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Sufentanil Increases Intracranial Pressure in Patients with Head Trauma

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Background: **Sufentanil is an intravenous opioid often used as a component of anesthesia during neurosurgical procedures. However, the effects of sufentanil on intracranial pressure in patients with diminished intracranial compliance are not well established, and remain controversial.**

Methods: **Ten patients with head trauma, in each of whom the trachea was intubated, were studied for the effects of sufentanil on intracranial pressure (ICP) and on cerebral perfusion pressure (CPP). In all patients, ICP monitoring was instituted before the study. Sedation was obtained using a propofol infusion, and paralysis was achieved with vecuronium. After obtaining control of ICP (between 15 and 25 mmHg) hemodynamic values and blood gas tensions (Pa_{CO_2} between 30 and 35 mmHg), the level of sedation was deepened with an intravenous injection of sufentanil (1 μg/kg over 6 min), followed by an infusion of 0.005 $\mu g \cdot kg^{-1} min^{-1}$. Mean arterial pressure (MAP), ICP (fiberoptic intracranial pressure monitor), and end-tidal CO_2 were continuously measured and recorded at 1-min intervals throughout the 30-min study period.**

Results: **Sufentanil injection was associated with a statistically significant increase in ICP of 9 ± 7 mmHg (+53%), which peaked at 5 min. Then ICP gradually decreased and returned to baseline after 15 min. This was accompanied by a significant decrease in MAP (24% decrease) and, thus, CPP (38% decrease). After 5 min, MAP and CPP gradually increased, but remained significantly decreased throughout the study.**

Conclusions: **The results of the current study indicate that caution should be exercised in the administration of sufentanil bolus to patients with abnormal intracranial elastance, particularly if ICP is significantly increased. (Key words: Anesthetics, opioid: sufentanil. Brain: intracranial pressure. Trauma: head.)**

AN important objective in the medical treatment of severely head-injured patients is the maintenance of an adequate cerebral perfusion pressure (CPP). This can be done by controlling intracranial pressure (ICP) and maintaining adequate mean arterial blood pressure (MAP), blood gases, temperature, serum glucose concentration, electrolytes, and osmolarity. Nociceptive stimulation may induce an increase in ICP, and may thereby decrease CPP. Often, sedation using opioids and hypnotic drugs is used to prevent such an undesirable side effect. However, controversy persists regarding the effect of opioids on ICP and CPP.[1–10] Most animal studies report no increase in ICP associated with opioids. However, it has been suggested that opioids can increase cerebral blood flow (CBF), which may lead to an increase in ICP[2,4,7] in the presence of intracranial pathology.[3] Reports in humans vary.[8–10] Several investigators have found no increase in ICP after the use of sufentanil[5,10] and alfentanil.[8] Cerebrospinal fluid pressure (CSFP) has not been shown to vary after the use of sufentanil, alfentanil, and fentanyl.[6] However, some authors have reported that sufentanil, alfentanil, and fentanyl do increase CSFP in patients with brain tumors.[2] Recently, a study showed that sufentanil and fentanyl do increase ICP and decrease CPP.[9]

Because of the somewhat contradictory results, the aim of the current study was to examine the effects of bolus and infusion of sufentanil on ICP, MAP, and CPP in patients with abnormal intracranial elastance secondary to severe head trauma.

Materials and Methods

After approval by the ethics Committee of our institution, informed consent was obtained from members of the patient's families. We studied ten males admitted to the Intensive Care Unit (ICU) with severe head injury (Glasgow Coma Scale (GCS) score ≤ 8). Intracranial pathology, age, initial diagnosis, initial GCS score, associated injuries, and outcome of the study patients are reported in table 1. Control of ICP (between 15 and 25 mmHg) and sedation were performed using a con-

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Table 1. Clinical Characteristics of the Ten Study Patients

