Anesthesiology
76:71–76, 1992

Effects of Alfentanil on Intracranial Pressure in Children Undergoing Ventriculoperitoneal Shunt Revision

Barry P. Markovitz, M.D., Ann-Christine Duhaime, M.D.,† Leslie Sutton, M.D.‡, Mark S. Schreiner, M.D.,§, David E. Cohen, M.D.§*

The effects of alfentanil on intracranial pressure in patients with diminished intracranial compliance has not been established. Ten patients with hydrocephalus of varying etiologies, ages 16 months to 20 yr, presenting for ventriculoperitoneal shunt revision were studied. Following induction of anesthesia with thiopental, nitrous oxide/oxygen, and isoflurane, the trachea was intubated and anesthesia was maintained with isoflurane (0.5%), nitrous oxide (70%), and oxygen. After a minimum of 30 min and after the new shunt was placed, alfentanil was administered in increments of 10, 20, and 40 μg/kg at 3-min intervals, and intracranial pressure was measured over 12 min *via* the new shunt. In these unstimulated, normocapnic (PET_{CO_2} 32–38 mmHg) patients, heart rate, mean arterial pressure, and cerebral perfusion pressure declined from 110 ± 26 beats/min, 90 ± 11 mmHg, and 71 ± 14 mmHg, to 84 ± 25 beats/min, 66 ± 11 mmHg, and 45 ± 16 mmHg (mean ± SD), respectively, by 3 min after the third dose ($P < 0.001$). Intracranial pressure did not change from baseline (19 ± 14 mmHg *vs.* 21 ± 11) after any dose of alfentanil. Contrary to earlier studies in adult patients with brain tumors, the authors found that alfentanil, in pediatric patients with hydrocephalus anesthetized with oxygen, nitrous oxide, and isoflurane, did not increase intracranial pressure within a 9-min study period. The significant decreases in cerebral perfusion pressure observed merit concern and further study. (Key words: Anesthesia: pediatric. Anesthetics: intravenous; opioid; alfentanil. Brain: intracranial pressure; perfusion pressure; hydrocephalus. Surgery: neurologic.)

ANESTHETIC MANAGEMENT of patients with intracranial hypertension commonly uses techniques to reduce and prevent further increases in intracranial pressure (ICP). One of the most commonly performed neurosurgical procedures in the pediatric population is placement or revision of a ventriculoperitoneal shunt for hydrocephalus. These children usually receive an anesthetic designed to blunt an increase in their ICP and frequently receive fentanyl as part of the anesthetic. However, in our clinical experience, a typical dose of fentanyl (5–10 μg/kg) given upon induction with thiopental, using nitrous oxide and isoflurane for maintenance, is often associated with delayed emergence. This may be a result of the patients' preoperative depressed level of consciousness, the short duration of the procedure, and the relative lack of postoperative discomfort. Alfentanil represents a potential alternative opioid, with an elimination half-life and duration of action significantly shorter than those of fentanyl.[1,2] Alfentanil has been satisfactorily used in neurosurgical anesthesia,[3,¶] but there are conflicting reports regarding its effect on ICP in adults with vascular malformations or mass lesions.[4,5,**] There are no reports of its use in pediatric patients with intracranial hypertension from hydrocephalus. Therefore, we undertook this investigation to characterize the effects of alfentanil on the ICP of pediatric patients with hydrocephalus undergoing ventriculoperitoneal shunt revision.

Materials and Methods

After receiving institutional review board approval and written, informed, parental consent, we studied ten patients, ages 16 months to 20 yr, undergoing ventriculoperitoneal shunt revision. Nine patients had chronic obstructive hydrocephalus from aqueductal stenosis or insults in early infancy, *e.g.*, intraventricular hemorrhage, meningitis, or trauma. One patient developed hydro-

* Fellow, Pediatric Anesthesia and Critical Care Medicine, The Children's Hospital of Philadelphia. Current affiliation: Department of Anesthesia, St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, Missouri 63110.

† Associate Neurosurgeon, The Children's Hospital of Philadelphia; Assistant Professor of Neurosurgery, University of Pennsylvania School of Medicine.

