Comparison of fentanyl, sufentanil and alfentanil during awake craniotomy for epilepsy

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Neurolept anaesthesia is used during awake craniotomy for epilepsy surgery. This study compares analgesia, sedation and the side effects of the newer opioids sufentanil and alfentanil, with those of fentanyl in patients undergoing awake craniotomy. Thirty patients were randomized into three groups, each received droperidol, dimenhydrinate and the chosen opioid as a bolus followed by an infusion. The opioid doses used were fentanyl 0.75 $\mu g \cdot kg^{-1}$ plus 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$; sufentanil 0.075 $\mu g \cdot kg^{-1}$ plus 0.0015 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and alfentanil 7.5 $\mu g \cdot kg^{-1}$ plus 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. There were no differences in the requirements for droperidol, dimenhydrinate or in the incidence of complications among the three groups. The total doses of the opioids required were fentanyl 4.9 ± 1.3 $\mu g \cdot kg^{-1}$, sufentanil 0.6 ± 0.2 $\mu g \cdot kg^{-1}$ and alfentanil 149 ± 36 $\mu g \cdot kg^{-1}$. Two patients became uncooperative requiring general anaesthesia. The conditions for surgery, electrocorticography and for stimulation testing were satisfactory in all other patients. We conclude that the newer opioids did not offer any benefit over fentanyl.

Le traitement chirurgical de l'épilepsie par craniotomie se fait souvent à l'état vigile sous neuroleptanalgésie. Cette étude vise à comparer l'analgésie, la sédation et les effets secondaires des nouveaux morphiniques sulfentanil et alfentanil avec le fentanyl chez des malades en cours de cranitomie vigile. Trente patients sont distribués au hasard en trois groupes, chacun recevant dropéridol, dimenhydrinate et un des morphiniques en bolus suivi d'un perfusion. La posologie est pour le fentanyl de 0,75 $\mu g \cdot kg^{-1}$ et par la suite de 0,01 $\mu g \cdot kg^{-1} \cdot min^{-1}$; pour le sufentanil de 0,075 $\mu g \cdot kg^{-1}$ et par la suite de 0,0015 $\mu g \cdot kg^{-1} \cdot min^{-1}$ et pour l'alfentanil de 7,5 $\mu g \cdot kg^{-1}$ et par la suite de 0,5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Les besoins de dropéridol et de dimenhydrinate et l'incidence de complication ont été les mêmes pour les trois groupes. La dose totale est pour le fentanyl 4,9 ± 1,3 $\mu g \cdot kg^{-1}$, le sufentanil, 0,6 ± 0,2 $\mu g \cdot kg^{-1}$ et l'alfentanil de 149 ± 36 $\mu g \cdot kg^{-1}$. Deux malades qui ont cessé de collaborer, doivent être anesthésiés. Les conditions de la chirurgie, de l'électrocorticographie et des tests de stimulation sont satisfaisantes pour tous les autres patients. Nous concluons que les nouveaux morphiniques n'offrent aucun avantage sur le fentanyl.

Key words

ANAESTHETICS INTRAVENOUS: fentanyl, sufentanil, alfentanil;
ANAESTHETIC TECHNIQUES: neurolept;
SURGERY: craniotomy.

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Awake craniotomy is often performed on patients with pathological lesions located near areas of eloquent brain function, such as in patients with intractable seizures.[1] The aim of anaesthesia is to have a comfortable yet alert patient. Local anaesthesia with neurolept analgesia allows for electrocorticographic (ECoG) localization of the seizure focus and delineation of eloquent areas of brain function. The most common neurolept agents used are fentanyl and droperidol.[2,3] The purpose of this study was to compare the effectiveness of the newer opioids, sufentanil and alfentanil with fentanyl in providing adequate analgesia with minimum side effects during awake craniotomy for epilepsy surgery.

Methods

After approval from the Ethics Committee of the University of Western Ontario, written, informed consent was obtained from 30 adult patients presenting for awake craniotomy for intractable epilepsy. Each patient was randomly assigned to receive one of the three opioids, fentanyl, sufentanil or alfentanil in a double-blinded manner.

All patients were receiving anticonvulsant therapy, but the dose was tapered or the drug discontinued before surgery. The patients were unpremedicated. A field block of the scalp using approximately 60 ml bupivacaine 0.33% was performed by the surgeon before the patient arrived in the operating room. On arrival, the patient was placed as comfortably as possible in a lateral position

on the operating table. The monitors used included an ECG (lead 2), non-invasive automated blood pressure and a pulse oximeter. Supplemental oxygen was given using nasal prongs that were adapted for the monitoring of end tidal CO_2 and respiratory rate. Maintenance intravenous fluid consisted of Ringers lactate at 50 ml · hr^{-1}.

