Double blind comparison of alfentanil N₂O and fentanyl N₂O for outpatient surgical procedures

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Alfentanil – nitrous oxide and fentanyl – nitrous oxide techniques were compared in outpatients undergoing therapeutic abortion or dilatation and curettage. Thirty patients were studied in each group. Time to awakening was similar in both groups but patients who received alfentanil responded to verbal commands one minute sooner and were alert 1.5 minutes before those who received fentanyl. At ten minutes post anaesthesia the recovery scores were the same for both groups. Patients who received alfentanil were not street-worthy earlier than those who received fentanyl. During the procedure approximately two thirds of the patients moved. This movement was vigorous in 23 per cent of the patients who received alfentanil and in 30 per cent of those given fentanyl. We conclude that: (1) a more flexible dosage schedule is required in order to prevent disturbing movement of the patient during the procedure and (2) patients who received alfentanil were not street-worthy earlier than those who were given fentanyl.

Key words

ANALGESICS, NARCOTIC: fentanyl, alfentanil; SURGERY: outpatients.

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Alfentanil is a new narcotic analgesic with a rapid onset and short duration of action.^{1,2} Because of its pharmacokinetic properties, alfentanil should be particularly appropriate for use in outpatients undergoing short surgical procedures.³⁻⁵ This study was undertaken to compare alfentanil with fentanyl as a supplement to thiopentone – nitrous oxide anaesthesia for short outpatient procedures, with particular interest in whether or not patients given alfentanil were ready for discharge earlier than those given fentanyl.

Methods

Local ethics committee approval was obtained and all patients provided informed consent. Sixty female patients between the ages of 15 to 70 years were chosen at random from the outpatient surgical list. Fifty-six underwent first trimester abortion and four had dilatation and curettage. All patients were unpremedicated. Each patient completed a Trieger Dot Test⁶ prior to the administration of any drugs.

The study was double blinded by having the hospital pharmacist provide, according to a grid known only to him, four syringes for each patient. Each 3 ml syringe contained either alfentanil 500 µg·ml⁻¹ or 50 fentanyl µg·ml⁻¹. Three 1 ml tuberculin syringes contained either alfentanil 500 µg·ml⁻¹ or fentanyl 50 µg·ml⁻¹. The drugs were prepared in this way so that initial and top-up doses would be the same (in ml·kg⁻¹) for each patient regardless of which of the study drugs she received.

All patients were given droperidol 0.625 mg IV. This was followed in three minutes by either 15 µg·kg⁻¹ of alfentanil or 1.5 µg·kg⁻¹ of fentanyl. Anaesthesia was induced with thiopentone 5 mg·kg⁻¹ and maintained with nitrous oxide and oxygen in a ratio of 70:30. Narcotic supplementation was given when required as indicated by patient movement, hypertension or tachycardia. Patients in the alfentanil group received 5 µg·kg⁻¹ increments of alfentanil while the fentanyl group of patients received

0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl. If, after three top-up doses, the patient still appeared to be lightly anaesthetized then an additional 50–150 mg of thiopentone was administered.

Baseline systolic, diastolic and mean blood pressures (DINAMAP[®] Critikon), pulse and respiratory rates were recorded for each patient. These measurements were repeated one minute after the study drug was administered and then every five minutes after induction until surgery was completed. Then the nitrous oxide was switched off and the patient was given 100 per cent oxygen to breathe.

A stop watch was activated when the nitrous oxide was turned off. This was considered to be the end of the anaesthetic. Time intervals from this point to: (1) first nonspecific sign of awakening; (2) response to command – “lift your left arm”; (3) orientation as to time, place, surgeon's name and procedure; and (4) completion of a finger-to-nose test, were recorded. A trained observer stayed with each patient from the arrival time in the post anaesthetic recovery room (PARR) until all discharge criteria were met. The Trieger Test was administered on arrival in the PARR, and 30 and 60 minutes later. A PARR score (Table I) was completed for all patients at 1, 5, 10, 15, 20, 25 and 30 minutes after arrival in the recovery room.

