

Comparison of alfentanil, fentanyl and enflurane as supplements to general anaesthesia for outpatient gynaecologic surgery

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We compared two narcotic/N₂O anaesthetic techniques and an inhalational anaesthesia/N₂O technique for outpatient surgery in 59 women undergoing short gynaecological procedures. All patients received droperidol 0.625 mg IV, thiopentone and 70 per cent N₂O in O₂ plus either alfentanil (15 µg·kg⁻¹), fentanyl (1.5 µg·kg⁻¹) or enflurane. The narcotics were given in a double-blind fashion and all anaesthetic techniques were assigned randomly. Cardiorespiratory parameters remained stable in all groups, with few clinically important changes occurring. Recovery was significantly faster in the group receiving alfentanil, with the time to respond to verbal commands and the time to establish alertness significantly faster than with either fentanyl or enflurane. All techniques provided satisfactory anaesthesia; however, the patients receiving alfentanil had significantly more adverse events than those receiving fentanyl.

Key words

ANAESTHESIA: general, outpatient; ANAESTHETICS, INTRAVENOUS: alfentanil, fentanyl; ANAESTHETICS, INHALATIONAL: enflurane.

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Alfentanil is a new narcotic analgesic with a chemical structure similar to that of fentanyl. Alfentanil may be particularly suited for outpatient anaesthesia because of its rapid onset, short duration of action and fast recovery. To determine whether alfentanil offers advantages over drugs currently used in outpatient anaesthesia, we compared alfentanil to fentanyl as adjuncts to thiopentone/N₂O anaesthesia. We also compared these two techniques to an enflurane/N₂O anaesthetic, since the latter is a common technique for short procedures in our institution.

Methods

After approval by the Human Subjects Review Committee at the University of Toronto, informed consent was obtained from 59 unpremedicated females, undergoing elective minor gynaecological surgery as outpatients. The patients were ASA physical status Class I or II and between the ages of 18 and 60. Before surgery, a medical history, physical examination and appropriate laboratory tests were obtained. All patients were fasted for at least eight hours and randomly assigned to one of three groups: Group A – alfentanil/N₂O; Group F – fentanyl/N₂O; Group E – enflurane/N₂O. There were 20 patients in each of the narcotic groups and 19 in Group E.

An electrocardiogram was monitored continuously. Arterial blood pressure (systolic, diastolic and mean) and pulse rate were recorded with a Datascope® oscillonometric, non-invasive monitor with recorder. Respiratory rate (RR), complications and recovery data were recorded by a single trained observer, who was blinded to the identity of the narcotic but not to the inhalational anaesthetic. Vital signs were recorded on arrival in the operating room, immediately after administration of the test drug, immediately after surgical stimulation and every five minutes thereafter during the procedure. After an intravenous

cannula was inserted on arrival in the operating room, droperidol 0.625 mg was given IV to all patients to minimize postoperative nausea and vomiting.¹⁻³ After administration of droperidol, the patients in Group A were given alfentanil 15 $\mu\text{g}\cdot\text{kg}^{-1}$ and those in Group F were given fentanyl 1.5 $\mu\text{g}\cdot\text{kg}^{-1}$. All narcotics were administered slowly over 20-30 seconds in a double-blind fashion. Two minutes after the narcotic, thiopentone (3-5 $\text{mg}\cdot\text{kg}^{-1}$) was administered in incremental doses intravenously until the patient was anaesthetized. The onset of anaesthesia was determined by the loss of eyelash reflex. In the alfentanil and fentanyl groups, anaesthesia was maintained with 70 per cent N_2O in O_2 . Additional doses of thiopentone (50 mg increments up to a total dose of 500 mg), or smaller increments of alfentanil or fentanyl (5-10 $\mu\text{g}\cdot\text{kg}^{-1}$ or 0.5-1.5 $\mu\text{g}\cdot\text{kg}^{-1}$ respectively) were given intravenously as needed to maintain satisfactory anaesthesia and surgical conditions.

Supplemental anaesthesia was given in accordance with signs of light anaesthesia and/or patient movement. If the patient received a total of 500 mg of thiopentone and the maximum dose of narcotic (alfentanil 30 $\mu\text{g}\cdot\text{kg}^{-1}$; fentanyl 5 $\mu\text{g}\cdot\text{kg}^{-1}$) and if further anaesthesia was needed, enflurane or isoflurane was administered with the anaesthetist using the drug of his/her choice.