‡ Senior Neurosurgeon, The Children's Hospital of Philadelphia; Associate Professor of Neurosurgery, University of Pennsylvania School of Medicine.

§ Assistant Anesthesiologist, The Children's Hospital of Philadelphia; Assistant Professor of Anesthesia and Pediatrics, University of Pennsylvania School of Medicine.

Received from the Department of Anesthesiology and Critical Care Medicine and the Department of Neurosurgery, The Children's Hospital of Philadelphia, and the Department of Anesthesia and the Division of Neurosurgery, The University of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication September 23, 1991. Presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 22, 1990.

Address reprint requests to Dr. Markovitz: Department of Anesthesia, St. Louis Children's Hospital, Washington University School of Medicine, 400 South Kingshighway, St. Louis, Missouri 63110.

¶ Dubois M, Hatendi A, Kaufman J, Schwartz S: Alfentanil infusion in neurosurgical patients. J Neurosurg Anesth 1: 328–332, 1989

** Marx W, Shah N, Long C, Arbit E, Galicich J, Mascott C, Mallya K, Bedford R: Sufentanil, alfentanil, and fentanyl: Impact on cerebrospinal fluid pressure in patients with brain tumors. J Neurosurg Anesth 1: 3–7, 1989

cephalus following resection of a cerebellar tumor. All presented with symptoms typical of shunt malfunction, such as headache, lethargy, or vomiting, and several were treated preoperatively with dexamethasone and/or acetazolamide. No patient received opioids preoperatively, and none had evidence of pulmonary disease. Demographic, preoperative, and background anesthetic information are presented in table 1.

One child received an inhalation induction with oxygen, nitrous oxide, and halothane; all others were given thiopental 4–6 mg/kg. Patients were not considered to be at risk for vomiting and aspiration, because their emesis was presumed to be central in etiology. Laryngoscopy and tracheal intubation followed manual hyperventilation with oxygen, nitrous oxide, and isoflurane, and intravenous administration of vecuronium (0.1 mg/kg), lidocaine (1—1.5 mg/kg), and additional thiopental (1–2 mg/kg) if deemed appropriate. After tracheal intubation and throughout the period of study, anesthesia was maintained with isoflurane 0.5% (expired) and 70% nitrous oxide in oxygen, with an end-tidal CO_2 partial pressure of 32–37 mmHg, as determined by mass spectroscopy (Perkin-Elmer, Advantage 2000). A minimum of 30 min passed between induction of anesthesia and initiation of the study period. During this time, the operation commenced and the shunt, either proximally or distally, or both, was exposed. Neuromuscular blockade was maintained by intermittent doses of vecuronium.

In patients requiring a proximal shunt revision, a new intraventricular catheter was inserted, free flow of two to three drops of cerebrospinal fluid (CSF) was demonstrated, and sterile pressure tubing was attached. Patients receiving a distal shunt revision had a new shunt connected to the intact proximal intraventricular catheter, and sterile pressure tubing was attached to the free distal end. Similarly, only two to three drops of CSF was released to demonstrate patency. ICP was then electronically transduced directly *via* the shunt, referenced to the ear, and displayed to ensure an appropriate waveform (Hewlett-Packard, model 78534C). The electronically integrated mean, in millimeters mercury, was considered to be the measured ICP. Heart rate (HR) was recorded from the electrocardiogram channel, and mean arterial pressure (MAP) was determined by automatic oscillotonometer (Dinamap, Critikon, Inc.).[6] ICP, MAP, and HR were recorded every minute for the 12-min study period.

