Clinical experience with alfentanil for induction of anaesthesia; a comparison with thiopentone

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Alfentanil, a new short-acting narcotic was clinically evaluated as an intravenous anaesthetic induction agent in 19 patients and compared to 20 patients receiving thiopentone. Alfentanil was superior to thiopentone in cardiovascular stability, both during induction of anaesthesia and tracheal intubation. However, alfentanil does not behave like a typical induction agent, time to unconsciousness is longer and more variable and is often accompanied by muscle rigidity. The results of this study suggest that alfentanil is more difficult to use as an induction agent than thiopentone, but alfentanil is recommended for short procedures when haemodynamic stability is important.

Key words

ANAESTHETICS, INTRAVENOUS: Alfentanil, thiopentone; ANAESTHETIC TECHNIQUES; induction.

Alfentanil is a new narcotic analgesic, chemically related to fentanyl, but has a more rapid onset of action, a shorter duration and a potency one third that of fentanyl.¹ Nauta *et al.* suggested that the rapid onset, short duration and lack of cardiovascular side effects may make alfentanil a suitable agent for induction of anaesthesia.² In a recent study they

found that alfentanil compared favourably with thiopentone as an induction agent, but was superior with respect to cardiovascular stability.³ Alfentanil is currently undergoing clinical trials in Canada, and the purpose of this study was to evaluate alfentanil for induction of anaesthesia and attenuation of the cardiovascular response to tracheal intubation. Induction of anaesthesia by alfentanil was followed by a number of different anaesthetic techniques and because of this we have not included any specific information on postoperative outcome.

Methods

The approval of the University of Calgary's ethics committee and patient informed consent were obtained prior to commencement of the study. Forty female ASA physical status class I patients about to undergo plastic surgery were randomly allocated to one of two groups, A or B. Patients with known allergies or who were pregnant or lactating were excluded. The study was conducted under open conditions; the authors had no previous experience with alfentanil, and therefore it was considered unethical to maintain double blind conditions.

Patients in both groups received diazepam 10 mg orally 60–90 minutes prior to induction of anaesthesia. Following the introduction of an 18 gauge intravenous cannula on the dorsum of the hand, ECG monitoring and blood pressure monitoring with a sphygmomanometer cuff on the upper arm were established. Once the patient was stable, preinduction values for heart rate and systolic blood pressure were recorded. Other monitoring included the observation of sweating or lacrimation and measurement of the diameter of the pupil. The

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pupils were measured with a linear scale graded in millimeters under constant ambient lighting conditions.

Following a three-minute period of preoxygenation, group A patients received thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$ as an IV bolus over ten seconds, whereas group B patients were given alfentanil $120 \mu\text{g} \cdot \text{kg}^{-1}$ also as an IV bolus over ten seconds; this dose of alfentanil had been recommended by previous workers.² After injection of the drugs the time to unconsciousness in both groups was recorded. In those patients receiving alfentanil, unconsciousness was defined as the moment when the patient failed to respond verbally or physically to command; fine purposeful facial movements were considered a positive response. However, loss of the eyelash reflex was arbitrarily chosen as the end point for the onset of unconsciousness for those patients receiving thiopentone. Failure to achieve unconsciousness after two minutes in the alfentanil group was followed by further incremental boluses of 1–2 mg of alfentanil until the patients were unconscious. At the time of unconsciousness, heart rate, systolic blood pressure, and pupil size were measured and the presence of lacrimation or sweating noted.

Furthermore, pain on injection, rigidity of chest or limbs, involuntary movements and dysrhythmias were also recorded. The patients were questioned about any sensation of chest rigidity and any decreased chest wall compliance was noted during manual ventilation by face mask. Both groups of patients then received succinylcholine $1 \text{ mg} \cdot \text{kg}^{-1}$ and were ventilated using a mask for one minute with 66 per cent nitrous oxide in oxygen. Then blood pressure, heart rate, and pupil size were measured again, and the presence of lacrimation or sweating were also noted. Patients in both groups underwent laryngoscopy for 20 seconds with a Macintosh blade, and a further set of observations and haemodynamic measurements were made. The trachea was intubated with a lubricated (lidocaine gel) PVC tracheal tube and was followed by immediate inflation of the cuff. One minute after this all variables were recorded again. Anaesthesia was continued using techniques appropriate to the surgery. Postoperatively, after establishing that patients were able to recall the moments immediately prior to anaesthesia, they were questioned regarding awareness during the intubation period and whether injection of the induction agent was

painful. Administration of drugs and measurement of blood pressure and heart rates were all by one investigator, whereas intubation and other observations were made by a second investigator; the time was kept by a third observer. Results were subjected to statistical analysis by paired and unpaired Student's *t* test and analysis of variance, as appropriate. Probability values < 0.05 were considered significant.