Following transfer from the PARR to the Day Surgery Unit, patients were monitored in the usual way by the nurses. At 60 minutes post anaesthesia and every ten minutes thereafter, blood pressure and pulse rate were recorded lying, sitting and standing. If rates were within 20 per cent of baseline rates, the patient was asked to walk a straight line. If patients completed this successfully, they were considered fit for discharge.

Data analysis

Data are presented as group mean values $\pm$ standard error of the mean (SEM). Between-group differences in cardiovascular variables were assessed using Student's *t* test for unpaired data. Comparison of control values utilized raw values while subsequent time points were compared using “difference from control” values. Since only two time points (post-drug and post-first surgical stimulus) were available with reasonably complete data for all patients, with a substantial decline in patient data thereafter (due to the brevity of the surgical procedure), it was felt that *t* tests would be appropriate and allow use of all available data.

Recovery data (time to awakening, alertness, Trieger Test etc.) were evaluated using the Mann-Whitney U Test or, when proportions were compared, the Fisher's Exact Test. The use of “significant” throughout the text denotes statistical significance at the 5 per cent level (two-tailed).

TABLE I PARR score. Scored at 1, 5, 10, 15, 20, 25, 30, 40, 50 and 60 minutes

Motor Performance: 0–2
2 Able to move 4 extremities voluntarily or on command
1 Able to move 2 extremities voluntarily or on command
0 Able to move 0 extremities voluntarily or on command
Respiration: 0–2
2 Able to breathe deeply and cough freely
1 Dyspnoea or limited breathing
0 Apnoeic
Consciousness: 0–2
2 Fully awake
1 Arousable on calling
0 Not responding
Pain claimed by patient: 0–3
3 Severe
2 Moderate
1 Uncomfortable
0 None

Results

Demographic data are summarized in Table II. Both treatment groups had similar requirements for maintenance doses of narcotic and thiopentone.

Baseline mean arterial pressure (MAP) was significantly higher in the alfentanil group (Table III). There were no differences between the changes in heart or respiratory rates for the two groups. Decreases in blood pressure (systolic, diastolic and mean) were more pronounced in the alfentanil group. At the five minute post-induction observation, the fentanyl group showed a pressor response (mean increase of 12.5 mmHg MAP) while MAP in the alfentanil group remained below baseline value.

Time to awakening was similar in both groups (Table IV). However, patients in the alfentanil group responded to verbal commands sooner (by approximately one minute) and were quicker to establish alertness (by about

TABLE II Demographic data

	Alfentanil	Fentanyl
No. of patients:	30	30
ASA physical status		
of patients: I	28	27
II	—	1
NR*	2	2
Age Mean $\pm$ SEM:	24.9 $\pm$ 1.3	23.9 $\pm$ 1.0
Range:	17–44	17–36
Weight (kg):	63.3 $\pm$ 2.2	59.7 $\pm$ 1.6
Height (cm):	161.0 $\pm$ 2.1	163.1 $\pm$ 1.3

*NR = not recorded.

TABLE III Cardiovascular variables (Mean $\pm$ SEM)

