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An open, randomized comparison of alfentanil, remifentanil and alfentanil followed by remifentanil in anaesthesia for craniotomy

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Summary

We studied 52 adults undergoing elective craniotomy, allocated randomly to one of three opioid treatments: alfentanil 50 μg kg^{-1} followed by 0.833 μg kg^{-1} min^{-1} until dural closure (group Alf.); alfentanil 50 μg kg^{-1} followed by 0.833 μg kg^{-1} min^{-1} for 2 h, then remifentanil 0.25 μg kg^{-1} min^{-1} (group Alf.–Remi.); or remifentanil 1 μg kg^{-1} followed by 0.5 μg kg^{-1} min^{-1} reducing to 0.25 μg kg^{-1} min^{-1} after craniotomy (group Remi.). Anaesthesia was maintained with infusion of propofol and 66% nitrous oxide in oxygen. Infusions of propofol and remifentanil were stopped at head bandaging. Group Remi. had the least intraoperative haemodynamic responses and group Alf. the most ($P<0.05$). Times to tracheal extubation and obey commands were similar in all groups. In all patients in group Alf.–Remi. and group Remi., the trachea was extubated 27 min from the end of anaesthesia; three patients in group Alf. were slower to recover. Use of analgesia in the recovery room and time to transfer to the neurosurgical unit were similar in the three groups. (*Br. J. Anaesth.* 1998; **81**: 361–364).

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Remifentanil is a new opioid analgesic with similar pharmacodynamic effects to alfentanil. Preliminary reports suggest that remifentanil does not alter cerebral blood flow carbon dioxide reactivity[1] and has minimal effects on intracranial pressure and cerebral blood flow.[2]

We have reported previously pharmacokinetic simulations which suggested that sequential administration of a less expensive longer lasting opioid followed by terminal infusion of remifentanil might preserve the rapid early wakening associated with remifentanil while providing satisfactory intraoperative conditions and early recovery.[3 4] We report a preliminary controlled study which evaluated the sequential alfentanil–remifentanil technique.

Patients and methods

Adult patients undergoing elective craniotomy gave written informed consent to participate in the study which was approved by the local Ethics Committee.

OPIOID TREATMENTS AND ANAESTHESIA

Shortly before anaesthesia, patients were allocated randomly to one of three opioid treatments using sealed envelopes containing treatment codes generated by a computer program (Excel 5.0a, Microsoft Inc.). Group Alf. received a bolus injection of alfentanil 50 μg kg^{-1} followed by an infusion of 0.833 μg kg^{-1} min^{-1} until the start of dural closure. Group Alf.–Remi. received sequential treatment with two opioids: after an initial bolus of alfentanil 50 μg kg^{-1}, an infusion of alfentanil 0.833 μg kg^{-1} min^{-1} was continued for 2 h, when it was stopped and replaced by infusion of remifentanil 0.25 μg kg^{-1} min^{-1}. Group Remi. received a bolus injection of remifentanil 1 μg kg^{-1} followed by an infusion of 0.5 μg kg^{-1} min^{-1} reducing to 0.25 μg kg^{-1} min^{-1} after craniotomy. All patients received propofol for induction of anaesthesia (0.5 mg kg^{-1} bolus and 10 mg every 10 s until anaesthetized) and 100 μg kg^{-1} min^{-1} until dural closure, reducing by 16.7 μg kg^{-1} min^{-1} every 10 min thereafter to a minimum of 50 μg kg^{-1} min^{-1}. Neuromuscular block was achieved with atracurium and the lungs were ventilated to an end-tidal carbon dioxide partial pressure of 4.5–5 kPa with 66% nitrous oxide in oxygen. Infusions of propofol and remifentanil were stopped at head bandaging.

The mean rates of administration of propofol, alfentanil and remifentanil were calculated by dividing the total dose of drug administered by the time over which it was given. Times to adequate spontaneous respiration (judged clinically), extubation and to obey a verbal command were recorded.

