Anesthesia for Craniotomy: A Double-blind Comparison of Alfentanil, Fentanyl, and Sufentanil

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Using a prospective, randomized, and double-blind study design, alfentanil (n = 15), fentanyl (n = 14), or sufentanil (n = 16), in combination with N_2O, were administered to patients undergoing craniotomy for supratentorial tumor resection. Physicians were given two syringes, one of which was labeled as "load" for the initial loading dose and the other as "maintenance" for continuous infusion. The concentration of drug in each syringe was adjusted to permit administration on a milliliter per kilogram basis. The target loading doses for alfentanil, fentanyl, and sufentanil were 75, 10, and 1 μg/kg, respectively, and initial infusion rates were 33.5, 2.0, and 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively. Additional supplementary boluses and changes in maintenance infusion rate were made according to predetermined guidelines. Isoflurane, in increasing 0.2% inspired increments, was used only when the maximum allowed opioid dose had been given (i.e., supplementary bolus doses equal to 75% of the calculated loading dose or supplementary bolus doses equal to 50% of the calculated loading dose combined with a 50% increase in the maintenance infusion rate). Opioid infusions were stopped at the time of bone flap replacement. Antihypertensive medications and naloxone were subsequently given at the discretion of the anesthesiologist. Group demographics were not different. Total volumes of drug were similar among groups indicating equipotent preparations. Administration of isoflurane, antihypertensive medications, and naloxone were not different among groups. Although decreases in blood pressure seen with induction were similar among groups, alfentanil-treated patients received ephedrine more frequently before intubation. Thirty minutes after entry into the postanesthesia recovery area, respiratory rate and pH were lowest in sufentanil-treated patients. Level of consciousness among groups in the postanesthesia recovery area was not significantly different, although there appeared to be a tendency for alfentanil-treated patients to be more alert. No other variables, including brain condition upon dural opening, durations of intubation following either discontinuance of the maintenance infusion or completion of the head dressings, duration of intensive monitoring following surgery, or final discharge neurologic status were found to distinguish one opioid as superior to the others. Pharmacy opioid acquisition cost per procedure was greatest for the alfentanil-treated group. (Key words: Anesthesia: neurosurgical. Anesthetics, intravenous: alfentanil; fentanyl; sufentanil. Surgery: neurosurgery.)

MANY DRUGS HAVE BEEN USED to provide general anesthesia for intracranial neurosurgical procedures. One popular approach involves induction of anesthesia with thiopental, followed by one of the potent synthetic opioids (alfentanil, fentanyl, or sufentanil) combined with N_2O. This combination is well tolerated hemodynamically and emergence is usually rapid, allowing early postoperative neurologic assessment. While each of the three opioids is widely used and has been found to be satisfactory,[1–4] there is little comparative clinical information regarding the relative advantages and disadvantages of the three drugs. This is of interest for several reasons. First, there are major pharmacokinetic differences among the three agents. Second, it has been suggested that alfentanil and sufentanil may cause modest increases in cerebral blood flow (CBF), intracranial pressure (ICP), or lumbar cerebral spinal fluid pressure (CSFP).[5–7] Finally, there are substantial differences in cost. Unfortunately, it is not known if any of these issues translates into clinically meaningful differences among the three drugs when used in neurosurgical patients. To resolve these concerns, we performed a prospective, randomized, and double-blind trial comparing the safety and efficacy of alfentanil, fentanyl, and sufentanil (combined with N_2O) in patients undergoing craniotomy for supratentorial tumor resection.

Materials and Methods

PATIENT SELECTION

Forty-six adults who were ASA physical status 2 or 3 and who were scheduled to undergo craniotomy for supratentorial tumor resection under general anesthesia were studied. The study was approved by the University of Iowa Institutional Review Board and informed consent was obtained before randomization. All patients were awake and oriented to person, place, and time; were able to follow commands; did not suffer from significant cardiopulmonary disease; and had no significant laboratory abnormalities. No attempt was made to limit concurrent medications that the patients were receiving.

STUDY DESIGN

Patients were assigned (by R.P.F.) to one of three opioid groups according to a predetermined random sequence. No one involved in direct patient care (faculty, resident,

surgeons, or nurses) knew which opioid was administered until completion of the entire study.‡ All anesthetics were carried out under the direction of one of three faculty anesthesiologists (D.S.W., M.M.T., and M.D.S.).

Immediately before each procedure, two syringes were prepared. The "load" syringe contained either 375 μg/ml alfentanil, 50 μg/ml fentanyl, or 5 μg/ml sufentanil. The "maintenance" syringe contained either 375 μg/ml alfentanil, 25 μg/ml fentanyl, or 3.75 μg/ml sufentanil. These dilutions were chosen so that equipotent doses of each drug would be contained in equivalent volumes of fluids. (See appendix for calculations.)