Patient No.	Age (yr)	Initial GCS Score	Intracranial Pathology	Associated Injuries	ISS	SAPS	Duration of Hospitalization (days)	Outcome
1	18	7	Cerebral contusion		25	10	13	GR
2	19	7	Cerebral contusion Epidural hematomas	Fracture of femur	34	10	14	MD
3	32	6	Cerebral contusion	Pulmonary contusion	34	10	25	GR
4	18	7	Cerebral contusion		25	10	14	MD
5	32	6	Cerebral contusion Intraventricular hemorrhage	Pulmonary contusion Fracture of humerus	38	12	45	SD
6	20	8	Cerebral contusion		25	9	30	GR
7	45	5	Cerebral contusion	Fracture of femur	34	14	20	GR
8	24	4	Cerebral contusion Subdural hematoma		25	9	24	SD
9	50	7	Cerebral contusion	Fracture of femur	34	9	17	GR
10	24	4	Cerebral contusion Epidural hematomas	Pulmonary contusion	34	8	19	GR

GR = good recovery; MD = moderately disabled; SD = severely disabled; GCS = Glasgow coma scale; ISS = injury severity score; SAPS = simplified acute physiologic score.

tinuous infusion of propofol (3 $mg \cdot kg^{-1} \cdot h^{-1}$), and neuromuscular blockade was achieved using a continuous infusion of vecuronium bromide (8 mg/h). Arterial Pa_{CO_2} was maintained between 30 and 35 mmHg. The level of sedation was deepened with a 6-min sufentanil (1 $\mu g/kg$) loading dose followed by a continuous infusion of 0.005 $\mu g \cdot kg^{-1} \cdot min^{-1}$, both administered by an automatic intravenous infusion pump (Bard Mini Infuser, model 950, North Readen, MA). These doses were selected to provide an opioid effect sufficient for sedation.[11] Heart rate (HR), hemoglobin oxygen saturation ($Sp0_2$), end-tidal CO_2 ($ETCO_2$), and invasive arterial blood pressure were continuously monitored with a component monitoring system (model 66, Hewlett-Packard, Waltham, MA). Intracranial pressure was continuously monitored with a Camino catheter system (OLM Intracranial Pressure Monitoring Kit, Camino Laboratories, San Diego, CA), which uses a subarachnoid bolt and sterile miniature ICP transducer. Heart rate, MAP, CPP (MAP minus PIC), $Sp0_2$, and $ETCO_2$ were continuously measured and recorded at 1-min intervals throughout the 30-min study period. Arterial blood gases were obtained at baseline and 10 and 30 min after sufentanil administration. Increased ICP deemed clinically dangerous was treated by the critical care nurse in accordance with standard therapy in the critical care unit.

Results are presented as mean ± SD. Baseline values represent an average of the six measurements obtained during 1 h before drug administration. Analysis of variance for repeated measurements and Dunnett's test were used to determine the effect of sufentanil on ICP, HR, MAP, and CPP. A $P < 0.05$ was considered significant.

Results

Changes in HR, MAP, ICP, and CPP are presented in table 2. The ICP averaged 17 ± 3 mmHg at baseline (range 12–20 mmHg). Sufentanil produced a 53% increase in ICP ($P < 0.05$), which peaked at 5 min (26 ± 8 mmHg, range 15–38 mmHg) and returned to baseline after 15 min. This was accompanied by a significant decrease in MAP (24% decrease, $P < 0.05$) and in CPP (38% decrease, $P < 0.05$). In five patients, CPP of less than 45 mmHg for 4 min was noted. After 5 min, MAP and CPP gradually increased, but remained significantly decreased (22% and 23% decrease, respectively). Heart rate changed from baseline and significantly decreased (15% decreased, $P < 0.05$). No modification was observed in $Sp0_2$ and $ETC0_2$, nor in arterial blood gases (table 3). Patient number 2 required additional hyperventilation during the study period to attenuate an ICP greater than 30 mmHg with CPP less than 40 mmHg for more than 3 min. Intracranial pressure returned to baseline within 2 min, and CPP was reestablished > 50 mmHg within 3 min (fig. 1). No other intervention was deemed necessary in any other patient, because modifications in ICP and CPP were of short duration