TABLE 1. Demographics, Preoperative Status, and Background Anesthetic

Patient Number	Age (yr)	Diagnosis	Symptoms	Preoperative Medications	Induction	Time from Induction to Study (min)	End-tidal Isoflurane (%)	End-tidal CO_2 (mmHg)
1	5	Cerebellar tumor resection	Lethargy	Dexamethasone	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	70	0.49–0.51	32–34
2	8	Trauma in infancy	Nausea, headache	None	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	65	0.51–0.52	31–35
3	8	Myelomeningocoele/ Arnold-Chiari malformation	Headache, nausea	None	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	89	0.47–0.50	32–35
4	13	Hydrocephalus	Headache	None	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	72	0.48–0.57	36–37
5	9	Dandy Walker cyst	Headache, vomiting	Dexamethasone, acetazolamide, phenobarbital, carbamazepine	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	36	0.44–0.49	33–37
6	20	Aqueductal stenosis	Headache, blurry vision	Dexamethasone acetazolamide	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	47	0.47–0.52	31–32
7	2	Posthemorrhagic hydrocephalus	Irritability	None	O_2/N_2O/Halothane, vecuronium, lidocaine	111	0.51–0.52	33–36
8	7	Aqueductal stenosis	Irritability	None	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	60	0.45–0.47	33–36
9	1.3	Meningitis	Vomiting, irritability	Acetazolamide	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	52	0.39–0.42	30–35
10	12	Congenital hydrocephalus	Headache, lethargy	Dexamethasone, acetazolamide, carbamazepine, phenytoin	Thiopental, lidocaine, vecuronium, O_2/N_2O/isoflurane	46	0.46–0.50	32–35

After 3 min of baseline measurements, alfentanil 10 μg/kg was injected over 15 s into a rapidly flowing intravenous infusion. Three minutes later, 20 μg/kg alfentanil was administered. After an additional 3 min, 40 μg/kg was given. After a final interval of 3 min, the study period was terminated, and the shunt was disconnected from the monitoring apparatus. The remainder of the anesthetic course was determined by the anesthesiologist caring for the patient, but no additional alfentanil was given. Undesirable features of emergence (delay, vomiting, or airway obstruction after extubation) and any postoperative complications (apnea, airway obstruction, vomiting, or lethargy) were noted.

Results are presented as the mean ± the standard deviation of the mean. Cerebral perfusion pressure (CPP) was calculated as MAP − ICP in mmHg. The baseline values represent an average of the three measurements obtained prior to drug administration. An analysis of variance for repeated measures was used to determine the effect of alfentanil upon ICP, HR, MAP, and CPP. A $P < 0.05$ was considered significant. If a variable changed significantly over time, then a paired *t* test with Bonferonni correction was used to perform multiple comparisons between the baseline measurement and each subsequent measurement. Multiple contrasts were performed for each dose–response curve. By assigning a coefficient of +1 to the mean value of the first point in time and equally distributing a −1 coefficient to the mean values for all subsequent points in time, differences between the initial value and the mean of all subsequent values could be evaluated. If there was a significant difference, then the first point was eliminated and a coefficient of +1 was assigned to the second point and a coefficient of −1 again distributed equally to the remaining points. The process was repeated until no significant difference was found between the value assigned the +1 coefficient and all subsequent values. This analysis identifies the point on the dose–response curve beyond which no further change occurs.[7]

Results

The ICP averaged 19 ± 14 mmHg at baseline with a range of 7–52 mmHg. The baseline ICP in five of the ten patients exceeded 15 mmHg, and in two it exceeded 20 mmHg. There were no significant changes in ICP over time. One patient experienced an increase in ICP from 11 to 27 mmHg; in one patient ICP decreased from 51 to 42 mmHg. In all other patients, ICP did not vary by more than 4 mmHg during the course of the study (table 2 and fig. 1).

The HR, MAP, and CPP all declined significantly from their baseline values each minute for 3 min after the 10-μg/kg infusion of alfentanil, declined slightly more 1 min after the 20-μg/kg alfentanil infusion, and then remained unchanged throughout the rest of the experiment (table 2 and fig. 1). As a result of the decline of the MAP, the CPP decreased from a baseline value of 71 ± 14 to 57 ± 14 mmHg 1 min after 10 μg/kg alfentanil, decreased to 46 ± 12 mmHg one min after the 20-μg/kg dose, and remained stable thereafter.

All patients awoke promptly from their anesthetic, and their tracheas were extubated without incident in the operating room. There were no instances of prolonged emergence or postoperative complications.