ANESTHETIC MANAGEMENT

In the operating room, monitors consisted of a precordial (and later esophageal) stethoscope, continuous ECG, pulse oximeter, percutaneous radial artery catheter, and inspiratory/expiratory gas analyzer (multiplexed mass spectrometer). Additional monitors established following induction included a urinary catheter, esophageal thermistor, and a peripheral nerve stimulator.

Anesthesia was induced with 3–6 mg/kg thiopental (the exact dose adjusted according to clinical requirements). Ventilation *via* mask with O_2 100% was begun. End-tidal carbon dioxide (ET_{CO_2}) was maintained near 25 mmHg. Pancuronium (0.1 mg/kg) was given intravenously, and hyperventilation was continued with 60–70% N_2O in oxygen. Opioid loading was then started with a target dose of 0.2 ml/kg to be given from the load syringe over approximately 10 min. This was equal to 75 μg/kg alfentanil, 10 μg/kg fentanyl, or 1 μg/kg sufentanil. The loading dose could be adjusted upward or downward according to the patient's response and the judgment of the faculty anesthesiologist. Following opioid loading, the trachea was intubated and mechanical ventilation begun, again with 60–70% N_2O in O_2. Within 10 min after completing the loading dose, a maintenance infusion of the same opioid (from the maintenance syringe) was started at a rate of 0.08 ml·kg⁻¹·h⁻¹. This was equal to 33.5 μg·kg⁻¹·h⁻¹ alfentanil, 2 μg·kg⁻¹·h⁻¹ fentanyl, or 0.3 μg·kg⁻¹·h⁻¹ sufentanil. Additional thiopental (50–150 mg) was given as needed before application of the pin headholder.

The remainder of the anesthetic was conducted according to a series of previously established rules. When the faculty anesthesiologist judged the depth of anesthesia to be inadequate (movement, tearing, hypertension, or tachycardia), one of two interventions were taken. If the

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‡ One patient in the fentanyl-treated group developed severe brain swelling near the end of the surgical procedure. This patient was not awakened at the end of the procedure and drug identity was revealed to the surgeons and surgical intensive care staff. Data from this patient were not included in analyses.

change was judged likely to be transient, up to three 0.05 ml/kg supplementary boluses of opioid from the load syringe were given. (Each bolus was equal to 18.75 μg/kg alfentanil, 2.5 μg/kg fentanyl, or 0.25 μg/kg sufentanil.) If the change was thought to represent a more persistent condition, a 0.05 ml/kg bolus was given from the load syringe, and the maintenance infusion rate was increased to 125% of the starting rate (to 0.10 ml·kg⁻¹·h⁻¹). If this was still inadequate, a second 0.05 ml/kg bolus was given, and the infusion was increased to 150% of the starting rate (*i.e.*, 0.12 ml·kg⁻¹·h⁻¹). (This was equal to 45 μg·kg⁻¹·h⁻¹ alfentanil, 3 μg·kg⁻¹·h⁻¹ fentanyl, or 0.45 μg·kg⁻¹·h⁻¹ sufentanil.) If the depth of anesthesia was still judged inadequate following a maximal opioid complement (*i.e.*, three isolated boluses or two boluses and two increases in infusion rate), 0.2% isoflurane (inspired) was added and increased in 0.2% increments every 5–10 min until conditions were satisfactory. In contrast, if the depth of anesthesia was judged to be too deep, the maintenance infusion was decreased, again by increments of 0.02 ml·kg⁻¹·h⁻¹. Isoflurane was discontinued before any decrease in the opioid infusion rate was permitted.

Both isoflurane and the opioid infusion were discontinued when the bone flap was replaced. Any subsequent hypertension/tachycardia was treated with hydralazine, labetalol, or propranolol. After completion of the head dressing, residual neuromuscular blockade was reversed, N_2O was discontinued, and assisted spontaneous ventilation was continued with O_2 100%. Naloxone in 40–80 ug increments was given if needed. The trachea was extubated at the discretion of the faculty anesthesiologist, and patients were recovered in either the postanesthesia recover area (PARA) or in the surgical intensive care unit (SICU). The location of recovery was determined on the basis of the faculty surgeon and anesthesiologist's customary practice. Subsequent intensive monitoring was continued as clinically indicated.

