Haemodynamic stability and ketamine–alfentanil anaesthetic induction

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Summary

We have determined if alfentanil could obtund the haemodynamic instability commonly seen at induction of anaesthesia with ketamine. Five groups of ASA I and II patients received ketamine 1 mg kg⁻¹ i.v., preceded by saline (group 1) or alfentanil 10, 20, 30 or 40 μg kg⁻¹ (groups 2–5, respectively). Heart rate (HR), mean arterial pressure (AP), postoperative patient complaints and dysphoria were noted. All groups showed increases (P < 0.05) in both HR and AP after administration of ketamine, which were progressively smaller as the dose of alfentanil increased. After tracheal intubation, all groups showed further increases in HR and AP, with groups 3–5 (alfentanil 20–40 μg kg⁻¹) showing significant obtundation (P < 0.05) of these increases compared with group 1. No patient in any group reported postoperative dysphoria or dissatisfaction with their anaesthetic. Ketamine 1 mg kg⁻¹ with alfentanil 20–40 μg kg⁻¹ provided statistically significant obtundation of the haemodynamic instability that is common with ketamine alone. (Br. J. Anaesth. 1998; 81: 702–706).

Keywords: anaesthetics i.v., ketamine; analgesics opioid, alfentanil; anaesthetic techniques, induction; cardiovascular system, effects

Numerous agents and combinations of agents have been used in an effort to minimize haemodynamic instability during induction of anaesthesia.¹–⁶ Our recent study comparing thiopental (thiopentone), ketamine, thiopental with fentanyl and ketamine with fentanyl⁹ demonstrated that the combination of ketamine and fentanyl provided haemodynamic stability during induction that was superior to the other three induction regimens, while at the same time providing excellent patient satisfaction.

When given alone, ketamine produces rapid induction but may cause unpleasant psychological side effects; ketamine also results in catecholamine release with subsequent tachycardia and hypertension.¹⁰ Numerous medications, including midazolam and fentanyl,¹ have been shown to attenuate or prevent the hallucinations induced by ketamine, but while midazolam can significantly decrease the increase in arterial pressure (AP) normally seen after tracheal intubation when anaesthesia is induced with ketamine, midazolam provides little control of tachycardia after intubation.¹¹ Fentanyl has been shown to obtund the increase in both heart rate (HR) and AP after intubation with ketamine.⁹

Alfentanil has a more rapid onset and shorter duration of action than fentanyl,¹² properties which may be advantageous in short surgical cases where rapid induction is also desirable. However, at least one previous study has indicated that the ability of alfentanil to block increases in HR and AP during induction of anaesthesia is inferior to that of fentanyl.¹³ If ketamine with alfentanil is haemodynamically stable, this regimen might offer an attractive alternative to more conventional techniques, such as thiopental alone or in combination with fentanyl.

Examining the hypothesis that a combination of ketamine and alfentanil (an induction regimen not reported previously in the literature) might also provide pleasant and haemodynamically stable induction of anaesthesia, and in an attempt to determine the optimum dose of alfentanil for this purpose, we studied HR, mean AP, surgical duration, length of stay in the recovery room and problems in the recovery room, including dysphoria, in association with induction of anaesthesia with ketamine alone and with ketamine and four different doses of alfentanil.

Patients and methods

After obtaining approval from both Institutional Human Studies Committees and written informed consent, we studied 100 patients, ASA I–II, undergoing elective surgery expected to last at least 30 min (greater than the expected duration of action of an induction dose of ketamine) and requiring general anaesthesia, including tracheal intubation. Power analysis showed that for an SD value of 15, alpha 0.05 and beta 0.2, a difference of 20 units (HR or AP) would be detected with 10 patients per treatment group, and for a difference of 10 units, 38 patients per treatment group would be required.

Patients were allocated randomly to receive one of five induction regimens according to a list prepared before the start of the study. Groups were compared after every 25 patients and the study was considered to be concluded when statistically significant differences between groups were found for both HR and AP. All patients with a history of cardiac disease, cerebrovascular disease, psychosis or recent drug abuse were excluded. No preoperative sedation was administered. Induction agents were administered and tracheal intubation was carried out by experienced residents or nurse anaesthetists who were...
aware of the agents and doses given. Drugs were prepared by the operating room pharmacist (Montefiore) or by the resident or nurse anaesthetist assigned to each patient (Northport VA). The study was conducted in a blinded manner in that neither patients nor study members recording data were aware of which technique was used. In cases where the assigned attending anaesthetist was a study team member, they recorded the induction data but were not informed of which technique had been used until induction was completed and all data recorded. In such cases, another attending anaesthetist was requested to be available but was not required to be physically present in the operating room.

