

## *Fentanyl and Sufentanil Increase Intracranial Pressure in Head Trauma Patients*

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Although opioids frequently are administered to patients with severe head trauma, the effects of such drugs on intracranial pressure are controversial. Nine patients with severe head trauma were studied for the effects of fentanyl and sufentanil on intracranial pressure (ICP). In all patients, ICP monitoring was instituted before the study. Full neuromuscular blockade was achieved with vecuronium bromide before the administration of either fentanyl ( $3 \mu\text{g} \cdot \text{kg}^{-1}$ ) or sufentanil ( $0.6 \mu\text{g} \cdot \text{kg}^{-1}$ ) as an intravenous bolus over a 1-min period in a masked and random fashion. Patients received the other opioid in the same fashion 24 h later. Arterial blood pressure, heart rate, and ICP were recorded continuously for the 1 h after drug administration. Fentanyl was associated with an average ICP increase of  $8 \pm 2$  mmHg, and sufentanil with an increase of  $6 \pm 1$  mmHg. These increases were statistically significant. Both drugs produced clinically mild decreases in mean arterial blood pressure (fentanyl,  $11 \pm 6$  mmHg; sufentanil,  $10 \pm 5$  mmHg) that nevertheless were statistically significant. No significant changes in heart rate occurred. These results indicate that modest doses of potent opioids can significantly increase ICP in patients with severe head trauma. (Key words: Anesthetics, opioids: fentanyl; sufentanil. Brain: intracranial pressure. Trauma: head.)

OPIOIDS FREQUENTLY ARE used during neurosurgical anesthesia.<sup>1,2</sup> However, controversy persists regarding the effects of opioids on intracranial pressure (ICP).<sup>3-9</sup> Most animal studies report no increase in ICP associated with opioids,<sup>4,5,8</sup> although it has been suggested that increases in cerebral blood flow (CBF) may lead to an increase in ICP in the presence of intracranial pathology.<sup>4</sup> Reports in humans vary. Although several investigators have found no increase in ICP after sufentanil,<sup>6</sup> alfentanil,<sup>9</sup> or cere-

brospinal fluid pressure after sufentanil, alfentanil, and fentanyl,<sup>7</sup> others have reported that sufentanil and alfentanil do increase CSFP in patients with brain tumors.<sup>3</sup>

This study was designed to examine the effects of fentanyl and sufentanil on ICP in patients with severe head trauma. This patient population was selected because these patients frequently have an abnormal intracranial compliance and altered cerebral autoregulation and are likely to be sensitive to most factors that may effect ICP. Thus, any effect of the potent opioids on ICP should be most apparent and have the greatest clinical significance in these patients.

### Materials and Methods

After Institutional Review Board approval and informed consent from nearest of kin, we studied nine patients with head trauma severe enough to require ICP monitoring and mechanical hyperventilation. The patients were enrolled in the study 1-3 days after injury. None of the patients had surgery before completing the study. All patients were maintained on their existing regimen of supportive care, which included mechanical hyperventilation, ICP monitoring, midline placement and elevation ( $15^\circ$ ) of the head, sedation with midazolam in seven patients, and osmotherapy within 12 h of the study in one patient. Arterial blood gas and serum osmolality analyses were obtained, and each patient received vecuronium bromide 10 mg intravenously 15 min before the investigation. An additional 5 mg vecuronium bromide was administered if peripheral ulnar nerve stimulation revealed any residual neuromuscular function. The patients then received either sufentanil  $0.6 \mu\text{g} \cdot \text{kg}^{-1}$  or fentanyl  $3 \mu\text{g} \cdot \text{kg}^{-1}$  in an equal volume (5 ml) as an intravenous bolus over 1 min in a randomized, double-masked fashion. These doses were selected to provide a sufficient opioid effect and yet have a small effect on blood pressure. All nine patients received the second drug, in the same manner, 24 h later.

Heart rate and invasive arterial blood pressure were continuously monitored with a Component Monitoring System<sup>®</sup> (model 66, Hewlett-Packard, Waltham, MA). ICP was continuously monitored with a Camino<sup>®</sup> Catheter System (OLM Intracranial Pressure Monitoring Kit,

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Camino Laboratories, San Diego, CA), which uses a subarachnoid bolt and sterile miniature ICP transducer. Heart rate, blood pressure, and ICP were recorded for 1 h after administration of the study drug. The protocol allowed for a member of the research team to treat a decrease in systolic blood pressure of more than 30% from baseline by the administration of intravenous phenylephrine 25 µg every minute until the systolic pressure returned to at least 70% of baseline. Increased ICP deemed clinically dangerous was treated by the critical care nurse in accordance with standard therapy in the critical care unit.