DATA COLLECTION

Heart rate (HR) and mean arterial blood pressure (MABP) were recorded continuously, and the following specific values were compared among the three groups: 1) HR and MABP before induction (baseline); 2) minimum MABP before intubation and its corresponding HR; and 3) HR and MABP immediately before and 1 min after intubation. Ephedrine (5–10 mg) was given to treat hypotension as deemed necessary, and the frequency of ephedrine administration before intubation was compared among groups.

After opening the dura, the condition of the brain was assessed by the surgeons on a three-point scale: 1 = excellent; 2 = acceptable; and 3 = swollen. The frequency

with which mannitol (0.25–0.5 g/kg) was requested by the surgeon was also recorded.

Level of consciousness was assessed at two time points: 1) in the operating room just before departure, and 2) 30 min after arrival in the PARA or SICU. A five-point scale was used: 1 = alert (oriented to person, place, and time; responds to commands); 2 = awake (not oriented; responds to commands); 3 = drowsy (opens eyes; moves spontaneously or in response to pain; does not respond to commands); 4 = asleep (does not respond to commands or pain); 5 = asleep and/or intubated.

Heart rate, MABP, axillary temperature, and respiratory rate were recorded on arrival to the PARA or SICU; arterial blood gases were analyzed 30 min after arrival. Frequency of naloxone administration was recorded.

The following time intervals were recorded: 1) induction of anesthesia to lowest MABP before intubation; 2) induction of anesthesia to intubation; 3) duration of opioid infusion (infusions were started within 10 min after the loading dose and continued until bone flap replacement); 4) duration of surgery (from incision to completion of head dressing); 5) discontinuation of opioid infusion to extubation; 6) duration of intubation following completion of the head dressing; 7) duration of intensive monitoring following surgery (in PARA or SICU); and 8) length of hospital stay following surgery.

Through chart review, neurologic status at the time of discharge was compared to the patient's status at admission. The opioid used was not known to the reviewer. The following classes were established: 1 = worsened; 2 = no change; and 3 = improved. At the end of the anesthetic, the faculty anesthesiologist and resident were each asked to identify the opioid they believed had been administered.

Pharmacy acquisition costs per procedure (1989 prices) of 5 ml ampules were used to determine the cost for each opioid. Alfentanil (Alfenta®) and sufentanil (Sufenta®) were purchased from Janssen Pharmaceutica (Piscataway, NJ). Fentanyl was purchased from Janssen Pharmaceutica (Sublimaze®) and Elkins-Sinn (Cherry Hill, NJ).

STATISTICAL METHODS

One-way analysis of variance (ANOVA) followed by Newman-Keuls test, if indicated by a significant F ratio, was applied to continuous data. The chi-squared (χ^2) test was applied to discreet (categorical) data, and Fisher's exact test was used when sparse cell count warnings suggested χ^2 may not be valid. Two-way (time and group) ANOVA with repeated measures on the time factor was used to assess hemodynamic changes. The frequency with which the anesthesiologists successfully identified the drugs used (relative to chance) was examined using a nor-

mal approximation test of a proportion. $P < 0.05$ was considered statistically significant. Continuous data are expressed throughout as mean ± SD.

Results

There were no differences among the three faculty anesthesiologists with respect to the number of cases done or the distribution of study drugs. Twenty-three anesthesia residents were involved, with each participating in one to five cases. Procedures were done by one of six neurosurgeons.

DEMOGRAPHIC, OPERATIVE, AND POSTOPERATIVE DATA

Demographics are shown in table 1. There were no significant differences among study groups with respect to age, height, weight, body mass index,[8] gender, or ASA physical status. Duration of surgery, estimated blood loss, fluid replacement (crystalloid), and urine output were similar. Two patients in the alfentanil-treated group and one in the sufentanil-treated group received intraoperative blood replacement. Temperatures following surgery were similar. Thirty minutes after entry into the PARA or SICU, respiratory rate was lowest in the sufentanil-treated group, while the alfentanil- and fentanyl-treated groups were similar. Arterial pH was lowest in the sufentanil-treated group, although Pa_{CO_2} values did not achieve a statistically significant difference. Neurologic status at hospital discharge was not different among opioid groups.

DRUG DATA

Drug data are shown in tables 2 and 3. Preoperative anticonvulsant therapy did not differ among groups (table 2). Total doses of thiopental and pancuronium were similar. Patients in the alfentanil-treated group received ephedrine more frequently, with the drug being given almost exclusively before intubation. There was no difference in the frequency of intraoperative mannitol administration. Neither the number of patients requiring isoflurane supplementation nor the maximum percent inspired isoflurane concentration differed among groups. The doses and frequency of use of antihypertensive medication and frequency of naloxone administration were not statistically different among treatment groups.