Results

Twenty patients received thiopentone and 19 patients received alfentanil; one patient in the alfentanil group was excluded because of a protocol violation. Table I shows patient data for age, weight, and height for the two groups and analysis of variance indicates no significant difference between them.

During induction of anaesthesia with thiopentone $5 \text{ mg} \cdot \text{kg}^{-1}$ no further supplementation was required to induce sleep. The mean time to the loss of the eyelash reflex was 33.1 seconds (SD 7.4). Unconsciousness was induced in thirteen of the 19 patients in group B with the bolus or $120 \mu\text{g} \cdot \text{kg}^{-1}$ of alfentanil, the mean time to unconsciousness in the 13 patients was 109.9 seconds (SD 60.7). Six patients in the alfentanil group required supplemental boluses, as sleep had not been achieved two minutes after the initial $120 \mu\text{g} \cdot \text{kg}^{-1}$ bolus. These patients ultimately required a mean dose of $220 \mu\text{g} \cdot \text{kg}^{-1}$ (SD 60.5), the dosage ranged in these patients from 151.1–300 $\mu\text{g} \cdot \text{kg}^{-1}$. These patients had a mean time to unconsciousness of 320.6 seconds (SD 177).

Analysis of cardiovascular responses was examined in two parts. Cardiovascular stability following administration of the induction agents was determined by comparing preinduction values for heart rate and blood pressure with those when loss

TABLE I Patient data. Mean (range of values)

	Number of Patients	Age (yrs)	Weight (kg)	Height (cm)
Group A Thiopentone	20	30.6 (16–55)	59.7 (44–84)	159.9 (147–175)
Group B Alfentanil	19	31.1 (19–48)	66.2 (46–104.9)	163.2 (152.2–170)

TABLE II Mean (SD) cardiovascular changes during the induction period

	<i>Preinduction</i>	<i>Postinduction</i>
Group A (Thiopentone)		
Heart rate/min	79.1 (14.5)	91.75* (14.8)
Blood Pressure mmHg	105 (15.5)	92.4† (11.3)
Rate pressure product	8457.1 (2415)	8546.2 (2093)
Group B (Alfentanil)		
Heart rate/min	72.4 (12.9)	66 (12.3)
Blood Pressure mmHg	102.3 (12.3)	93.5 (19.6)
Rate pressure product	7469.2 (1906)	6299.2 (2288.3)

**p* < 0.02.†*p* < 0.01.

of lash reflex or lack of response had been achieved in the thiopentone and alfentanil groups respectively; Table II summarises these findings. Patients in the alfentanil group showed no significant change in heart rate, blood pressure or rate pressure product (RPP) during induction. However, thiopental administration resulted in a significant rise in heart rate accompanied by a fall in systolic arterial pressure.

The effectiveness of alfentanil for attenuation of the cardiovascular response to intubation was determined by comparison of mean prelaryngoscopy heart rate and mean systolic blood pressure with the values seen after 20 seconds of laryngoscopy and one minute after intubation. The findings for the

intubation period are summarised in Table III. There was a significant rise in both heart rate, blood pressure and rate pressure product in Group A after laryngoscopy and one minute post intubation. By contrast, there was a significant transient slowing in heart rate at the time of laryngoscopy in patients receiving alfentanil Group B; however, there was no significant change in blood pressure or rate pressure product.

The other clinical signs of autonomic activity commonly monitored during anaesthesia were also analysed. Among the patients who received alfentanil, there were no changes in pupil size, sweating or lacrimation during the periods of laryngoscopy and endotracheal intubation. However, there was an initial decrease in pupil size immediately after induction with alfentanil. On the other hand 15 of the 20 patients who received thiopentone had markedly increased lacrimation during the periods of laryngoscopy and endotracheal intubation. Sweating was present in four patients and pupil diameter became larger in one.