	Heart rate	Systolic pressure	Diastolic pressure	Mean pressure	Respiration rate
Control:					
A	80.1 $\pm$ 2.0	124.9 $\pm$ 2.2	70.9 $\pm$ 1.7	89.3 $\pm$ 1.7	18.0 $\pm$ 0.6
F	76.0 $\pm$ 2.1	120.3 $\pm$ 2.0	69.4 $\pm$ 1.8	83.4 $\pm$ 1.9	19.0 $\pm$ 0.7
Immediately post test drug:					
A	83.1 $\pm$ 2.1	117.5 $\pm$ 1.9	66.9 $\pm$ 1.7	83.6 $\pm$ 1.8	14.6 $\pm$ 0.9
F	79.4 $\pm$ 2.9	118.0 $\pm$ 1.8	65.8 $\pm$ 1.5	82.8 $\pm$ 1.8	17.4 $\pm$ 0.9
Immediately post first surgical stimulus:					
A	75.0 $\pm$ 1.8	106.9 $\pm$ 1.5	62.5 $\pm$ 1.5	73.3 $\pm$ 1.9	11.1 $\pm$ 1.1
F	76.0 $\pm$ 2.5	116.3 $\pm$ 2.5	70.9 $\pm$ 2.5	86.5 $\pm$ 2.7	15.1 $\pm$ 0.8
Five minutes post stimulus:					
A	76.9 $\pm$ 3.1	115.9 $\pm$ 2.9	70.4 $\pm$ 2.7	85.9 $\pm$ 2.6	11.0 $\pm$ 1.4
F	82.0 $\pm$ 2.4	126.6 $\pm$ 3.1	80.6 $\pm$ 2.6	96.0 $\pm$ 2.7	15.1 $\pm$ 1.5

TABLE IV Duration of surgery/anaesthesia

	Measures of recovery		
	Alfentanil %	fentanyl %	
Duration of surgery (minutes):			
<5	77	73	
>5	23	27	
Mean $\pm$ SEM	5.0 $\pm$ 0.42	4.8 $\pm$ 0.33	
Duration of anaesthesia (minutes):			
<5	3	3	
6-10	53	37	
>10	43	60	
Mean $\pm$ SEM	11.0 $\pm$ 0.96	11.7 $\pm$ 0.67	
Time to awakening (minutes):			
1-2	40	30	
3-5	37	37	
>5	23	33	
Mean $\pm$ SEM	4.0 $\pm$ 0.58	4.4 $\pm$ 0.55	
Time to response to verbal commands (minutes):			
1-2	33	20	
3-5	43	23	
6-10	13	53	
>10	10	3	
Mean $\pm$ SEM	4.67 $\pm$ 0.60	5.7 $\pm$ 0.56	p < 0.05
Time to establish alertness (minutes):			
1-2	30	17	
3-5	47	13	
6-10	13	63	
>10	10	7	
Mean $\pm$ SEM	4.7 $\pm$ 0.59	6.4 $\pm$ 0.56	p < 0.05
Completed finger-to-nose test (minutes):			
<5	77	33	
6-10	10	53	
>10	13	13	
Mean $\pm$ SEM	4.8 $\pm$ 0.7	7.2 $\pm$ 0.8	p < 0.05

1.5 minutes). Similarly, alfentanil treated patients successfully completed the finger-to-nose test sooner (by about 2.5 minutes). This more rapid return of orientation and coordination was also reflected in the Trieger Test, with alfentanil patients performing better at the 30-minute evaluation (Table V). Patients in the alfentanil group attained a perfect PARR score sooner than did those in the fentanyl group (Table VI). Side effects were reported in 80 per cent of the alfentanil and 73 per cent of the fentanyl group. With the exception of movement these were infrequent and not serious (Table VII).

Discussion

For outpatient therapeutic abortions it is advisable to avoid the use of volatile anaesthetic agents, to minimize blood loss.^{7,8} Fentanyl has been commonly used to supplement nitrous oxide for these procedures. However, because of its pharmacokinetic properties, alfentanil should be a better choice of narcotic supplement than fentanyl.² There is a rapid decline in plasma alfentanil levels so that, as the drug equilibrates between central and peripheral compartments, 90 per cent of an administered dose leaves the plasma within 30 minutes. In addition, alfentanil has a more rapid onset of action than fentanyl,³ suggesting it to be more useful in techniques where repeated top-up doses might be necessary.