Volumes (total milliliters) of opioids for the loading dose and maintenance infusion were not different (table 3). While it was necessary to modify the loading dose of opioid (increase or decrease) in some patients for medical reasons, the number of patients in which this was required did not differ among groups. There were no differences in the total number of times it was necessary to alter the

TABLE 1. Patient and Operative Demographics by Opioid Used for Anesthesia

	Alfentanil (n = 15)	Fentanyl (n = 14)	Sufentanil (n = 16)	P
Age (yr)	53 ± 17	52 ± 20	47 ± 19	NS
Height (cm)	165 ± 12	170 ± 10	169 ± 10	NS
Weight (kg)	70.4 ± 13.1	78.8 ± 16.7	67.8 ± 16.1	NS
Body mass index (kg/m²)	25.6 ± 3.3	28.1 ± 5.9	23.7 ± 5.0	NS
Gender (female/male)	10/5	6/8	10/6	NS
ASA physical status (2/3)	8/7	8/6	10/6	NS
Duration of surgery (min)	316 ± 102	293 ± 119	308 ± 80	NS
Esimtated blood loss (ml)	525 ± 594	357 ± 406	307 ± 301	NS
Fluid replacement (crystalloid) (ml)	2407 ± 1420	2280 ± 915	2377 ± 1175	NS
Urine output (ml)	1353 ± 845	1465 ± 720	1222 ± 628	NS
Temperature on arrival to PARA or SICU (° C)	36.2 ± 0.8	36.5 ± 0.9	35.8 ± 0.7	NS
30 min after arrival in PARA or SICU				
Respiratory rate (breaths/min)	17 ± 6	15 ± 4	12 ± 4	0.03*
pH	7.40 ± 0.0	7.38 ± 0.0	7.34 ± 0.0	0.02†
Pa_{CO_2} (mmHg)	36.9 ± 6.2	40.2 ± 5.2	42.2 ± 4.1	NS
Neurologic status at discharge (1/2/3)‡	1/12/2	4/8/2	2/12/2	NS

* Sufentanil *versus* alfentanil.
† Sufentanil *versus* alfentanil and fentanyl.

‡ 1 = worsened; 2 = no change; 3 = improved.

maintenance infusion rate (increase or decrease). Volumes for supplementary bolus doses are shown.

HEMODYNAMIC DATA

Despite randomization, baseline HR for the fentanyl-treated group (60 ± 11 beats per min) was significantly less than either the alfentanil- (73 ± 15 beats per min) or sufentanil-(73 ± 13 beats per min) treated groups. There were no differences in preoperative MABP (95 ± 12, 97 ± 9, and 91 ± 15 mmHg for the alfentanil-, fentanyl-, and sufentanil-treated groups, respectively). There were no differences among groups in either the lowest observed MABP or in the change of MABP in response to intubation (fig. 1). The time interval from induction to lowest MABP was similar for all three groups (8.5 ± 3.6, 7.1 ± 3.8, and 8.1 ± 3.2 min for the alfentanil-, fentanyl-, and sufentanil-treated groups, respectively).

TABLE 2. Perioperative Drugs by Type of Opioid Used for Anesthesia

Drug	Alfentanil (n = 15)	Fentanyl (n = 14)	Sufentanil (n = 16)	P
Preoperative anticonvulsant therapy (yes/no)*	13/2	12/2	15/1	NS
Thiopental (total) (mg/kg)	8.4 ± 4.3	6.7 ± 2.4	7.5 ± 3.6	NS
Pancuronium (total) (mg/kg)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	NS
Ephedrine 5–10 mg prior to intubation (yes/no)	5/10	0/14	1/15	0.018†
Mannitol 0.25–0.5 (g/kg) (yes/no)	8/7	7/7	6/10	NS
Isoflurane				
Frequency of use (yes/no)	8/7	5/9	5/11	NS
Maximum % inspired	0.7 ± 0.4	0.5 ± 0.3	0.4 ± 0.1	NS
Antihypertensive drugs				
Hydralazine (mg)	21.05 ± 5.7	20.0 ± 12.2	12.7 ± 5.2	NS
Labetalol (mg)	19.2 ± 8.6	18.0 ± 10.2	19.4 ± 8.6	NS
Propranolol (mg)	1.5 ± 0.6	1.6 ± 1.1	2.0 ± 0.0	NS
Frequency of use (yes/no)	13/2	11/3	13/3	NS
Naloxone				
Frequency of use (yes/no)	0/15	2/13	2/14	NS

* Phenytoin sodium or carbamazepine.