After positioning, neurolept anaesthesia was started by the administration of droperidol 0.014 mg · kg^{-1} *iv*, dimenhydrinate, 0.25 mg · kg^{-1} *iv* and the opioid bolus followed by the infusion according to the doses shown in Table I. Whenever more analgesia was required, an incremental dose of one half the initial bolus dose was administered to the patient. Throughout the procedure, patients were given additional droperidol and dimenhydrinate for sedation, nausea, and vomiting at the discretion of the anaesthetist.

The infusion of the opioid was continued until the dura was opened. Then, all drug administration was stopped in order to have the patient as alert as possible during the ECoG and stimulation testing. In all patients, at least 30 min of ECoG were performed. This was followed by electrostimulation of the cortex to delineate the eloquent areas such as speech, sensory and motor function. On completion of the testing, an incremental dose of the opioid was administered and the infusion restarted for resection of the lesion. Once the resection was completed, the infusion and drugs were once again stopped to allow for post-resection ECoG. Then, if no further resection was required, the opioid infusion and, if needed, an incremental bolus of any of the drugs were administered for closure of the craniotomy.

All complications such as nausea, vomiting, seizures, excessive pain, oxygen desaturation less than 90%, increase in end tidal CO_2 (>45 mmHg), decrease in respiratory rate, excessive sedation, inability to cooperate and the induction of general anaesthesia were documented. At any time during the procedure, if a patient developed seizures, they were treated by the administration of a small intravenous dose of thiopentone (25–50 mg).

In the recovery room, pain was treated with codeine (30–60 mg) *im*. The patient was examined for the presence of any motor or sensory deficits and for any impairment in brain function such as speech or memory. The neurological assessments of the patients in the recovery room and at time of discharge were documented.

The total dose of all drugs required and the incidence of complications were tabulated for each patient. Statistical analysis was performed using analysis of variance. Where significance was found, a Student Newman-Keuls test for multiple comparisons was performed. $P < 0.05$ was considered significant. Chi-square testing was used for the analysis of the complications.

TABLE I Protocol for opioids

Opioid	*Bolus* ($\mu g \cdot kg^{-1}$)	*Infusion* ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
Fentanyl	0.75	0.01
Sufentanil	0.075	0.0015
Alfentanil	7.5	0.5

Incremental dose = 1/2 bolus dose.

Results

There were no differences among the three groups in age, weight, sex and length of surgery (Table II). The total requirements of the opioids, and other drugs by each group of patients are shown in Table III. The total amounts of droperidol, dimenhydrinate and the postoperative codeine for analgesia in the recovery room were not different among the three groups. The total amounts of opioid required by the three groups were different; the amount of alfentanil used was greater than both fentanyl and sufentanil. The cost of the opioids used was calculated on the average requirement of each opioid per average weight of patients within each group and the average duration of the procedure. The cost of fentanyl used was $5.82, sufentanil $3.51 and alfentanil $66.24. Thus, alfentanil was the most expensive drug.

The incidence of complications is shown in Table IV. There were no differences among the three groups in all the complications that occurred. None of the patients in any group had a "tight" brain on dural opening. The condition of the brain was satisfactory for surgery throughout the procedure in all patients. The ability of the patients to cooperate for stimulation testing and the conditions for ECoG were satisfactory in all patients except in two patients in the fentanyl group. These two patients became very uncooperative and required the induction of general anaesthesia. One patient, a 52-yr-old man with seizures related to a temporal lobe arteriovenous malformation developed excessive pain and bleeding and became uncooperative after four hours of surgery. The initial ECoG and stimulation testing had been completed. The other patient was a 39-yr-old man who became uncooperative after three and a half hours of the procedure, during surgical resection of the temporal lobe.

As the number of patients in our study was small, the power of our study was calculated. The power was greater than 0.80 for all except the difference between sufentanil and alfentanil for nausea, vomiting and increased $P_{ET}CO_2$ and the difference between fentanyl and sufentanil for an increase in $P_{ET}CO_2$. Thus a type II error may have occurred in these groups.

The incidence of postoperative seizures and neurological deficits was not different among the three groups.

TABLE II Demographic results

	Fentanyl	*Sufentanil*	*Alfentanil*
Age (yr)	37 ± 12	31 ± 10	30 ± 11
Weight (kg)	72 ± 10	65 ± 17	78 ± 13
Sex (M:F)	4 : 6	7 : 3	5 : 5
Length of surgery (hr)	5.4 ± 1.2	5.5. ± 1.4	5.0 ± 1.0

Values are mean ± SD.