HAEMODYNAMIC RESPONSES AND HYPOTENSION

An adverse haemodynamic response was defined as mean arterial pressure >100 mm Hg or heart rate >90 beat min^{-1}. These were treated with alfentanil 15 μg kg^{-1} (group Alf. and group Alf.–Remi. in the first 2 h) or remifentanil 1 μg kg^{-1} and an increase in the infusion rate of 0.125 μg kg^{-1} min^{-1} (group Remi. and group Alf.–Remi. after 2 h). If hypertension or tachycardia was present 2 min later, the treatment was repeated (and the infusion rate of alfentanil increased by 0.25 μg kg^{-1} min^{-1} in group Alf. or group Alf.–Remi. in the first 2 h). If the haemodynamic

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Table 1 Patient characteristics, duration of anaesthesia and drug administration rates (mean (SD), median (range) or number)

	Group Alf.	Group Alf.–Remi.	Group Remi.
Age (yr)	53.8 (14.6)	49.6 (13.5)	53.1 (11.8)
Sex (M:F)	7:12	11:5	4:13
Weight (kg)	70.5 (13.4)	75.4 (13.7)	68.5 (15.9)
Duration of anaesthesia (min)	206 (101–337)	210 (137–689)	201 (113–558)
Propofol administration ($\mu g\ kg^{-1}\ min$)	87.7 (15.0)	85.8 (15.7)	80.7 (10.7)
Alfentanil administration ($\mu g\ kg^{-1}\ h^{-1}$)	1.37 (0.48)	1.50 (0.25)	
Remifentanil administration ($\mu g\ kg^{-1}\ min^{-1}$)		0.27 (0.08)	0.37 (0.06)

response persisted for another 2 min, the infusion rate of propofol was increased by 33.3 $\mu g\ kg^{-1}\ min^{-1}$. In group Alf., haemodynamic responses occurring after alfentanil had been discontinued were treated with labetolol or hydralazine. If clinically appropriate, infusion rates which had been increased were subsequently reduced at the anaesthetist's discretion. For hypotensive episodes (mean arterial pressure <60 mm Hg) which did not respond to a fluid bolus, the infusion rate of propofol was reduced. The number of haemodynamic responses and hypotensive episodes were recorded.

MANAGEMENT AFTER SURGERY

Between the end of anaesthesia and subsequent discharge from the recovery room, analgesia was provided with morphine 2 mg i.v. at 5-min intervals as necessary to a maximum dose of 10 mg. If a patient became hypertensive despite apparently adequate analgesia, labetolol or hydralazine was administered. Administration of morphine and discharge from the recovery room were at the discretion of the nursing staff who were blinded to the opioid treatment. Use of morphine, antihypertensive agents and time of discharge from the recovery area to the neurosurgical intensive care unit were recorded.

STATISTICAL ANALYSIS

Statistical analysis was performed using Excel 5.0a (Microsoft Inc.) and Statview 4.01 (Abacus Concepts Inc.) on an Apple Macintosh 7100/80 computer running operating system B1–7.5. Duration of anaesthesia, recovery times and recovery room discharge times were compared using the Kruskal–Wallis test. Drug administration rates were calculated from the total amount of drug given and were compared using unpaired t tests. Haemodynamic responses, requirement for analgesia and hypotensive episodes were compared using the chi-square test. $P<0.05$ was considered significant.

Results

We approached 57 patients to participate in the study and 53 consented. After surgical difficulties, one patient in group Alf.–Remi. received intraoperative thiopental and underwent elective ventilation after surgery. Data from this patient were excluded. Therefore, we present an analysis of data from 52 patients.

Two patients in group Alf.–Remi. had shorter operations than envisaged, with dural closure commencing within 2 h of the start of anaesthesia (i.e. the alfentanil infusion was still running and remifentanil had not been started). In these cases infusion of alfentanil was stopped and no remifentanil was given. Data from these patients were analysed on an "intention to treat" basis and included in group Alf.–Remi. One patient in group Alf. did not recover from surgery and required artificial ventilation for more than 48 h. Data from this patient were included in the analysis of intraoperative characteristics but excluded from analysis of recovery from anaesthesia.

Although we had intended to study 100 patients, the study was terminated after recruiting 53 patients because of investigator dissatisfaction with the relatively slow recovery of some patients and a clinical impression that the use of nitrous oxide and a propofol infusion of 100 $\mu g\ kg^{-1}\ min^{-1}$ provided an excessively hypnotic component to the anaesthetic.

The treatment groups were similar in age, weight and duration of anaesthesia, although there were mostly males in group Alf.–Remi. and mostly females in group Alf. and group Remi. (table 1).

HAEMODYNAMIC STABILITY AND ANALGESIA

The number of patients with haemodynamic responses during the period of opioid infusion and total number of responses varied significantly between groups, with group Remi. having the least responses and group Alf. the most (table 2). The use of labetolol or hydralazine as antihypertensive treatments after cessation of opioid infusion and the use of morphine analgesia in the recovery area did not vary significantly between growps (table 2).