TABLE V Trieger dot test (Mean $\pm$ SEM)

	Alfentanil	Fentanyl	
Number of dots missed at:			
Control	3.9 $\pm$ 0.7	3.4 $\pm$ 0.7	
0 minutes	29.9 $\pm$ 1.5	30.8 $\pm$ 1.7	
30 minutes	12.3 $\pm$ 1.3	18.8 $\pm$ 2.1	p < 0.05
60 minutes	10.2 $\pm$ 1.3	13.7 $\pm$ 2.2	

TABLE VI Parr scores - Time to perfect score

	Minutes in PARR			
	1	5	10	15
Number of patients				
Alfentanil	2	20	5	3
Fentanyl	2	7	19	2

Induction was considered satisfactory in the majority of patients. However, maintenance of anaesthesia was unsatisfactory in about 25 per cent of both groups. The principal problem was movement of patients during surgery, necessitating repeated top-up doses of narcotic and, in almost 20 per cent in both groups, requiring one or two incremental doses of thiopentone. This may be a function of the dose of drug we chose to study. Rosow *et al.*¹⁰ found least movement in patients who received 20 $\mu\text{g}\cdot\text{kg}^{-1}$ of alfentanil compared to those who were given 10 $\mu\text{g}\cdot\text{kg}^{-1}$ of alfentanil or 1 or 2 $\mu\text{g}\cdot\text{kg}^{-1}$ of fentanyl. Hull and Jacobson¹¹ gave 100 μg of fentanyl or 700 μg of alfentanil to their patients but still a high percentage of their patients moved in response to the surgical stimulus. Such a high frequency of physical response is unacceptable. The "roller-coaster" level of anaesthesia drug concentration, attendant upon intermittent drug boluses, could be avoided by a continuous infusion technique resulting in a smoother anaesthetic experience.¹² Whether such is suitable for brief outpatient procedures remains to be established.

There were no statistically significant differences in heart rate between the two groups intraoperatively. The alfentanil treated patients had decreases in systolic, diastolic and mean arterial pressures at the time of the first surgical stimulus similar to those described by Coe, Shafer and White.¹³ In contrast, the fentanyl group showed a pressor response five minutes after induction. However, values in both groups were clinically acceptable.

Measurements of recovery are always difficult. We tried to choose parameters which are simple to measure and easy to reproduce. Immediate recovery was better in the alfentanil group as evidenced by the response to verbal commands, the time to establish alertness, the successful completion of the finger-to-nose test and the 5-minute PARR score. This speedy recovery has been demonstrated by several studies¹³⁻¹⁶ where alfentanil has been compared to fentanyl or halothane. However, other studies found no difference in recovery times when comparing treatment with alfentanil and fentanyl.^{11,18,19} By ten minutes, there was no difference in PARR performance scores between our two subject groups. But, the alfentanil group scored better on the 30-minute

TABLE VII Side effects: all reports

	Alfentanil		Fentanyl	
	%	n	%	n
Chest wall rigidity	—	—	—	—
Laryngospasm	3	(1)	—	—
Bronchospasm	—	—	—	—
Tachycardia	—	—	7	(2)
Bradycardia	—	—	—	—
Other arrhythmias	—	—	—	—
Hypertension	—	—	7	(2)
Hypotension	17	(5)	—	—
Allergic skin reaction	—	—	—	—
Coughing	3	(1)	—	—
Venous pain on injection	—	—	—	—
Nausea	7	(2)	17	(5)
Vomiting	3	(1)	7	(2)
Movement	67	(20)	63	(19)
Other: apnoea	10	(3)	7	(2)
Patients with side effects	80	(24)	73	(22)

Trieger test than did the fentanyl group: the significance of this isolated observation remains to be determined.

For day surgery patients, one is most concerned about patient readiness for discharge. We chose to evaluate cardiovascular variables and the ability of the patient to walk a straight line. If the patients met the preset criteria, they were considered fit for discharge. These are admittedly crude measures of "street worthiness" in comparison with other tests of recovery,²⁰⁻²² but none have been shown to be more accurate than those selected for this study. That we failed to detect a difference between the alfentanil and fentanyl groups as to the time of discharge implies little functional advantage of one drug over the other in utilization in day surgery facilities.