All data are reported as mean ± standard error of the mean. Blood gas values and serum osmolality were analyzed by paired *t* tests, change in heart rate, ICP, mean arterial blood pressure (MAP), and cerebral perfusion pressure by analysis of covariance using BMDP software (1D and 2V routines; BMDP, Inc., Los Angeles, CA). Statistical significance was set at a *P* value of <0.05.

### Results

Our patient population consisted of six men and three women aged 34 ± 5 yr, weighing 78 ± 6 kg, with a Glasgow Coma Scale Score of 6 ± 1. One other patient was enrolled in the study but died of brain herniation within 24 h after receiving the first study drug (sufentanil); this patient was not included in the summary statistics. The results for serum osmolality and arterial blood gas analyses are shown in table 1. There was no difference in any of these values between the fentanyl and sufentanil groups. The results for baseline and minimum heart rate, minimum MAP, maximum ICP, and minimum cerebral perfusion pressure during the study period are presented in table 2. There were no differences in the baseline values between the two groups. Heart rate changes from baseline in both the fentanyl and sufentanil groups were not statistically significant. The average MAP decrease from baseline was 11 ± 6 mmHg in the fentanyl group and 10 ± 5 mmHg in the sufentanil group.

The average maximum ICP increase was 8 ± 2 mmHg from baseline in the fentanyl group, and 6 ± 1 mmHg in the sufentanil group. These ICP changes were statistically significant for both fentanyl (*P* = 0.004) and sufentanil (*P* = 0.006). There were no significant differences in ICP

TABLE 2. Intracranial Pressure, Mean Arterial Blood Pressure, Cerebral Perfusion Pressure, and Heart Rate Data for the Fentanyl and Sufentanil Groups

	Fentanyl	Sufentanil
Intracranial pressure (mmHg)		
Baseline	9.7 ± 1.8	7.1 ± 1.8
Maximum	17.4 ± 2.9*	13.2 ± 2.8*
Mean arterial blood pressure (mmHg)		
Baseline	92 ± 5	92 ± 5
Minimum	81 ± 6*	82 ± 4*
Cerebral perfusion pressure (mmHg)		
Baseline	82 ± 3	85 ± 3
Minimum	65 ± 4*	72 ± 3*
Heart rate (beats · min <sup>-1</sup> )		
Baseline	99 ± 5	85 ± 6
Minimum	93 ± 4	87 ± 4

\* Significant differences (*P* < 0.05) when compared to baseline.

effects between the two drugs. Although no patient had a baseline ICP of 20 mmHg or more, four of the nine patients experienced an increase to greater than 20 mmHg after the administration of fentanyl and/or sufentanil. Three patients required additional hyperventilation during the study period to attenuate an ICP increase that was deemed clinically excessive. No other interventions were required for either increased ICP or decreased MAP.

The mean cerebral perfusion pressure decrease from baseline was 13 ± 4 mmHg in the fentanyl group and 10 ± 4 mmHg in the sufentanil group. Both of these decreases were significant.

The time course of the ICP changes in a representative patient after the administration of fentanyl and sufentanil is shown in figure 1. The time course of the average MAP and average ICP for the fentanyl group is shown in figure 2. The blood pressure nadir occurred 10 min after fentanyl administration and the ICP maximum at 6 min after drug administration. The time course of the average MAP and average ICP for the sufentanil group is shown in figure 3. The blood pressure nadir after sufentanil occurred at 8–15 min after drug administration and the ICP maximum at 4 min after drug administration.

### Discussion

The application of greater than analgesic doses of opioids in neuroanesthesia, as in other branches of anesthesiology, is based primarily on their ability to provide systemic hemodynamic stability. Nevertheless, in neurosurgery, and especially in neurosurgical patients whose intracranial compliance is decreased, avoiding further exacerbations in ICP is of primary importance. Thus, knowing the effect of opioids on ICP is important. This investigation suggests that the potent synthetic opioids fentanyl

TABLE 1. Serum Osmolality and Arterial Blood Gas Values for the Fentanyl and Sufentanil Groups

	Fentanyl	Sufentanil
Serum osmolality (mOsm · kg <sup>-1</sup> )	295 ± 4	293 ± 2
PaO <sub>2</sub> (mmHg)	106 ± 10	102 ± 6
PaCO <sub>2</sub> (mmHg)	27 ± 1	26 ± 1
pH	7.50 ± 0.01	7.51 ± 0.01