TABLE III Total drug requirements

Drug	*Fentanyl*	*Sufentanil*	*Alfentanil*
Opioid ($\mu g \cdot kg^{-1}$)	4.9 ± 1.3	0.6 ± 0.2	149 ± 36*
Droperidol (mg)	2.5 ±0.6	1.8 ± 1.4	1.9 ± 1.1
Dimenhydrinate (mg)	40 ± 21	32 ± 20	48 ± 28
Recovery room codeine (mg)	32 ± 48	33 ± 32	33 ± 30

Values are mean ± SD.
*Different from fentanyl and sufentanil.
$P < 0.05$.

TABLE IV The incidence of intraoperative complications

	Fentanyl	*Sufentanil*	*Alfentanil*
Nausea/vomiting	5	3	7
Seizures	1	3	1
Uncooperative	1	0	1
Induction of general anaesthesia	2	0	0
Oversedation	1	0	1
Desaturation	0	2	1
Increased $P_{ET}CO_2$	2	5	2

Eight patients (fentanyl 3, sufentanil 3, alfentanil 2) had neurological deficits immediately postoperatively. These deficits consisted of dysphasia, aphasia or extremity weakness. Most deficits were improving and in one case had completely recovered by the time of discharge from hospital.

In total, five patients had at least one seizure during the operative procedure. None of the patients had seizures in the recovery room. Five patients were continuing to have seizures at the time of discharge.

Discussion

The aim of anaesthesia for awake craniotomy for epilepsy surgery is to have the patient comfortable enough to remain immobile during a long procedure but also alert and cooperative enough to comply with testing.[2] In our study, we assessed the use of two newer opioids, sufentanil and alfentanil in comparison with the traditionally used opioid fentanyl and found that conditions for surgery were satisfactory with all three techniques.

The effects of fentanyl, sufentanil and alfentanil on the electroencephalogram and the central nervous system are similar.[4,5] There are differences in the clinical effects of these three opioids due to their different pharmacokinetic properties and there is also a wide individual variability.[6–9] The dose of fentanyl used in our study represented the average dose used traditionally at our institution for an awake craniotomy. There is some debate in the literature with regard to the potency ratios of the three opioids studies. Analgesic potency ratios for sufentanil to fentanyl are in the range of 5:1 to 10:1.[10,11] For the purposes of our study, we used a potency ratio of sufentanil 10:1 to fentanyl. The alfentanil to fentanyl potency ratios have been reported from 1:3 to 1:10; we used a ratio of 1:10.[11,12] Various infusion rates of alfentanil have been used for the maintenance of general anaesthesia.[8,13,14] We chose a low-dose infusion in our study of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in order to have the patients only mildly sedated. The purpose of our study was not to perform a precise pharmacological comparison among the three opioids but to use doses that were compatible with the aims of the procedure. Thus, potential discrepancies exist with the relative opioid doses in our study.

Patients who are treated with one or more anticonvulsants on a chronic basis have a higher fentanyl requirement for the maintenance of general anaesthesia.[15] There is also a linear dose effect relationship between fentanyl requirements and the number of anticonvulsants in chronic use by the patient. All our patients were receiving at least one anticonvulsant preoperatively. There was no difference among the three groups in the number of anticonvulsants the patients were taking. Thus, the opioid requirements should be similar for all three groups. However, the amount of alfentanil used was more than three times greater than that of fentanyl, making this the most expensive technique used.

Previous reports have analyzed retrospectively the anaesthetic management of patients for awake craniotomy.[2,3] Alfentanil has also been used successfully with a bolus and infusion technique.[16] Alfentanil was found to be useful due to its relatively rapid onset and short duration of action thus allowing it to be administered more easily to achieve changing levels of awareness and cooperation. In this case report, the doses of alfentanil and droperidol used were markedly greater than in our study. This probably reflects the differences in patient population and surgical expectations.

The clinical conditions were satisfactory with all three drugs used. The incidence of complications that occurred in our study did not show any differences among the three groups. The number of patients in our study was small and a type II error may have occurred. In comparing the overall incidence of complications with those

in a previous retrospective review, we found a higher incidence of nausea and vomiting, which may be because our study was prospective and each complication was carefully documented.[3] The conditions for the surgical procedure were satisfactory in all patients except in the two that required general anaesthesia.

Oversedation of patients during awake craniotomy can result in many problems. The patient may be too sedated to cooperate, especially during stimulation testing for localization of the areas of eloquent brain function. An increase in $PaCO_2$ that occurs with respiratory depression may result in excessive brain swelling. In our study, five patients in the sufentanil group had episodes of increased end tidal CO_2 but this was not different from the other two groups. None of these patients required pharmacological intervention for excessive sedation. The incidence of postoperative neurological deficits or seizures was not influenced by the opioid used.

In conclusion, we found that all three opioids used with a bolus and infusion technique provided satisfactory conditions for surgery, ECoG and stimulation testing. The newer opioids did not have any advantage over the traditional drug, fentanyl.

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