Discussion

The use of fentanyl as a component of anesthesia for patients with reduced intracranial compliance is firmly established. If ventilation is controlled and cerebral metabolism does not increase (*e.g.*, because of seizures), cerebral blood flow, and presumably cerebral blood volume, are maintained.[8] The assumption that all fentanyl ana-

TABLE 2. Effect of Alfentanil on Heart Rate, Mean Arterial Pressure, Cerebral Perfusion Pressure, and Intracranial Pressure in Children Undergoing Venticuloperitoneal Shunt Revision

		Alfentanil 10 μg/kg			Alfentanil 20 μg/kg			Alfentanil 40 μg/kg			ANOVA
	Baseline	1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	*P* Value
HR (beats per min)	110 ± 26*	96 ± 28†	88 ± 25‡	88 ± 24§	84 ± 26	84 ± 25	82 ± 25	83 ± 26	83 ± 26	84 ± 25	0.0001
MAP (mmHg)	90 ± 11*	76 ± 10†	72 ± 9‡	72 ± 9§	65 ± 9	64 ± 9	66 ± 10	65 ± 10	65 ± 13	66 ± 11	0.0001
CPP (mmHg)	71 ± 14*	57 ± 14†	52 ± 13‡	53 ± 13§	46 ± 12	44 ± 13	46 ± 15	45 ± 13	45 ± 17	45 ± 16	0.0001
ICP (mmHg)	19 ± 14	19 ± 13	20 ± 12	20 ± 11	19 ± 10	20 ± 11	20 ± 11	20 ± 10	21 ± 11	21 ± 11	0.93

Results are mean ± SD. n = 10.

The baseline values for HR, MAP, and CPP are significantly greater than all subsequent values ($P < 0.01$).

* $P < 0.005$ compared to all subsequent values using paired t tests and multiple contrasts.

† $P < 0.01$ for the 1-min value compared to all subsequent values.

‡ $P < 0.05$ for the 2-min value compared to all subsequent values.

§ $P < 0.05$ for the 3-min value compared to all subsequent values using multiple contrasts.

There were no further significant changes after the decline in HR, MAP, and CPP at 4 min.