RECOVERY FROM ANAESTHESIA

Median times to tracheal extubation and obey commands were similar in all three groups (table 3). In all patients in group Alf.–Remi. and group Remi., the trachea was extubated 27 min from the end of anaesthesia. Three patients in group Alf. were slower to recover (fig. 1). The total anaesthesia times for these three patients were not especially prolonged (191, 236 and 251 min). The process of recovery was qualitatively different in group Remi., with patients emerging suddenly with near synchronous return of respiration, tracheal extubation and response to commands (table 3).

Times to discharge from the recovery room to the

Table 2 Haemodynamic responses during opioid infusion (mean arterial pressure > 100 mm Hg or heart rate > 90 beat min^{-1}), hypotension (mean arterial pressure <60 mm Hg at any time during anaesthesia) and use of antihypertensive agents and analgesia. Data are number of patients (number of episodes)

	Group Alf.	Group Alf.–Remi.	Group Remi.	*P* value (chi-square test)
Haemodynamic responses	15 (33)	9 (33)	3 (8)	<0.01
Hypotension	13 (26)	9 (23)	13 (37)	0.76
Use of antihypertensive agents	11	6	8	0.67
Use of analgesia in recovery room	10	8	11	0.84

Table 3 Recovery from anaesthesia and discharge from recovery room to the neurosurgical unit. Times are median (range) from discontinuation of propofol and nitrous oxide. There were no significant differences between groups (Kruskal–Wallis test)

	Group Alf.	Group Alf.–Remi.	Group Remi.
Adequate respiration (min)	10 (0–46)	13 (6–27)	11 (7–18)
Tracheal extubation (min)	14 (7–48)	16 (6–27)	11 (9–21)
Obey verbal command (min)	16 (6–123)	19.5 (6–63)	12.5 (7–50)
Discharge from recovery room (min)	119 (86–225)	111 (45–243)	111.5 (58–158)

neurosurgical unit were similar in the three groups (table 3).

Discussion

We have compared remifentanil and alfentanil and evaluated a sequential infusion scheme. We did not demonstrate significant benefit in terms of recovery from anaesthesia with remifentanil compared with alfentanil and in this context the sequential scheme was difficult to evaluate. Nevertheless, remifentanil reduced the number of haemodynamic responses without excess hypotension. Haemodynamic stability is desirable in neuroanaesthesia and this effect may be clinically important.

Guy and colleagues[1] conducted a double-blind comparison of fentanyl and remifentanil during long neurosurgical procedures (mean duration 6 h) and reported that ihtracranial pressure and cerebral perfusion pressure were similar in the two groups and both recovered rapidly with a median time to tracheal extubation of 5 min after remifentanil and 4 min after fentanyl.[1] However, seven of 31 patients who received fentanyl required naloxone and in two the trachea was still intubated at 1 h because of "excessive somnolence". The design of this study was unusual with isoflurane reserved for patients showing persistent haemodynamic responses not responsive to additional opioid and the majority of patients received only nitrous oxide as a hypnotic. In addition, the double-blind design required that the first three haemodynamic responses were treated with bolus injections when the pharmacokinetic profile of remifentanil suggests that an increase in infusion rate would have been more appropriate.

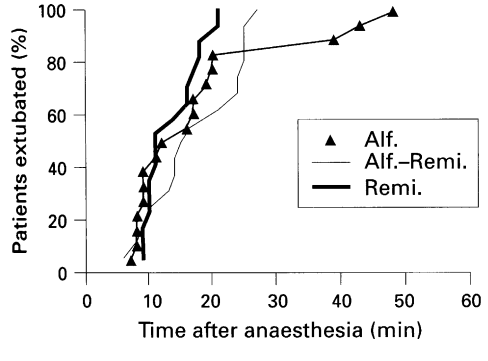

Figure 1 Percentage of patients in whom the trachea was extubated in the first hour after anaesthesia in group Alf. (alfentanil 50 μg kg^{-1} followed by 0.833 μg kg^{-1} min^{-1} until dural closure), group Alf.–Remi. (alfentanil 50 μg kg^{-1} followed by 0.833 μg kg^{-1} min^{-1} for 2 h, then remifentanil 0.25 μg kg^{-1} min^{-1}) and group Remi. (remifentanil 1 μg kg^{-1} followed by 0.5 μg kg^{-1} min^{-1} reducing to 0.25 μg kg^{-1} min^{-1} after craniotomy). Recovery times are in minutes from termination of anaesthesia.

In our study, we considered carefully the feasibility of a double-blind treble dummy design but felt that considerations of patient safety and opportunities for error in drug administration made this inappropriate. The majority of clinical studies with remifentanil have used an open design and this seemed sensible for this study. The design of our study imposed a rigid procedure for management of haemodynamic responses and hypotension, and the end-points were relatively clearly defined, thereby limiting the influence of possible investigator bias.