Comparison of the cardiovascular changes among the thiopentone patients who had changes in these autonomic signs, with those thiopentone patients who had no changes, revealed no significant differences in heart rate, systolic blood pressure or RPP. The incidence of side effects with thiopentone and alfentanil are summarised in Table IV. Dysrhythmias were all ventricular in origin and were either bigeminy or premature ventricular

TABLE III Mean (SD) cardiovascular response to intubation

	<i>Prelaryngoscopy</i>	<i>Laryngoscopy</i>	<i>1 min postintubation</i>
Group A (Thiopentone)			
Heart rate	95.9 (14.7)	107.4* (15.4)	105.9† (14.5)
Systolic blood pressure (mmHg)	116.5 (18.6)	144.4‡ (27.7)	137.8§ (23.3)
Rate pressure product	11168 (2386.4)	15551.6‡ (3873.5)	14680.9‡ (3579.1)
Group B (Alfentanil)			
Heart rate	67.8 (14.4)	59.1† (10.2)	65.6 (12.2)
Systolic blood pressure (mmHg)	95 (21.9)	90.4 (16.6)	96.4 (15.4)
Rate pressure product	6657 (2750)	5470 (1722.5)	6176.5 (1642.6)

**p* < 0.02.†*p* < 0.05.‡*p* < 0.001.§*p* < 0.01.

TABLE IV Summary of side effects

	Group A (Thiopentone)	Group B (Alfentanil)
Total number of patients	20	19
Bradycardia	0	7
Ventricular Dysrhythmia	5	0
Pain on injection	2	3
Chest stiffness	1	5
Involuntary movements/ Rigidity	2	10
Awareness	0	1

contractions; these rhythms were exclusively seen in the thiopentone group. Involuntary movements, stiffness of the upper limbs and chest were more common observations among the alfentanil group of patients.

Slowing of the heart rate was seen among seven patients induced with alfentanil; however, it only reached statistical significance at the time of concurrent vagal stimulation during laryngoscopy; none of the seven patients required active treatment. Awareness of tracheal intubation occurred once in the alfentanil group in a patient considered to have reached a state of unconsciousness. However, this patient volunteered that it was not an unpleasant experience. No patient in the thiopentone group experienced awareness.

Because of the variety of different anaesthetic techniques which followed the induction of anaesthesia with alfentanil, no specific observations were made on the patients in the postoperative period. However, all the patients in the study left the recovery room within 30–45 minutes and no respiratory or other problems were reported by the recovery room staff.

Discussion

A new narcotic analgesic, such as alfentanil, has to justify its place if it is to replace similar drugs already available. Alfentanil is chemically related to fentanyl but is more rapid in onset and shorter acting than fentanyl, thus making it more suitable for short procedures and perhaps for induction of anaesthesia.¹ Furthermore, its shorter action may result in a reduced incidence of postoperative respiratory depression. However, the short duration of action of alfentanil demands that maintenance of

anaesthesia would be better by continuous intravenous infusion.

Although other studies have investigated dosage of alfentanil for induction of anaesthesia, time to unconsciousness, haemodynamic stability and common side effects, they have not emphasised the clinical behaviour of alfentanil during induction.^{2,3} The present study has evaluated the efficacy and practical aspects of administering alfentanil for induction. Alfentanil does not behave like a conventional anaesthetic induction agent, probably because of a different site of action. Typically, a bolus injection of alfentanil was followed by sedation and rapidly progressive respiratory depression. Apnoea was often seen prior to the onset of unconsciousness. Before this, patients were easily aroused by command but eventually were only able to respond by small facial movements. Absence of any response to command was taken as the onset of unconsciousness. Not infrequently the eyes were still open and deviated upwards. The eyelash reflex may have been lost only to be present subsequently when elicited seconds later. The respiratory depression that precedes the onset of sleep is easily managed by a period of preoxygenation and if required, by assisted ventilation by mask. Unlike thiopentone and similar induction agents there was initially some difficulty on our part in deciding whether patients were unconscious after alfentanil. Lack of familiarity with its behaviour almost certainly accounted for the single case of awareness.

After induction, rigidity in the upper limbs with spontaneous movements were common but were not always accompanied by subjective or objective evidence of chest stiffness. Nauta *et al.* have suggested that benzodiazepine premedication and pretreatment with small doses of competitive muscle relaxants may reduce the incidence of rigidity.² However, in a second study by the same group the incidence of rigidity was still as high as 55 per cent.³ In the present study rigidity, which was always accompanied by some involuntary movements, was seen in 52 per cent of the alfentanil group but clinically apparent chest wall stiffness was seen in only 26 per cent; in the thiopentone group ten per cent of patients demonstrated some involuntary movements. All patients had intravenous cannulae placed in the dorsum of the hand and

the incidence of pain during injection was not significantly different with the two drugs. Patients were not monitored specifically for thrombotic or inflammatory sequelae around the injection site in the following days, but there were no spontaneously reported problems of this nature.