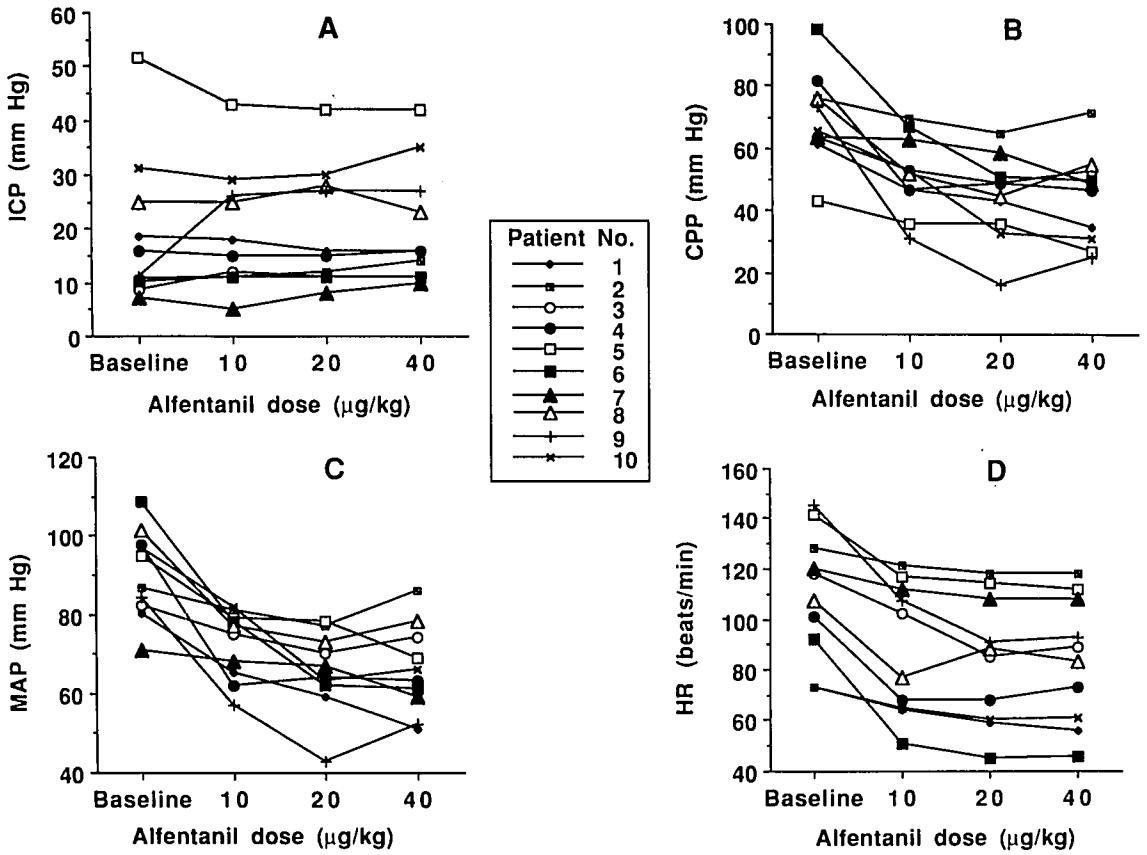

FIG. 1. Individual data for intracranial pressure (*A*), cerebral perfusion pressure (*B*), mean arterial pressure (*C*), and heart rate (*D*). Points represent values at baseline and three minutes following 10, 20, and 40 μg/kg of alfentanil.

logues would behave similarly has been questioned, with conflicting reports of the effects of sufentanil and alfentanil on ICP and cerebral blood flow.[4,5,9–11,**] We investigated alfentanil in pediatric patients undergoing revision of ventriculoperitoneal shunt because, in general, they have decreased intracranial compliance and because monitoring ICP during drug administration is easily accomplished. The mean baseline ICP in the ten patients studied was abnormally increased, at 19 ± 14 mmHg. We found that 10, 20, and 40 μg/kg alfentanil, administered to normocapnic patients anesthetized with isoflurane and nitrous oxide, reduced CPP *via* a decrease in the MAP, whereas ICP did not change. We cannot adequately explain why one patient's ICP increased after the 10-μg/kg dose of alfentanil: either alfentanil did affect this patient's ICP directly, or we observed a coincidental spontaneous rise in ICP.

Our method of administering alfentanil—three boluses of increasing dose 3 min apart, during an isoflurane–nitrous oxide–oxygen anesthetic—warrants explanation. The time of administration during the anesthetic was dictated by the patients' condition; with obstructed proximal shunts, many could not be monitored prior to shunt replacement. The dosage schedule was constructed to produce a compressed dose–response curve for alfentanil in these patients. Administration of one dose of the drug in this setting would raise the question of the threshold response. If we had given only 10 μg/kg and seen no effect, one might reasonably suspect that the dose was inadequate. If a single larger dose was chosen with an effect observed, then the question of what would happen with a smaller dose would be unanswered. With this administration technique and our results, we can reasonably conclude that profound hemodynamic effects can occur in anesthetized patients given 10 μg/kg alfentanil, resulting in significant reductions in CPP. In addition, within 9 min of 10 μg/kg, 6 min of 20 μg/kg, or 3 min of 40 μg/kg of alfentanil, ICP did not change in these patients.

Criticism could be raised that not enough time lapsed between doses of the drug. However, previous studies have found significant hemodynamic and ICP responses within the 3-min time frame used in our study.**,†† Con-

†† Lutz LJ, Milde JH, Milde LN: Cerebral effects of alfentanil in dogs with reduced intracranial compliance (abstract). J Neurosurg Anesth 1: 169–170, 1989

sidering the response time in these studies, and given the prompt hemodynamic effect in our patients, an effect on ICP would be expected by 9 min after the initial dose, particularly with the addition of two larger intervening doses. This presupposes that any intracranial effects of the drug would be mediated by vascular smooth muscle. If the drug were to affect ICP by altering production or resorption rates of CSF, the time course might be expected to be more prolonged. We are aware of no evidence that opioids exert such an effect.