Side effects were similar in both groups. As in Cartwright's study,¹⁷ no patient showed any chest wall rigidity, although this has been reported by others.^{13,23} Perhaps the lack of rigidity is due to our slow injection, over a two-minute period, of the narcotics. Apnoea occurred in two patients receiving alfentanil and in one receiving fentanyl, but was easily managed. Only the patient given fentanyl required naloxone in the operating room. In other studies, significant respiratory depression has occurred with doses as low as 6 $\mu\text{g}\cdot\text{kg}^{-1}$ of alfentanil.^{11,24-26} Perhaps contributed to by premedication.¹⁷ Patients involved in this study were unpremedicated and received the drugs slowly both of which factors may have reduced the incidence of significant respiratory depression.

Nausea and vomiting were not disturbing in either group although more commonly reported with fentanyl (17 per cent) than alfentanil (seven per cent). All patients were pretreated with droperidol 0.625 mg for its antiemetic effect. These results are similar to other studies.^{10,13,15,27}

In summary, alfentanil and fentanyl were compared as supplements to thiopentone nitrous-oxide anaesthesia for outpatients undergoing first trimester therapeutic abortion or dilatation and curettage. The only major problem in patients receiving either drug was frequent, sometimes vigorous, movement during the surgical procedure. Perhaps a more flexible dosage schedule would eliminate that problem. Continuous infusion of alfentanil might provide a better alternative. Patients who received alfentanil showed significantly faster immediate recovery than those in the fentanyl group but no ability to be discharged earlier. Therefore, it would seem that in our hands alfentanil showed no advantages over fentanyl for short outpatient procedures.

