autoregulation is impaired, abolished, or preserved in these patients. Some authors suggest that autoregulation is preserved after injury but that its upper and lower limits are shifted to the right; therefore, higher CPPs are necessary to maintain an optimal CBF.[15] Using this approach, characterizing autoregulation according to cerebrovascular resistance (CPP:CBF ratio) may be misleading, because in patients with an impaired or abolished vasoconstrictory response to increased CPP, increases in MABP often induce a parallel increase in tissue pressure. Consequently, as some other authors have suggested,[19,24,25] we believe that changes in both observed ICP and estimated CBF could be more useful to better characterize autoregulatory impairment.

According to Obrist *et al.*,[26] approximately one half of patients with severe head injury has a variable degree of autoregulation impairment. It has been demonstrated both clinically and in experimental models that autoregulation and carbon dioxide reactivity can be impaired

independently of each other in many brain insults, the so-called dissociated vasoparalysis.[27] Also, complete vasoparalysis (impaired autoregulation and carbon dioxide reactivity) seems to be infrequent and found only in the very damaged brain.[27] In the present series, although all patients showed preserved carbon dioxide reactivity on both days of study, 56.7% of them had impaired or abolished autoregulation; a very similar percentage was found in a recent study by our group.[17] In nine patients, no change or even a decrease in estimated CBF was observed concomitant to a significant (more than 2 mmHg) increase in ICP. They were classified as having impaired or abolished autoregulation, following the hypothesis of "false" autoregulation or pseudoautoregulation that was first proposed by Miller et al.[24] and subsequently elaborated by Enevoldsen and Jensen.[28] These authors hypothesized that in patients with apparently preserved autoregulation, CBF was maintained constant by an increase in interstitial pressure in a microcirculatory bed devoid of the protective mechanisms of the arteriolar vasoconstriction.

The main target variable in our study was ICP and not CPP, because although in the past decade CPP management has been proposed as a therapeutic strategy for patients with head injury,[15] this variable was not found to be a predictor of outcome in the Traumatic Coma Data Bank Study.[29] Regarding the relationship between autoregulatory status and the tissue pressure effects of morphine and fentanyl, our initial hypothesis was that ICP would only increase in the intact-autoregulation group and would follow MABP or remain unchanged in the impaired-autoregulation group. However, although MABP moderately decreased in similar ranges in both groups (3–4 mmHg), we did not find significant differences in ICP increases between patients with intact and impaired autoregulation, and in both groups estimated CBF was maintained constant after the administration of morphine and fentanyl.

Other mechanisms, besides autoregulatory vasodilation, that could be implicated in the ICP increases reported after opioid administration and could explain the lack of statistical differences in the present study are changes in cerebral metabolism and direct cerebral vasodilation. Opioids are known to inhibit the release of different neurotransmitters in the central nervous system, which may be expected to decrease cerebral metabolism.[30] However, the metabolic responses to opioids appear to be related to the background anesthetic conditions. In the absence of a cerebral vasodilator such as nitrous oxide, Milde *et al.*[31] studied in dogs the effect of fentanyl upon CBF and CMR_{O_2} and found a small decrease in CMR_{O_2} and a 14% increase in CBF. Likewise, more recent studies with positron emission tomography on human brain revealed significant regional CBF increases and failed to demonstrate a global suppression of neuronal activity after the administration of fentanyl.[32] In addition, central administration of morphine has been reported not to influence CMR_{O_2} in pentobarbital-anesthetized dogs, and it had no effect on CBF or CMR_{O_2} in healthy volunteers.[33,34] Thus, at doses commonly used for analgesia and in the absence of cerebral vasodilators, morphine and fentanyl may have negligible effects on CMR_{O_2}, suggesting a role for opioids in the control of CBF independent of changes in cerebral metabolism.

In fact, opioids may interact directly with receptors located on brain blood vessels. Different types of opioid receptor binding have been demonstrated on cerebral microvessels, and μ receptor activation through some endogenous agonists and selective synthetic analogs have been proved to cause pial artery dilation.[35,36] The CSF concentration of endogenous μ agonists is increased after injury, and recently it has been demonstrated that opioids may contribute to the pathophysiologic control of cerebral circulation during brain injury.[37,38]

Some consideration should be given to the methods used in this study. First, as this study was powered to detect only differences in ICP and not in autoregulation status, increasing the sample size could yield different results, and this should affect our conclusions. Second, we used TCD sonography and AVD_{O_2} as an estimation of CBF. When interpreting TCD results, relative changes in V_{mean} within each individual correlate well with changes in CBF.[39] Monitoring relative changes in AVD_{O_2} has been accepted as a reliable method for studying the effects on drugs on autoregulation and may allow a bedside assessment of autoregulation and carbon dioxide reactivity in patients with severe head injury.[21,16] On the other hand, using AVD_{O_2} in testing CBF changes after morphine and fentanyl assumes that CMR_{O_2} is not altered by opioids. Decreases or no change in CMR_{O_2} have been reported after opioid administration (as noted previously), but we speculated that at the doses studied and in absence of nitrous oxide, cerebral metabolism was unchanged by the administration of morphine and fentanyl. Although direct measurements of CBF would have provided more evidence, it is our opinion the lack of change in AVD_{O_2} concomitant with no significant variations in TCD sonographic data accurately reflects the lack of change in CBF in these patients. Finally, the background sedation with full neuromuscular blockade during the study may not

produce a state relating to normal unsedated patients but instead a lowered basal brain metabolism. Decreases in both CBF and CMR_{O_2} have been reported after midazolam infusion;[40] however, results presented here indicate that basal estimated CBF did not differ between the morphine and the fentanyl groups.

In conclusion, we found no evidence to support the hypothesis that cerebrovascular autoregulation is the only probable mechanism responsible for morphine- and fentanyl-induced increases in ICP in patients who have suffered head trauma. Although little is known concerning the effects of endogenous or synthetic opioids on cerebral hemodynamics in the injured brain, it is reasonable to assume that the ICP increases also could be related to some intrinsic properties of opioids such as direct cerebral vasodilation. However, despite a clear decrease in MABP after morphine and fentanyl administration, this decrease (3–4 mmHg) could not be sufficient to stimulate the vasodilatory cascade even in patients with preserved autoregulation. Thus, concomitant hemodynamic changes should be closely monitored if opioids are given to patients with severe head injury.

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