We acknowledge that it is not possible to conclude whether the further decline in HR, MAP, and CPP at 4 min after the first dose of alfentanil, or 1 min after the second dose, was due to the first or second dose. It is clear, however, that a dose as small as 10 μg/kg alfentanil, in patients anesthetized with isoflurane and nitrous oxide, reduced CPP significantly by decreasing MAP. Though we did not include a placebo group or time controls, we did establish a baseline measurement period of 3 min, and patients were in a steady state without stimulation, well beyond the induction of anesthesia, and no CSF decompression occurred during the study period. The marked hemodynamic changes we observed after alfentanil administration could have influenced the measured ICP in the following manner: if cerebral autoregulation was deranged, then a decline in CPP may have resulted in a diminished cerebral blood volume, thus potentially blunting an increase in ICP if alfentanil were to cause cerebral vasodilatation. However, there is no reason to suspect a defect in autoregulation in these patients, and other investigators did not identify different effects on ICP when MAP was held constant.[4]

Our results appear to contrast with those of some investigators with regard to alfentanil's effect on ICP.[4,5,**] Studying adults with intracranial mass or vascular lesions, these investigations demonstrated significant increases in lumbar CSF pressure after alfentanil administration. However, the absolute value of the increases was clinically insignificant; ICP was inferred from lumbar CSF pressure; and the baseline pressure was normal in these patients. Our study uniquely examined patients with intracranial hypertension at baseline, and we measured ICP directly with an intraventricular catheter. The presence of intracranial hypertension at baseline is of pivotal value. This suggests that our patients were functioning on the "steep" slope of the intracranial volume–pressure relationship. Small changes in intracranial volume from even minimal vasodilatation due to alfentanil might have been expected to increase ICP. That this did not occur suggests that alfentanil caused little or no cerebral vasodilatation. The variable patient neuropathology, including the time course of the disorder, may also account for the differences among studies. Our patients with shunt malfunctions had acutely elevated CSF volume; Jung *et al.*[4] studied patients with brain tumors, all treated preoperatively for several weeks with dexamethasone, and Cuillerier *et al.*[5] investigated patients with vascular abnormalities.

The role of the background anesthetic merits attention in this regard. If alfentanil were to cause cerebral vasodilatation as a mechanism for increasing ICP, the presence of the known cerebral vasodilators nitrous oxide and isoflurane[8,12] may have either augmented or potentiated the ability of the opioid to produce this effect in our patients. If patients were already partially vasodilated from these agents, then a small amount of additional vasodilatation from alfentanil might have resulted in marked ICP increases. Alternatively, if our patients were already maximally vasodilated from the isoflurane and nitrous oxide, alfentanil's ability to produce additional vasodilatation may have been limited. We believe the latter view is unlikely with 70% nitrous oxide and an end-tidal isoflurane concentration of only 0.5%.[13,14] The presence of this background anesthetic may limit the purity of the observations regarding alfentanil's effect on ICP, but clinical practice commonly uses opioids with nitrous oxide and isoflurane.

Other reports are more consistent with our findings. Lutz and co-workers found no effect of a single high dose (300 μg/kg) of alfentanil on cerebral blood flow in dogs with acute intracranial hypertension.¶ McPherson *et al.* found the cerebral blood flow response to hypercapnia and hypoxia to be similar in dogs anesthetized with alfentanil (320 μg/kg) and pentobarbital.[15] Finally, Herrick *et al.* found no significant increase in brain retractor pressure associated with alfentanil administration.[16]

The decrease in MAP and therefore in CPP after alfentanil administration raises concern. The CPP in these patients decreased to less than the commonly believed lower limits of autoregulation for adults.[17] There is no information on the appropriate CPP for pediatric patients, although common sense dictates it to be proportionately less relative to their normally lower blood pressure. The significant decrease in HR and MAP after alfentanil injection was expected, given our study design. These patients were already adequately anesthetized, were receiving no surgical stimulation, and were then given a bolus of alfentanil, with significant vagotonic activity. If we administered atropine, allowed stimulation to proceed, or minimized the other anesthetics, the decrease in blood pressure would possibly have been attenuated. Significant reductions in CPP still might occur upon induction of anesthesia with thiopental and alfentanil, and further study is clearly indicated prior to adoption of this technique.