The patients in Group E (enflurane) did not receive any narcotic. After induction with thiopentone, enflurane was administered with N_2O in O_2 in the concentration deemed clinically necessary. The protocol was otherwise the same as the narcotic groups.

At the end of the procedure, the anaesthetic was discontinued and the patients were transferred to the Recovery Room. Supplemental oxygen was administered by face mask and vital signs were recorded every 15 minutes for at least one hour. The patients were assessed by the same blinded observer for: (1) the time to recover eyelash reflex; (2) the time to respond appropriately to verbal commands; (3) the time to establish alertness (orientation, simple addition, and date of birth); and (4) the time to discharge. This observer remained with the patient until the assessment was completed. Immediately prior to discharge, the patients were questioned about

perioperative awareness and amnesia, and asked to give their impression of the anaesthetic experience. Further, the patient's level of pain and need for postoperative analgesics were recorded as were all intra- and postoperative events, such as chest wall rigidity and nausea and vomiting. The anaesthetists were also asked to evaluate the patients' induction, intraoperative course and recovery.

Data are presented as mean value and standard error of the mean (SEM). Recovery data were evaluated using the Kruskal-Wallis Test for overall significance, with the Mann-Whitney U Test, *p* value modified according to Ryan⁴ for pair-wise comparisons. Proportional data were evaluated using the Chi-square or Fisher's Test, as required. Differences in cardiovascular variables were determined using the repeated measures two-way analysis of variance. Between group differences were based on change from control. Use of "significant" denotes statistical significance at the five per cent level (two-tailed).

Results

Demographic data for all three groups showed no significant between-group differences. The majority of patients underwent a dilatation and curettage (D&C), and were ASA physical status I or II. The mean ages of the three groups ranged from 32-42 years. The average duration of surgery and anaesthesia was less than ten minutes.

The mean initial alfentanil dose was 15.3 $\mu\text{g}\cdot\text{kg}^{-1}$ with four patients requiring supplemental doses (Table I). The initial mean dose of fentanyl was 1.5 $\mu\text{g}\cdot\text{kg}^{-1}$ with three patients requiring supplemental doses. The initial thiopentone dose was similar in all groups. Four patients in Group A, two in Group F and none in Group E required supplements of thiopentone. The induction was rated as good or satisfactory in all patients in all groups, except for one in Group E which was rated as bad.

The intraoperative cardiovascular variables are summarized in Figures 1 and 2. With the exception of diastolic blood pressure in Group E, all treatments showed significant ($p < 0.05 - p < 0.001$) within group changes in the cardiovascular variables assessed. Group E showed a significant ($p < 0.05$) decrease in systolic blood pressure

TABLE I Drug dosages (mean)

Drug	Initial dose	Patients requiring supplemental doses	Total dose in patients requiring supplements
Alfentanil	15.3 $\mu\text{g}\cdot\text{kg}^{-1}$	4 (20%)	25.4 $\mu\text{g}\cdot\text{kg}^{-1}$
Fentanyl	1.5 $\mu\text{g}\cdot\text{kg}^{-1}$	3 (15%)	2.1 $\mu\text{g}\cdot\text{kg}^{-1}$
Thiopentone			
Group A	4.5 $\text{mg}\cdot\text{kg}^{-1}$	4 (20%)	5.2 $\text{mg}\cdot\text{kg}^{-1}$
Group F	4.5 $\text{mg}\cdot\text{kg}^{-1}$	2 (10%)	5.9 $\text{mg}\cdot\text{kg}^{-1}$
Group E	4.4 $\text{mg}\cdot\text{kg}^{-1}$	0 (0%)	n/a

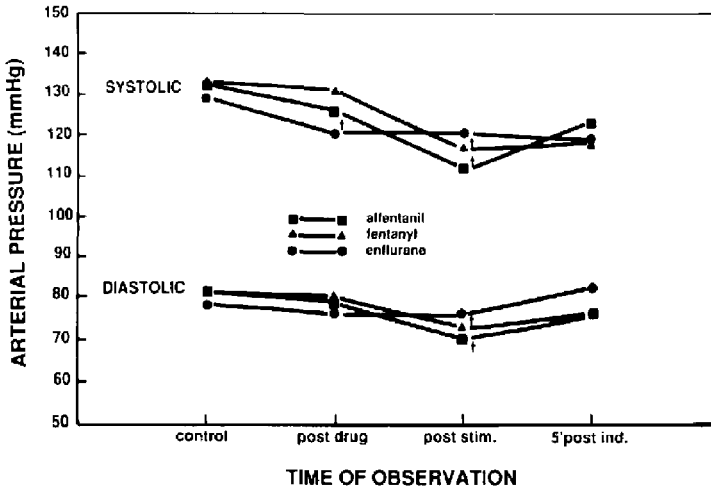


FIGURE 1 Arterial blood pressure measurements (*indicates significant change from control).