† Alfentanil *versus* fentanyl and sufentanil.

FROM *ET AL.*

TABLE 3. Opioids Used for Anesthesia

	Alfentanil (n = 15)	Fentanyl (n = 14)	Sufentanil (n = 16)	P
Opioid initial loading dose				
Total ml	14.5 ± 2.9	16.1 ± 3.5	13.7 ± 3.3	NS
µg/kg	77.8 ± 8.4	10.2 ± 1.1	1.0 ± 0.1	0.001†‡
Opioid maintenance infusion				
Total ml	25.9 ± 9.5	30.9 ± 18	25.2 ± 10.3	NS
$\mu g \cdot kg^{-1} \cdot h^{-1}$	27.8 ± 5.8	2.0 ± 0.5	0.3 ± 0.1	0.0001†
Increased rate*	26	17	20	NS
Decreased rate*	5	4	4	NS
Opioid supplementary bolus				
Dose (ml)	11.1 ± 5.3	10.2 ± 7.0	8.5 ± 5.4	NS
µg/kg	58.7 ± 25.0	6.2 ± 4.0	0.7 ± 0.4	0.0001†
Number of boluses/group	19	20	18	—

* Total number of events in each group.
† Alfentanil *versus* fentanyl and sufentanil.
‡ Fentanyl *versus* sufentanil

INTRAOPERATIVE AND POSTOPERATIVE VARIABLES

Recorded durations are shown in table 4. (Total duration of surgery is presented in table 1). There were no intergroup differences. In particular, there were no differences in the time between completion of the head dressing and extubation. There were also no differences

TABLE 4. Intraoperative and Postoperative Durations by Type of Opioid Used for Anesthesia

	Alfentanil (n = 15)	Fentanyl (n = 14)	Sufentanil (n = 16)	P
Intraoperative				
Induction to intubation (min)	10 ± 5	9 ± 3	10 ± 3	NS
Duration of:				
Opioid infusion (min)	260 ± 99	256 ± 119	256 ± 79	NS
Intubation after discontinuation of infusion (min)	61 ± 15	44 ± 34	60 ± 13	NS
Intubation after completion of head dressing (min)	5 ± 3	7 ± 6	8 ± 8	NS
Postoperative				
Duration of intensive monitoring after surgery (h)*	44 ± 27	58 ± 45	42 ± 32	NS
Total hospitalization after surgery (days)	13 ± 6	9 ± 4	13 ± 6	NS

* One patient in the fentanyl-treated group was considered an "outlier" because of prolonged intensive monitoring for medical reasons unrelated to surgery. This patient was deleted from this analysis.

in either the duration of intensive monitoring or total postoperative hospital stay.

Brain conditions after opening the dura were not different (fig. 2). Level of consciousness in the operating room and PARA or SICU were not different among study
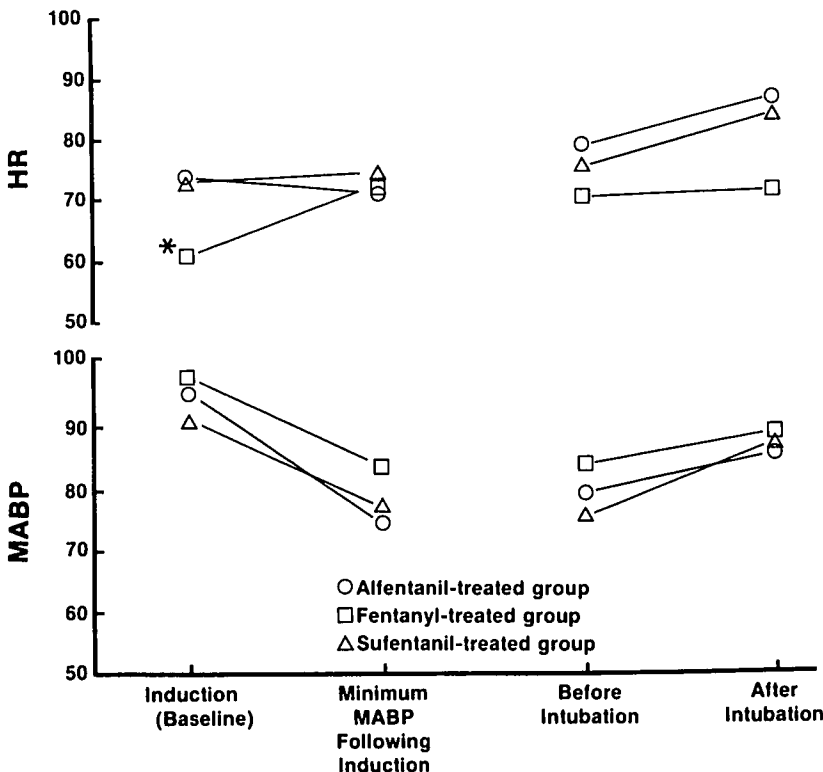

FIG. 1. Heart rate (HR) and mean arterial blood pressure (MAPB) immediately prior to induction of anesthesia (baseline) *versus* lowest MABP after induction (with corresponding HR); HR and MABP 1 min before *versus* 1 min after intubation. *Significant difference between fentanyl- and alfentanil/sufentanil-treated groups.