In the absence of pilot data, we were unable to conduct an *a priori* power calculation for this study. *Post hoc* calculations suggest that the study had a power of 54% to detect a 50% reduction in the time to extubation between two groups at a two-sided 5% significance level. To achieve a power of 80% would have required a total of 150 patients.

When designing the study we considered the use of target-controlled infusion systems to deliver propofol and the opioids, but such systems are not approved for use with opioids and their use would have reduced the relevance of our findings to clinicians without access to such equipment. We have simulated the alfentanil and remifentanil infusions during the first 120 min of anaesthesia using the pharmacokinetic modelling and drug infusion software Stanpump (version June 13 1995) (fig. 2). (Stanpump is freely available from Steven L. Shafer, MD, Anesthesiology Service (112A), PAVAMC, 3801 Miranda Avenue, Palo Alto, CA 94304, USA and on the world wide web at http://pkpd.icon.palo-alto.va.gov.) It is clear

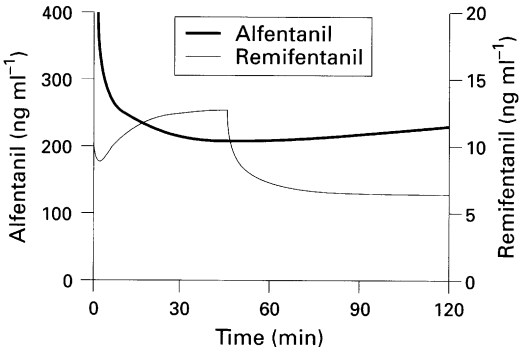

Figure 2 Pharmacokinetic simulations showing predicted plasma concentrations of alfentanil and remifentanil during the first 2 h of infusion. Note that remifentanil was reduced from 0.5 to 0.25 μg kg^{-1} min^{-1} at 45 min as this is approximately when drilling was ceased in a typical case.

from these simulations that the predicted plasma concentration of alfentanil is relatively stable during the first 2 h and that the relative concentrations of the two opioids are not grossly dissimilar when allowance is made for their potency ratio (we have used 20:1 although it could be higher or lower as published ratios range from 8:1 to 58:1).[5,6]

All of our patients received an infusion of opioid and, in this context, administration of nitrous oxide may have been unnecessary. Nitrous oxide was included in the anaesthetic because we were unfamiliar with the use of remifentanil in neuroanaesthesia and wished to ensure adequate hypnosis. In addition, a lower dose of propofol might have been adequate as both alfentanil and remifentanil have been shown to reduce propofol requirements for clinical anaesthesia.[7,8] These factors may have contributed to the relatively prolonged recovery times in all three groups. We chose doses of alfentanil and remifentanil which are in line with the recommendations of the manufacturers. Nevertheless, inter-patient pharmacokinetic variability and accumulation of alfentanil may also have contributed to the delayed recovery of three patients in group Alf.

Our alfentanil infusion scheme was based on previous experience with this drug. The remifentanil scheme used in group Remi. followed published doses.[9] A reduction in remifentanil dose has been recommended for elderly patients,[10,11] however, our study made no allowance for age. In group Remi., all three patients aged more than 65 yr had one or more episodes of hypotension as did 10 of 14 aged less than 65 yr. However, these numbers are too small to draw meaningful conclusions.

This was not a health economic investigation, however; using the current costs to our institution (remifentanil £5.50 for 1 mg and alfentanil £0.72 for 1 mg) and costing these agents in whole multiples of these amounts, the median opioid costs were: group Alf. £10.08, group Alf.–Remi. £18.24 and group Remi. £22.20. These costings make no allowance for the additional syringe and tubing used in group Alf.–Remi. Propofol cost £4.44 for 200 mg and the median propofol costs of the three groups were: group Alf. £35.80, group Alf.–Remi. £38.50 and group Remi. £33.00. Overall median costs of propofol with opioid were: group Alf. £47.86, group Alf.–Remi. £56.74 and group Remi. £55.20. Thus when used in combination with nitrous oxide and propofol, sequential treatment with alfentanil followed by remifentanil was more expensive than using remifentanil alone and did not confer any clinical advantage.

Our study was relatively small and should be interpreted cautiously. Although intraoperative conditions were generally satisfactory with improved haemodynamic stability in group Remi., recovery times may reflect excessive hypnosis and suggest that further improvements may be possible. Future investigations might usefully compare remifentanil and alfentanil, and possibly a sequential opioid infusion design without nitrous oxide and with a lower dose of propofol.

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