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References

- 1 Brown JH, Pleuvry BJ, Kay B. Respiratory effects of a new opiate analgesic, R39209, in the rabbit: comparison with fentanyl. *Br J Anaesth* 1980; 52: 1101-6.
- 2 Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R39209): a new opioid analgesic. *Anesthesiology* 1982; 57: 439-43.
- 3 Kay B. Editorial: Alfentanil. *Br J Anaesth* 1982; 54: 1011-2.
- 4 Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. *Br J Anaesth* 1982; 54: 871-5.
- 5 Stanski DR, Hug CC. Alfentanil - a kinetically predictable narcotic analgesic. *Anesthesiology* 1982; 57: 435-8.
- 6 Newman MG, Trieger N, Miller JC. Measuring recovery from anaesthesia: a simple test. *Anesth Analg* 1969; 48: 136-40.
- 7 Cullen BF, Margolis AJ, Eger EI II. The effects of anaesthesia and pulmonary ventilation on blood loss during therapeutic abortion. *Anesthesiology* 1971; 32: 108-13.
- 8 Dolan WM, Eger EI II, Margolis AJ. Forane increases bleeding in therapeutic suction abortion. *Anesthesiology* 1972; 36: 96-7.
- 9 Camu F, Gepts E, Rucquoi M, Heykants J. Pharmacokinetics of alfentanil in Man. *Anesth Analg* 1982; 61: 657-61.
- 10 Rosow CE, Latta WB, Keegan CR et al. Alfentanil and fentanyl in short surgical procedures. *Anesthesiology* 1983; 59: A345.
- 11 Hull CJ, Jacobson L. A clinical trial of alfentanil as an adjuvant for short anaesthetic procedures. *Br J Anaesth* 1983; 55: 173S-8S.
- 12 White PF, Coe V, Shafer A, Sung M. Comparison of alfentanil with fentanyl for outpatient anesthesia. *Anesthesiology* 1986; 64: 99-106.
- 13 Coe V, Shafer A, White PF. Techniques for administering alfentanil during outpatient anesthesia - a comparison with fentanyl. *Anesthesiology* 1983; 59: A347.
- 14 Kay B, Cohen AT. Intravenous anaesthesia for minor surgery: a comparison of etomidate or althesin with fentanyl and alfentanil. *Br J Anaesth* 1983; 55: 165S-7S.
- 15 Kay B, Venkataraman P. Recovery after fentanyl and alfentanil in anaesthesia for minor surgery. *Br J Anaesth* 1983; 55: 169S-71S.
- 16 Youngberg JA, Subaiya C, Graybar GB, Weng JT, Adler E, Texidor M. Alfentanil for day-stay surgery in children: an evaluation. *Anesth Analg* 1984; 63: 284.
- 17 Cartwright DP. Recovery after anaesthesia with alfentanil or halothane. *Can Anaesth Soc J* 1985; 32: 479-83.
- 18 Sinclair ME, Cooper GM. Alfentanil and recovery. *Anaesthesia* 1983; 38: 435-7.
- 19 Cooper GM, O'Connor M, Mark J, Harvey J. Effect of alfentanil and fentanyl on recovery from brief anaesthesia. *Br J Anaesth* 1983; 55: 179S-82S.
- 20 Doenicke A, Kugler J, Laub M. Evaluation of recovery and "street fitness" by EEG and psychodiagnostic tests after anaesthesia. *Can Anaesth Soc J* 1967; 14: 567-83.
- 21 Korhonen K, Linnoila M, Ertama P, Hakkinen S. Recovery and simulated driving after intravenous anaesthesia with thiopental, methohexital, propofol, or alphadione. *Anesthesiology* 1975; 43: 291-9.
- 22 Laborit G, Angiboust R, Papin JP. A study of eye movement for assessing recovery from anaesthesia. *Br J Anaesth* 1977; 49: 805-10.
- 23 Dechene JP. Alfentanil as an adjunct to thiopentone and nitrous oxide in short surgical procedures. *Can Anaesth Soc J* 1985; 32: 346-50.
- 24 Kallar SK, Keenan RL. Evaluation and comparison of recovery time from alfentanil and fentanyl for short surgical procedures. *Anesthesiology* 1984; 61: A379.
- 25 Kay B, Pleuvry B. Human volunteer studies of alfentanil (R39209) a new short acting narcotic analgesic. *Anaesthesia* 1980; 35: 952-6.
- 26 Kay B, Stephenson DK. Alfentanil (R39209): initial clinical experience with a new narcotic analgesic. *Anaesthesia* 1980; 35: 1197-201.
- 27 Brown EM, Kunjappan VE, Alexander GD. Fentanyl/alfentanil for pelvic laparoscopy. *Can Anaesth Soc J* 1984; 31: 251-4.

Résumé

Les techniques utilisant l'alfentanil-protoxyde d'azote et fentanyl-protoxyde d'azote ont été comparées chez les patientes externes devant subir un avortement thérapeutique ou un curetage et dilatation. Trente patientes étaient étudiées dans chaque groupe. Le temps de réveil était similaire dans les deux groupes mais les patientes ayant reçu l'alfentanil répondaient à l'ordre verbal une minute plus tôt et étaient plus alertes une minute et demie ayant celles qui ont reçu du fentanyl. Dix minutes après l'anesthésie les scores de récupération étaient les mêmes dans les deux groupes. Les patientes ayant reçu l'alfentanil n'étaient pas plus aptes au congé précoce comparativement à celles ayant reçu le fentanyl. Durant la procédure approximativement 8 des patientes ont bougé. Ces mouvements étaient vigoureux chez 23 pour cent des patientes ayant reçu l'alfentanil et 30 pour cent de celles qui ont reçu du fentanyl. On conclut que: 1) un dosage plus flexible est requis afin de prévenir les mouvements des patientes lors de la procédure et 2) les patientes ayant reçu l'alfentanil ne pouvaient être ambulantes plus précocement que celles ayant reçu du fentanyl.