○ Alfentanil-treated group
□ Fentanyl-treated group
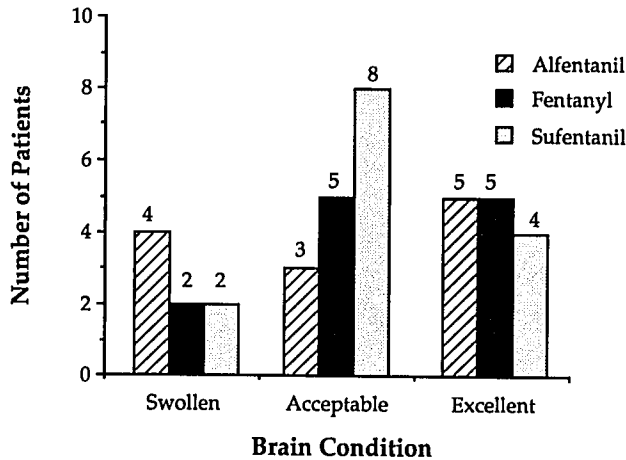△ Sufentanil-treated group

FIG. 2. Brain condition after opening the dura as evaluated by the surgeon who was unaware of the opioid administered. A three-point scale was used: 1 = excellent; 2 = acceptable; 3 = swollen. (Note: seven evaluations were not recorded during surgery.)

groups (fig. 3). However, when comparing the 30-min level of consciousness scores, there was a tendency toward a faster return to normalcy with alfentanil ($P = 0.06$).

OPIOID ACQUISITION COSTS

Pharmacy opioid acquisition costs per procedure were 56.6 ± 14.9, 7.0 ± 2.8, and 18.9 ± 5.7 for Alfenta®, Sublimaze®/fentanyl citrate injection, and Sufenta®, respectively. The cost of the Sublimaze®/fentanyl citrate injection was significantly less than either Alfenta® or Sufenta®.

PHYSICIAN DETERMINATIONS OF STUDY DRUG IDENTITY

Faculty anesthesiologists and anesthesia residents correctly identified the opioid used in 47% and 41% of cases, respectively. This did not differ from chance.

Discussion

Patients with chronic intracranial space-occupying lesions present unique concerns to the anesthesiologist. Among these are maintenance of hemodynamic and respiratory stability. In addition, despite the absence of outcome data to support this, it seems prudent to minimize transient changes in ICP and cerebral perfusion pressure (CPP). Finally, because of the value of the neurologic examination in the immediate postoperative period, a rapid emergence from anesthesia is warranted.

With the advent of synthetic opioids having relatively short durations of action (alfentanil, fentanyl, and sufen-

tanil), many of these demands appear to have been met. Pharmacokinetic data suggest that bolus administration followed by continuous intravenous infusions of any of these agents should allow a relatively predictable and rapid recovery from anesthesia.[9] However, it is not clear whether available pharmacokinetic data can be extrapolated to a neurosurgical patient population where drug distribution and clearance may be altered by age, hyperventilation,[10] or concurrent medications, e.g., anticonvulsants. The hemodynamic effects of high doses of these opioids, in combination with O_2, have been found to be acceptable even for patients with significant cardiovascular disease,[11–14] although, again, it is unclear whether these findings apply to neurosurgical patients in whom the drugs are used in lower doses and often in combination with N_2O. Early investigations showed synthetic opioids to have little or no effect on intracranial dynamics.[2,15] However, two later studies suggested that there may be differences among these drugs with respect to their effects on ICP or cerebral blood flow.[6,7]