Table 2. Effects of Sufentanil (Bolus Injection 1 μg/kg and Infusion 0.005 $\mu g \cdot kg^{-1} \cdot h^{-1}$) on Heart Rate (HR), Mean Arterial Pressure (MAP), Intracranial Pressure (ICP), and Cerebral Perfusion Pressure (CPP)

	Baseline	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min	20 min	25 min	30 min
HR (beats/min)	95 ± 22	90 ± 17*	88 ± 14*	86 ± 14*	86 ± 14*	84 ± 14*	83 ± 13*	82 ± 13*	81 ± 13*	81 ± 13*	81 ± 12*	81 ± 13*	82 ± 13*	82 ± 12*	83 ± 13*
Minimum	74	68	70	70	71	69	70	69	69	67	71	70	72	73	74
MAP (mmHg)	92 ± 11	86 ± 6*	79 ± 5*	75 ± 5*	74 ± 7*	73 ± 6*	72 ± 6*	71 ± 6*	71 ± 5*	70 ± 5*	72 ± 5*	71 ± 5*	71 ± 5*	72 ± 5*	72 ± 5*
Minimum	76	77	74	65	62	61	61	62	63	64	65	66	69	68	69
ICP (mmHg)	17 ± 3	20 ± 3*	22 ± 4*	24 ± 6*	26 ± 7*	26 ± 8*	26 ± 6*	26 ± 6*	25 ± 7*	24 ± 7*	21 ± 5*	18 ± 4	18 ± 5	18 ± 4	17 ± 4
Maximum	20	24	30	35	38	38	37	36	35	35	29	26	24	24	23
Minimum	12	15	19	18	16	15	15	15	14	14	15	13	13	10	10
CPP (mmHg)	73 ± 16	64 ± 9*	54 ± 6*	49 ± 9*	47 ± 10*	45 ± 11*	45 ± 10*	45 ± 11*	46 ± 11*	47 ± 10*	51 ± 8*	55 ± 7*	56 ± 7*	55 ± 7*	56 ± 7*
Minimum	57	53	44	35	35	35	34	36	36	36	42	45	50	52	53

Values are mean ± SD.

Results are presented for nine patients. Patient 2 was deleted from analysis because he required hyperventilation during the study period to treat an increase in ICP (see results and fig. 1). Minimum = lowest value recorded during the study period; Maximum = highest value recorded during the study period.

* $P < 0.05$.

(≤ 4 min). Six patients, including patient number 2, had good recovery and were discharged from the ICU.

Discussion

In managing patients with severe head injury, it is essential to use techniques and pharmacologic agents that do not unfavorably modify ICP and CPP. This study, and other animal[3,4,7] and human studies,[2,6,9] show that, in the presence of decreased intracranial elastance, a bolus injection of sufentanil is accompanied by an increase in ICP, a decrease in MAP, and a decrease in CPP. In the current study, CPP decreased to less than 45 mmHg during 4 min time in five patients after the bolus injection of sufentanil. However, during sufentanil infusion, ICP gradually returned to baseline.

One or more mechanisms can be discussed as an explanation for the increased ICP after administration of sufentanil. First, an increase in CBF is known to increase ICP if intracranial elastance is reduced. Milde *et al.*[3] recently documented that sufentanil (10–200 μg/kg) increases CBF in dogs at all the tested doses. This increase lasted approximately 20 min. They concluded that sufentanil was a direct cerebrovasodilator, because a decrease in cerebrovascular resistance accompanied the increase in CBF. Other authors have reported that cerebrovascular smooth muscle possesses μ and ∂ receptors that mediate dilatation after the use of opioid agonists.[12] However, these studies[3,12] are animal investigations, and their conclusions may not be extended to humans.

Second, an increase in cerebral metabolic rate for oxygen ($CMRO_2$) can increase CBF or increase ICP. This effect was demonstrated by Milde *et al.*[3] in dogs, and close evaluation of their data reveals that, initially, a statistically significant increase in $CMRO_2$ was observed. This is at variance with the effects observed with fentanyl, which has been shown to decrease $CMRO_2$ in dogs.[13] There is no clear explanation as to the difference observed between the two opioids.