at the "post drug" observation with no further decrease thereafter. Both Groups A and E showed a significant ($p < 0.001$) decrease in systolic pressure "post-surgical" stimulation, with diastolic pressure also decreasing significantly. Heart rate increased significantly in the Groups A and E "post-drug" and returned to control value only in Group A (remained elevated with enflurane). Group F had a significantly lower heart rate "post-surgical" stimulation. Respiratory rate slowed significantly with all treatment groups but returned to control after surgical stimulation in Group E only. At the "post-surgical" stimulation point, systolic blood pressure was significantly lower in Group A than in Group F, heart rate with enflurane was significantly higher than with fentanyl, and respiratory rate with both alfentanil and fentanyl were significantly

lower than with enflurane. Postoperative cardiovascular variables showed no significant within or between treatment differences.

The recovery data (Table II) all indicate that patients in Group A were alert and responded to verbal commands significantly faster than patients in either the fentanyl- or enflurane-treated groups. All patients were amnesic for the operation. Recovery was judged to be good or satisfactory in all patients in all groups.

Table III summarizes the adverse intra- and postoperative events which occurred. Two patients in Group A had particularly troublesome reactions: one patient moved and vocalized at the start of surgery, and when given more narcotic and thiopentone, developed chest wall rigidity and apnoea. This patient was ventilated manually with a

TABLE II Recovery data

	<i>Alfentanil</i>	<i>Fentanyl</i>	<i>Enflurane</i>
Time (min) to respond to verbal commands *(mean \pm SEM)	2.8 \pm 0.54	4.7 \pm 0.73	8.1 \pm 0.84
Time (min) to establish alertness *(mean \pm SEM)	5.6 \pm 0.52	7.7 \pm 0.68	10.8 \pm 0.86
Number of patients fully awake at			
1 min	5/20	4/20	0/19
5 min	19/20	18/20	12/19
10 min	20/20	20/20	17/19
20 min			19/19

*All pair-wise comparisons, i.e., A vs E, A vs F, F vs E, are significantly different using the Mann-Whitney U-Test, with adjustment of the critical p value according to Ryan to maintain an overall experiment-wise error rate of 0.05.⁴

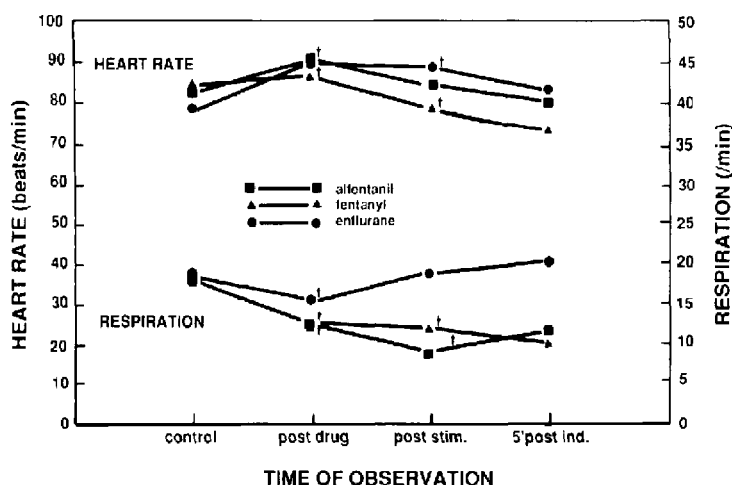


FIGURE 2 Heart rate and respiratory rate (†indicates significant change from control).

mask until spontaneous ventilation resumed at the end of the procedure. The second patient also moved at the start of surgical stimulation and was given more thiopentone without effect. When further alfentanil was given, chest wall rigidity and apnoea ensued which required succinylcholine administration to allow manual ventilation. Postoperative adverse events consisted mainly of nausea and vomiting. Overall, significantly more patients in Group A (55 per cent) had either intra- or postoperative adverse events compared with only 15 per cent in Group F.