The current study was designed, therefore, not as a pharmacokinetic comparison of these agents but rather
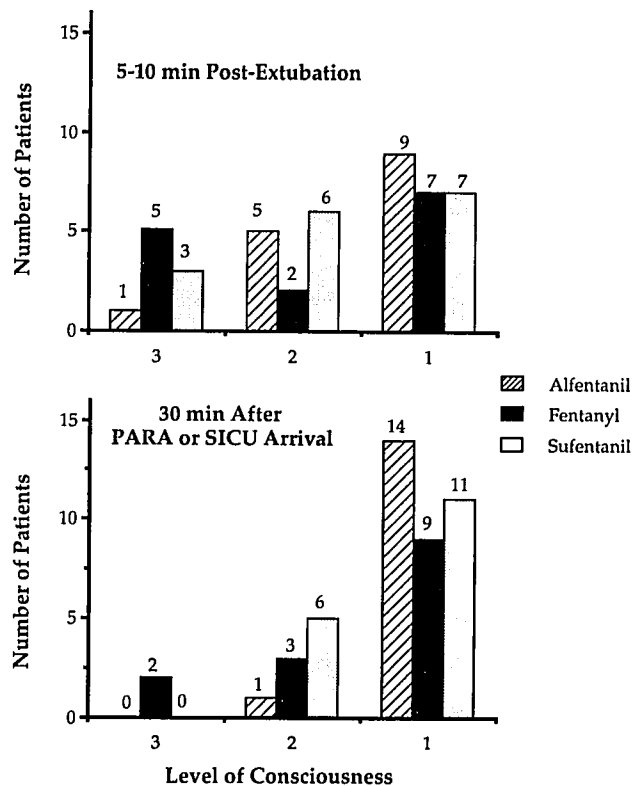

FIG. 3. Level of consciousness after extubation in the operating room (top) and 30 min after arrival in the PARA/SICU (bottom). A five-point scale was used: 1 = alert; 2 = awake; 3 = drowsy; 4 = asleep; 5 = asleep/intubated. No patient was scored greater than 3.

to determine if meaningful clinical differences could be observed among them. Our objective was to administer equivalent doses of the three drugs in a prospective, randomized, and double-blind fashion to a relatively uniform group of patients undergoing a common neurosurgical procedure. To minimize variability, we restricted the study to patients undergoing resection of supratentorial tumors. Examination of the demographic data show that the three groups were both similar and, we believe, typical of a neurosurgical population. Based on the observation that the total volumes of the solutions administered and the doses and frequency of isoflurane supplementation used were not different among groups, our doses also appear to be equivalent.

Other double-blinded investigations[16–25] were designed to directly compare these three agents, although none evaluated all three opioids in a single study. In some of these studies, alterations in drug dosage were made according to strict rules that were based on changes in hemodynamics.[18,20] Other investigations, including our own, administered the opioid up to the maximum dose calculated or when hemodynamic or anesthetic effects limited the dose.[17,19,21,22,25] Movement was not available as a sign of inadequate anesthesia from long-acting muscle relaxants in several studies,[16–21,23] and the current study. Thus, signs of autonomic hyperactivity (*e.g.*, diaphoresis, lacrimation, tachycardia, and hypertension) were used when movement was not available.[9,16–21,23] Since 42% of our patients were classified as ASA physical status 3 with an average age of 50 years, we believed that strictly defined hemodynamic limits were not safe for all study patients. With respect to the relative potencies of these drugs, our data are in close agreement with that of others who reported that fentanyl is about one tenth the potency of sufentanil.[16,19,20] Only one other blinded study mentioned the relative potency of alfentanil to fentanyl,[23] and its data are in slight disagreement with ours. We found alfentanil to have about one seventh the potency of fentanyl, whereas Asbury[23] reported that alfentanil has about one third the potency of fentanyl.

The three drugs studied here are known to have different pharmacokinetic profiles.[26] Despite this, we saw essentially no practical differences in the speed of emergence from anesthesia. Although patients receiving alfentanil may have had a somewhat higher level of consciousness 30 min after arrival in the recovery area, all but two patients in the fentanyl group were able to follow commands and were therefore sufficiently alert to permit an adequate neurologic evaluation. It should also be noted that one of the two patients receiving fentanyl underwent a 10-h resection of a large cholesteatoma (the longest procedure in the study) and did not return to a normal level of consciousness for 3 days following surgery. These findings suggest that variation in the pharmacokinetic behavior of these drugs in individual patients was as large or larger than the published differences among these drugs when given to a homogenous and young group of experimental subjects. Such variability, which may be large enough to conceal real pharmacokinetic differences between drugs, was discussed by Wood.[27] In addition, when intravenous drug dosage is carefully titrated to effect, as occurred in our study, the rapidity of emergence is optimized.[9]