In 66 per cent of the patients receiving alfentanil, a bolus injection of $120 \mu\text{g}\cdot\text{kg}^{-1}$ administered over ten seconds resulted in a mean time to unconsciousness of 109.9 seconds (SD 60.7). Although dosage and rate of administrations were not comparable, the time to unconsciousness in this study is similar to that in previous work.^{2,3} However, 34 per cent of the patients receiving alfentanil did not become unconscious with a bolus dose of $120 \mu\text{g}\cdot\text{kg}^{-1}$ and subsequently required almost twice this dose for induction of anaesthesia. The mean time to unconsciousness in this group was 320.6 seconds (SD 177). This variability in the time for onset of sleep may reflect an underestimate for the initial induction dose of alfentanil. Patients receiving $5 \text{ mg}\cdot\text{kg}^{-1}$ of thiopentone had a mean time to unconsciousness of 33.1 seconds (7.4). Thiopentone, in contrast to alfentanil, was faster in action, less variable in onset time and had an easily recognisable end point for the onset of unconsciousness.

Haemodynamic stability at the time of induction is one of the claimed advantages of alfentanil, and its superiority to thiopentone in this respect is confirmed by this study. Thiopentone induction was followed by a significant rise in heart rate and fall in systolic blood pressure. Alfentanil induction was accompanied by a fall in heart rate and blood pressure but neither change was statistically significant. Laryngoscopy and intubation are known to result in haemodynamic changes during the induction period.^{4,5} Many studies have attempted to avoid this haemodynamic response by the administration of additional agents including: topical and intravenous lidocaine, beta adrenergic antagonists, sodium nitroprusside, hydralazine and low and high doses of fentanyl.⁶⁻¹⁰ The majority of these agents have problems of their own, such as tachycardia and bradycardia. However, fentanyl has gained popularity, but when given in effective doses ($6 \mu\text{g}\cdot\text{kg}^{-1}$)¹⁰ its relatively long duration of action makes it unsuitable for short procedures; alfentanil with its shorter duration of action would be a better choice.

As in the study of Nauta *et al.*, the present study shows that alfentanil completely attenuated the haemodynamic response to laryngoscopy and intubation following bolus doses sufficient to render patients unconscious.³ Although alfentanil slowed the heart rate, this was not of sufficient clinical significance to need treatment in the seven patients affected. Thiopentone was ineffective for attenuation of the haemodynamic response during the intubation period; heart rate, systolic blood pressure, and rate pressure product were significantly greater than during the control period. Cardiac dysrhythmias, either bigeminy or premature ventricular contractions, were seen in 25 per cent of the thiopentone group. No ventricular dysrhythmias were observed following induction with alfentanil. Similarly, only the thiopentone group of patients experienced sweating and lacrimation, further evidence of autonomic activity during the intubation period. The postoperative consequences of alfentanil induction were not examined as the techniques for maintenance of anaesthesia were not standardised. However, the sequelae of anaesthesia with alfentanil induction and maintenance by infusion are being investigated currently in a follow-up study.

In conclusion, alfentanil has the advantage over thiopentone of maintaining haemodynamic stability during the induction and intubation period. However, alfentanil does not behave like a classical induction agent; induction time is longer, more variable and it is difficult to determine the onset of sleep. Side effects of involuntary movements and muscle rigidity are common but can be managed by preoxygenation, and muscle relaxants.

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Résumé

L'alfentanil est un nouveau morphinique à courte durée d'action qu'on a utilisé comme agent d'induction chez 19 patients qu'on a comparés à 20 autres patients ayant reçu du thiopentone. L'alfentanil assure la stabilité cardiovasculaire mieux que le thiopentone tant à l'induction qu'à l'intubation trachéale. Cependant, l'alfentanil n'est pas un véritable agent d'induction: le délai avant l'inconscience est plus long et plus variable qu'avec le thiopentone et il se complique souvent de rigidité musculaire. Ces constatations suggèrent que l'alfentanil est d'emploi plus difficile que le thiopentone pour l'induction de l'anesthésie mais l'alfentanil présente un intérêt certain pour les opérations courtes où la stabilité hémodynamique est particulièrement importante.