Children undergoing revision of an obstructed ventriculoperitoneal shunt may be obtunded and should be assumed to have intracranial hypertension. One alternative for an induction sequence calls for administration of

sufficient opioid to blunt the hemodynamic and ICP response to laryngoscopy and intubation. This approach presumes the opioid to have no deleterious effects on ICP or cerebral perfusion. Alfentanil's effect on ICP has been questioned. We found no effect of alfentanil 10–40 μg/kg on ICP in pediatric patients undergoing ventriculoperitoneal shunt revision. The decrease in CPP observed after alfentanil administration during the maintenance of anesthesia was significant. Further study of alfentanil's effect on ICP and cerebral perfusion upon induction of anesthesia in patients with varying intracranial pathology is warranted.

References

1. Bovill JG, Sebel PS, Blackburn CL, Heykants J: The pharmacokinetics of alfentanil (R39209): A new opioid analgesic. ANESTHESIOLOGY 57:439–443, 1982
2. Stanski DR, Hug CC Jr: Alfentanil, a kinetically predictable narcotic analgesic. ANESTHESIOLOGY 57:435–438, 1982
3. From RP, Warner DS, Todd MM, Sokoll MD: Anesthesia for craniotomy: A double-blind comparison of alfentanil, fentanyl, and sufentanil. ANESTHESIOLOGY 73:896–904, 1990
4. Jung R, Shah N, Reinsel, R, Marx W, Marshall W, Galicich J, Bedford R: Cerebrospinal fluid pressure in anesthetized patients with brain tumors: Impact of fentanyl vs. alfentanil during nitrous oxide-oxygen anesthesia. Anesth Analg 71:419–22, 1990
5. Cuillerier DJ, Manninen PH, Gelb AW: Alfentanil, sufentanil and fentanyl effect on cerebral perfusion pressure (abstract). Anesth Analg 70:S75, 1990
6. Park, MK, Menard, SM: Accuracy of blood pressure measurement by the Dinamap monitor in infants and children. Pediatrics 79: 907–914, 1987
7. Zar JH: Biostatistical Analysis. Englewood-Cliffs, Prentice-Hall, Inc., 1984, pp 196–198
8. Artru A: Relationship between cerebral blood volume and CSF pressure during anesthesia with isoflurane or fentanyl in dogs. ANESTHESIOLOGY 60:575–579, 1984
9. Milde LN, Milde JH, Gallagher WJ: Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 70: 138–46, 1990
10. Werner C, Hoffman WE, Baughman VL, Albrecht RF, Schulte am Esch J: Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs. Anesth Analg 72: 177–81, 1991
11. Mayer N, Weinstabl C, Podreka I, Spiss CK: Sufentanil does not increase cerebral blood flow in healthy human volunteers. ANESTHESIOLOGY 73:240–43, 1990
12. Archer DP, Labrecque P, Tyler JL, Meyer E, Trop D: Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. ANESTHESIOLOGY 67:642–648, 1987
13. Todd MM, Drummond JC: A comparison of the cerebrovascular and metabolic effects of halothane and isoflurane in the cat. ANESTHESIOLOGY 60:276–282, 1984
14. Madsen JB, Cold GE, Hansen ES, Bardrum B: The effect of isoflurane on cerebral blood flow and metabolism in humans during craniotomy for small supratentorial cerebral tumors. ANESTHESIOLOGY 66:332–336, 1987
15. McPherson RW, Krempasanka E, Eimerl D, Traystman RJ: Effects of alfentanil on cerebral vascular reactivity in dogs. Br J Anaesth 57:1232–1238, 1985
16. Herrick IA, Gelb AW, Manninen PH, Reichman H, Lownie S: Effects of fentanyl, sufentanil, and alfentanil on brain retractor pressure. Anesth Analg 72:359–63, 1991
17. Prough DS, Rogers AT: Physiology and pharmacology of cerebral blood flow and metabolism. Crit Care Clin 5:713–28, 1989