As noted earlier, it has been suggested that there may be differences among the synthetic opioids with respect to their effects on ICP and CBF. Marx *et al.*,[6] in an unblinded study, administered alfentanil (50 μg/kg followed by an infusion of 1 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}), fentanyl (5 μg/kg), or sufentanil (1 μg/kg) to patients with supratentorial tumors whose lungs were being mechanically ventilated with 60% N_2O in O_2. Lumbar CSFP and MABP were continuously monitored. Ten minutes after opioid administration (when maximal changes were observed), cerebral perfusion pressure (MABP-CSFP) was 57, 68, and 65 mmHg in alfentanil-, fentanyl-, and sufentanil-anesthetized patients, respectively. Although changes in CSFP at this interval were minimal (*i.e.*, 2.0, 1.2, and 4.4 mmHg for alfentanil, fentanyl, and sufentanil, respectively), MABP was significantly reduced in all three groups with the largest effect (-26 mmHg) occurring in the alfentanil group. In general, our data are consistent with those observations. In our more subjective assay, brain swelling was unaffected by the opioid administration as one might expect given the very small differences in maximal ICP changes observed by Marx *et al.*[6] Milde *et al.*[7] showed a transient increase in CBF following the bolus administration of sufentanil to dogs. However, Mayer *et al.*[28] administered increasing doses (0.5, 1.0, and 2.0 μg/kg) of sufentanil to neurosurgical SICU patients with either moderate or severe intracranial hypertension. Sufentanil (in any dose) did not alter ICP in either group. Of note, CPP was reduced in a dose-dependent manner due to reductions in MABP, with the patients having the more severe preexisting elevations in ICP exhibiting the greatest effect. Finally, Cuillerier *et al.*[29] concluded that there are no differences among the three opioids with respect to their effects on CPP in patients anesthetized for intracranial neurovascular procedures.

Available evidence leads us to conclude that the effects of alfentanil, fentanyl, and sufentanil on intracranial dynamics and the clinical course of neurosurgical anesthesia are similar. It is possible that differences do exist in the ICP effects of these drugs; however, we did not measure ICP. Nevertheless, if such differences were present, they were not reflected by differences in brain bulk, emergence from anesthesia, or final patient outcome. As a result, we

believe the three opioids can be used interchangeably in patients at risk for ICP increases.

In conclusion, using nearly 40 variables to compare the three groups of patients undergoing craniotomy for supratentorial tumor resection (where alfentanil, fentanyl, or sufentanil were administered by a milligram per kilogram dose and in a double-blinded and randomized fashion), we identified only four differences among these three agents: 1) hypotension before intubation required treatment with ephedrine more frequently in patients receiving alfentanil; 2) 30 min after entry into the PARA/SICU, respiratory rate was lowest in the sufentanil-treated group (although this did not present a clinical problem and did not require naloxone therapy); 3) there was some suggestion that patients receiving alfentanil were more alert 30 min after arrival in the recovery area; and 4) the opioid cost per anesthetic was greatest for Alfenta. In addition, our results indicate that the potency of alfentanil is about one seventh that of fentanyl, with fentanyl having one tenth the potency of sufentanil. Finally, there were no clinically significant differences in the condition of the brain upon dural opening, requirements for isoflurane supplementation, use of either antihypertensives or naloxone, rate at which patients returned to a level of conscious permitting neurologic evaluation, or final patient outcome.

Appendix

The opioid loading doses were chosen on the basis of published recommendations,[26] Janssen Pharmaceutica Inc. product literature (Alfenta® and Sufenta® Injection copyright © Janssen Pharmaceutica Inc. 1987), and clinical experience. The values for the loading dose and additional pharmacokinetic parameters used are shown in table 1A. Using these values, the plasma concentrations that would result from the chosen loading doses were then calculated using the following formula:

$$\text{calculated plasma concentration} = \text{loading dose}/Vd_{ss}$$

and resulted in calculated plasma concentrations of 6.4, 13.0, and 12.7 $ml \cdot kg^{-1} \cdot min^{-1}$ for alfentanil, fentanyl, and sufentanil, respectively. The initial infusion rates were then calculated according to the following formula:

$$\text{infusion rate} = \text{calculated plasma concentrations} \times \text{clearance}$$

TABLE 1A. Loading Dose and Additional
Pharmacokinetic Parameters

	Alfentanil	Fentanyl	Sufentanil
Loading dose (μg/kg)	75	10	1
Volume of distribution/ steady state ($V_{d_{ss}}$) (ml/ kg)	860	4000	2900
Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	6.4	13.0	12.7

and resulted in infusion rates of 33.48, 1.95, and 0.27 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for alfentanil, fentanyl, and sufentanil, respectively.§

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§ The actual infusion rates were rounded to 33.5, 2.0, and 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for alfentanil, fentanyl, and sufentanil respectively.

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