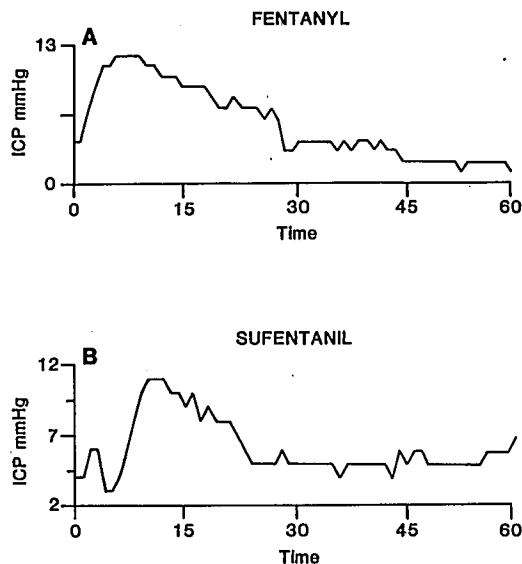


FIG. 1. The time course (minutes) of the intracranial pressure (ICP) (mmHg) in a single patient following the administration (at 0 min) of fentanyl (A) and sufentanil (B).

and sufentanil significantly increase ICP in patients with head trauma.

One or more mechanisms could underlie the exacerbation of ICP produced by opioids. An increase in CBF is known to increase ICP if intracranial compliance is reduced. However, several studies have documented a decrease in CBF after morphine,<sup>10</sup> fentanyl,<sup>11-13</sup> and sufentanil.<sup>14</sup> Nevertheless, species differences and the concomitant administration of other drugs, most frequently nitrous oxide, preclude drawing definitive conclusions

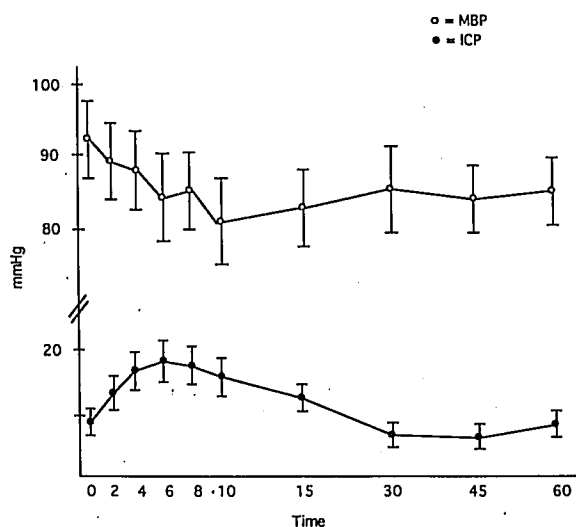


FIG. 2. The time course (minutes) of the average mean blood pressure (MBP) (mmHg) and intracranial pressure (ICP) (mmHg) for all patients who received fentanyl (at 0 min). The error bars represent SEM.

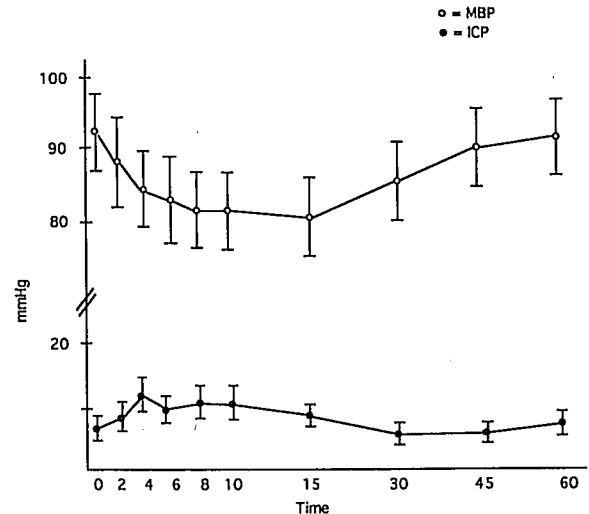


FIG. 3. The time course (minutes) of the average mean blood pressure (MBP) (mmHg) and intracranial pressure (ICP) (mmHg) for all patients who received sufentanil (at 0 min). The error bars represent SEM.

from such studies with regard to humans. Milde *et al.*<sup>4</sup> recently documented that sufentanil (10–200  $\mu\text{g}/\text{kg}$ ) increases CBF in dogs at all doses. This increase lasted approximately 20 min, approximately the same duration of changes in ICP found in our study. They did not note any increase in ICP or any significant change in systemic hemodynamics. They concluded sufentanil to be a direct cerebrovasodilator because a decrease in cerebrovascular resistance accompanied the increase in CBF. Others also have reported that cerebrovascular smooth muscle possesses  $\mu$  and  $\delta$  receptors that mediate dilatation after opioid agonists.<sup>15</sup> Again, however, that these two studies are animal investigations limits their validity for humans.