Discussion

As economic and social pressures are encouraging a shift toward day-care surgery from in-hospital surgery, the effects of the anaesthetic agents used should be predictably short and have minimal side effects. Alfentanil is a less potent derivative of fentanyl, with similar pharmacology but a faster onset and shorter duration of action.^{8,9-11} It has a greater total body clearance, a smaller volume of distribution and a shorter $t_{1/2}$ than either fentanyl or

sufentanil. It is this faster elimination and shorter duration of action which makes it attractive as a supplement to outpatient anaesthesia. In this study, we demonstrated that the use of alfentanil as an adjunct to thiopentone/ N_2O/O_2 anaesthesia produces a satisfactory anaesthetic state in most patients and results in faster recovery with respect to time to respond to verbal commands and to establish alertness, as compared with the fentanyl/ N_2O and enflurane/ N_2O anaesthetics.

Cardiovascular stability has been an important benefit with the use of fentanyl and its derivatives.¹³⁻¹⁷ All anaesthetics as used in this study resulted in a decrease in systolic blood pressure while heart rate decreased significantly only in the group receiving fentanyl. None of the changes was clinically important.

Nausea and vomiting continue to be a major problem in the outpatient setting. The incidence of this particularly unpleasant side effect is still quite high (25 per cent) with alfentanil as used in our study. These numbers are similar to previous findings.^{14,15} Of interest is that the group

TABLE III Adverse events

	Alfentanil	Fentanyl	Enflurane
Chest wall rigidity	3 (15%)	0	0
Apnoea	3 (15%)	0	0
Movement	2 (10%)	3 (15%)	2 (10%)
Coughing	0	1 (5%)	3 (15%)
Bronchospasm	0	0	1 (5%)
Laryngospasm	1 (5%)	0	0

receiving enflurane had only a ten per cent incidence of nausea and vomiting while no patients in the fentanyl group experienced nausea and vomiting. This observation cannot be readily explained since most other investigators have found at least a similar or higher incidence with fentanyl.⁹ Perhaps the combination of low-dose droperidol and fentanyl is important in producing this effect. Our observations should be confirmed in further studies.

We found that alfentanil caused chest wall rigidity and gross limb and body movement, which has been previously described in patients not receiving neuromuscular blocking drugs. The problem of chest wall rigidity can be minimized by a very slow injection of the drug. Although movement during these types of procedures is a common occurrence, it did not interfere with the surgery or pose a significant problem in any case. None of the patients was aware during the procedures with any technique.

In summary, we found no significant differences among the groups with respect to ease of anaesthetic induction, dose of induction agent (thiopentone), amnesia, postoperative pain or patient/anaesthetist satisfaction. Overall, significantly more patients in the alfentanil-treated group experienced either intra- or postoperative adverse events when compared with fentanyl-treated patients. The main problems intraoperatively were related to chest wall rigidity, and nausea and vomiting accounting for the postoperative problems. On the other hand, those same patients recovered significantly faster than patients in either of the other groups. The patients who received the fentanyl/N₂O/O₂ anaesthetics had the fewest side effects, notably a complete absence of postoperative nausea and vomiting and still achieved a rapid recovery.

The singular benefit of a rapid recovery may not be enough to promote alfentanil over fentanyl or enflurane, as used in this study, as adjuncts to N₂O/thiopentone for outpatient surgery.

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Résumé

On a comparé deux techniques anesthésiques utilisant des narcotiques avec protoxyde d'azote et une technique utilisant de l'enflurane protoxyde d'azote chez 59 patientes externes devant subir des procédures gynécologiques de courte durée. Toutes les patientes ont reçu du dropéridol 0.625 mg IV, du thiopentone et 70 pour cent de protoxyde d'azote dans l'oxygène et soit de l'alfentanil ($15 \mu\text{g}\cdot\text{kg}^{-1}$), du fentanyl ($1.5 \text{mg}\cdot\text{kg}^{-1}$) ou de l'enflurane. Les narcotiques ont été donnés à double insu et les techniques anesthésiques d'inhalation furent randomisées. Les paramètres cardiorespiratoires sont demeurés stables chez toutes les patientes dans les trois groupes et peu de changements cliniquement importants sont survenus. La récupération était significativement plus rapide chez le groupe ayant reçu de l'alfentanil avec un temps de réponse à la commande verbale significativement plus court que celui du fentanyl ou de l'enflurane. Toutes les techniques ont fourni une anesthésie satisfaisante. Cependant le groupe ayant reçu de l'alfentanil avait significativement plus d'effets secondaires que celui ayant reçu de fentanyl.