Third, opioids induce thoracic muscle rigidity,[14] which, in turn, can increase ICP. But in the current study, patients were paralyzed, and thoracic muscle rigidity in our patients cannot explain the observed increase in ICP.

A fourth mechanism that might explain ICP changes is that opioids induce histamine release.[15] Thus, sufentanil-induced histamine release may also augment CBF *via* a decrease in cerebral vascular resistance. However, White *et al.*,[16] using the model of isolated canine hind-

limb, reported that the opioids produce vasodilation by direct action on the peripheral vascular smooth muscle. This effect was reported to be independent of opioid receptors, neuronal integrity, and histamine release.

A change in cerebrospinal fluid production or absorption[17] is an unlikely explanation for the findings of the current study, because ICP increased very shortly after sufentanil injection and returned to baseline during infusion.

Finally, one other potential cause of an increase in ICP after sufentanil is an indirect cerebrovasodilation caused by autoregulatory compensation when MAP decreases. This has been shown in the study of Marx *et al.*,[2] in which ICP increased after a significant decrease in blood pressure. Interestingly, Werner *et al.*[10] did not find any significant changes in ICP in patients receiving sufentanil (3 μg/kg) when blood pressure was supported with phenylephrine. However, some data in the current study do not support changes in MAP as the only explanation for ICP change. Using sufentanil, a 53% increase in ICP was observed; however, the decrease in MAP was only 24% and, in addition, during sufentanil infusion, ICP values returned to baseline, while MAP remained decreased by 22%. Sufentanil usually produces only a modest decrease in systemic blood pressure. Milde *et al.*[3] found no significant decrease in MAP in dogs after sufentanil injection, but did find an increase in ICP. Marx *et al.*[2] described a significant blood pressure decrease in their study; however, the CSFP decreased after fentanyl injection (10%), and even increased after sufentanil injection (90%). This was accompanied by a similar decrease in MAP for both drugs. Weinstahl *et al.*[5] found no increase in ICP after sufentanil use in humans with a baseline ICP > 20 mmHg, although MAP decreased. Finally, Sperry *et al.*[9] found data similar to those of the current study, with a 12% decrease in MAP and a 114% increase in ICP, with an intravenous bolus of sufentanil (0.6 μg/kg over 1 min).

Table 3. Arterial Blood Gas Values at Baseline (T_0), after Bolus Injection ($T_{10\ min}$), and at the End of Sufentanil Infusion ($T_{30\ min}$)

	T_0	$T_{10\ min}$	$T_{30\ min}$
*p*H	7.49 ± 0.01	7.51 ± 0.01	7.50 ± 0.01
Pa_{O_2} (mmHg)	105 ± 12	101 ± 13	103 ± 12
Pa_{CO_2} (mmHg)	32 ± 2	29 ± 2	30 ± 2

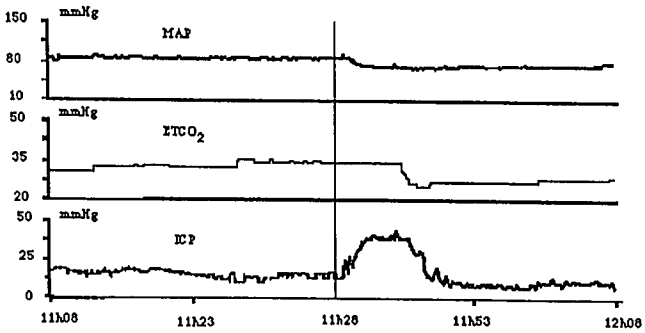

Fig. 1. The time course (minutes) of average MAP and ICP, and $ETCO_2$ recorded in patient number 2. Sufentanil was given at 11:28 AM (vertical bar).

In conclusion, the results of the current study indicate that caution should be exercised in the administration of sufentanil to patients at risk for decreased intracranial elastance, particularly if ICP is significantly increased. In these patients, it seems advisable to use this drug by continuous infusion for sedation, and to avoid bolus injections. If a rapid deepening of sedation is needed, another hypnotic drug, shown not to be associated with an increase in ICP, should be chosen, to avoid a sudden increase in ICP and a decrease in MAP and CPP.

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