Indirect mechanisms also may underlie cerebrovasodilation associated with opioid administration. An increase in the cerebral metabolic rate for oxygen ( $\text{CMR}_{\text{O}_2}$ ) could increase CBF and/or worsen ICP by exacerbating ischemia. Although some studies suggest that fentanyl<sup>13</sup> and sufentanil<sup>14</sup> decrease  $\text{CMR}_{\text{O}_2}$ , a focal and/or subcortical increase in  $\text{CMR}_{\text{O}_2}$  may occur with or without seizure activity.<sup>4,16,17</sup> Indeed, although Milde *et al.*<sup>4</sup> summarized their findings by concluding that sufentanil decreased  $\text{CMR}_{\text{O}_2}$  in dogs, close evaluation of their data reveals that, initially, a statistically significant increase in  $\text{CMR}_{\text{O}_2}$  occurred. If intracranial compliance is compromised, this initial burst in  $\text{CMR}_{\text{O}_2}$  could result in an increased ICP.

Although overt grand mal seizures have been reported after opioids,<sup>18</sup> electroencephalographic evidence of such phenomena after fentanyl<sup>19</sup> and sufentanil<sup>20</sup> in humans is lacking. Focal neuroexcitation on the electroencephalogram (*e.g.*, sharp wave activity), however, has been observed after opioids in humans.<sup>20</sup> Opioid-induced rigidity<sup>21</sup> could increase ICP, at least in part by increasing

CMR<sub>O<sub>2</sub></sub>, CBF, and/or cerebral blood volume. Because neuromuscular blockade was complete in our patients, it is unlikely that peripheral motor activity contributed to our observations.

Other remotely possible mechanisms that could increase ICP indirectly include opioid-induced histamine release and the effects of opioids on cerebral spinal fluid production and/or absorption. Although opioid-induced histamine release also might augment CBF *via* a decrease in cerebral vascular resistance, neither sufentanil nor fentanyl triggers histamine release.<sup>22,23</sup> Change in cerebrospinal fluid production and/or absorption is an unlikely explanation, at least for fentanyl-induced<sup>24,25</sup> changes in ICP. Increase in resistance to reabsorption of cerebral spinal fluid after sufentanil may occur,<sup>26</sup> although it seems unlikely that this is an important mechanism in the short time frame of our study.

Finally, systemic hypotension in the presence of an increased ICP may decrease cerebral perfusion pressure and produce ischemia. This ischemia can exacerbate the increased ICP. Although the potent opioids fentanyl and sufentanil usually produce only a modest decrease in systemic blood pressure, even a small decrease in blood pressure may produce ischemia in patients with head trauma. Milde *et al.*,<sup>4</sup> however, found no significant decrease in MAP in dogs after sufentanil but did find an increase in ICP. Marx *et al.*<sup>3</sup> did find a significant blood pressure decrease in their study; however, the CSFP did not decrease after fentanyl, even though the decrease in MAP was nearly identical for sufentanil and fentanyl. In addition, Weinstabl *et al.*<sup>6</sup> found no increases in ICP after sufentanil in humans with a baseline ICP > 20 mmHg, even though MAP decreased.

The changes in MAP in our patients were clinically modest but statistically significant. The change in ICP appears to precede the change in MAP. Thus, it appears unlikely that a decrease in systemic blood pressure and subsequent ischemia is the chief mechanism underlying our observations.

Studies in humans documenting opioid-induced increases in cerebrospinal fluid pressure<sup>3</sup> (measured *via* lumbar spinal catheter) and ICP (measured by ICP monitoring in our study) are opposed by findings in humans in other reports.<sup>6,7,9,27</sup> Closer scrutiny of these reports is initially even more confounding when one recognizes that Weinstabl *et al.*<sup>6</sup> did not find a similar ICP increase, even though their patient population and sufentanil dose were similar to ours. Their ICP measurements, however, were made by epidural ICP probes, whereas our probes were subdural. Perhaps this accounts for the different findings. Indeed, epidural methods of monitoring ICP have been argued to be insensitive to change due to the inelastic nature of the dura.<sup>28,29</sup> Markovitz *et al.*<sup>9</sup> may not have

found an opioid-induced ICP increase because of the concomitant administration of isoflurane and nitrous oxide.

Recommendations for clinical practice regarding the risk of administering fentanyl or sufentanil to patients with intracranial hypertension are difficult to make with any degree of certainty. The confusing state of the literature contributes to this difficulty. Human and animal studies apply different background anesthetic agents and different monitoring approaches; both may significantly affect experimental findings. Nevertheless, our results argue that caution be exercised in the administration of fentanyl or sufentanil to patients at risk for decreased intracranial compliance, particularly if ICP is significantly increased. Future studies are needed to confirm our findings and to address their underlying mechanisms.

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