Patients in group 1 received saline 10 ml, followed after 60 s by ketamine 1 mg kg\(^{-1}\). Patients in groups 2–5 were given alfentanil 10, 20, 30 and 40 \(\mu g\) kg\(^{-1}\) (diluted with saline to 10 ml), respectively, followed after 60 s by ketamine 1 mg kg\(^{-1}\). All patients received succinylcholine (suxamethonium) 1.25 mg kg\(^{-1}\) before tracheal intubation, at the point at which the patient became unresponsive to verbal commands and lost the eyelid reflex. All drugs were given as i.v. boluses. Laryngoscopy and tracheal intubation were begun 120 s after administration of ketamine. The lungs were ventilated with 100% oxygen by mask in the interval between administration of succinylcholine and laryngoscopy. If intubation could not be accomplished successfully within 30 s, the patient was dropped from the study and another patient substituted. After intubation, mechanical ventilation was instituted and anaesthesia maintained with nitrous oxide 4 litre min\(^{-1}\), oxygen 2 litre min\(^{-1}\) and 1% isoflurane (Ohmeda modulus anaesthesia machines with Cyprane vaporizers, calibrated for accuracy by Ohmeda Corporation, Madison, WI, USA, every 12 months). At 5 min after intubation, induction was considered to be over and the anaesthetic management after this point was at the discretion of the anaesthesia team in charge of the case. During this 5 min, all surgical stimulation was avoided.

HR was monitored by electrocardiography (Physiocontrol Corp., Redmond WA, USA or Hewlett-Packard, Boise, ID, USA). Mean AP was measured oscillometrically using Dinamap monitors (Critikon, Tampa, FL, USA) capable of determining AP every 20–30 s, HR and AP were recorded at nine times: baseline, 60 s after administration of saline or alfentanil, 30, 60, 90 and 120 s after administration of ketamine, and 30, 60 s and 5 min after placement of the tracheal tube.

Age, sex, time spent in the recovery room and duration of surgery were recorded. Continuous end-tidal \(PCO_2\) (Datascope Corp., Montvale, NJ, USA and Ohmeda) and oxygen saturation by pulse oximeter (Nellcor Co., Hayward, CA, USA and Ohmeda) were monitored during induction of anaesthesia to insure that haemodynamic instability, if present, was not caused by either hypoxia or hypercapnia. Patient complaints, dysphoria and adverse events in the recovery room were noted by the nurse assigned to each patient. Patients were discharged from the recovery room when they achieved an Aldrete score\(^{14}\) of 8 (2 points possible for level of consciousness, respiration, overall level of activity, oxygen saturation and arterial pressure).

To normalize for variations in baseline values, data for HR and AP were compared as change from baseline between groups. Continuous data were analysed both within and between groups by two-way analysis of variance (ANOVA) for repeated measures. Changes from baseline to peak HR and AP were analysed by one-way ANOVA between groups. The Fisher–PLSD (protected least significant difference) test was used in all cases for multiple comparisons. Nominal data (incidence of nausea, dysphoria and patient complaints) were analysed using chi-square. In all cases, \(P<0.05\) was considered statistically significant. Data for HR, AP, patient age, weight, surgical duration and time spent in the recovery room are reported as mean (SD).

## Results

Three patients were excluded from the study because of difficulty with tracheal intubation. One patient was excluded because of arterial pressure cuff malfunction during induction and one patient was excluded because of i.v. line infiltration, not detected until after induction had begun. Fifty-four women and 46 men (100 patients in total) were studied.

All groups experienced increases in both HR (table 1, fig. 1) and AP (table 2, fig. 2) after administration of ketamine but before intubation \((P<0.05)\), in addition to further increases in AP and HR after intubation \((P<0.05)\). These increases were significantly less than control \((P<0.05)\) in groups 3–5 (ketamine withalfentanil 20, 30 and 40 \(\mu g\) kg\(^{-1}\), respectively) compared with groups 1 and 2 (ketamine with saline and alfentanil 10 \(\mu g\) kg\(^{-1}\), respectively). At 5 min after intubation, AP and HR were still increased above baseline \((P<0.05)\) in groups 1 and 2, and in group 5 AP was slightly, but significantly, decreased compared with baseline.

No patient had oxygen saturation less than 95% at any time during the study. There were no statistically significant differences in end-tidal \(PCO_2\) between the groups.

One patient in group 4 received atropine at 1–5 min after tracheal intubation for a heart rate of 38 beat min\(^{-1}\) not associated with hypotension. All patients were considered by their anaesthesia teams to be clinically stable during this time.

After surgery, the trachea was extubated in the operating room and all patients were taken to the recovery room with stable vital signs. No patient suffered emergence delirium or dysphoria or had any complaints regarding anaesthesia in the recovery room. One patient in group 3 was diagnosed as suffering from negative pressure pulmonary oedema in the recovery room (low oxygen saturation and positive chest x-ray findings), thought to be secondary to an episode of laryngospasm on emergence from anaesthesia. This patient’s symptoms resolved over 3 h with mask oxygen and did not require reintubation. There were no other intra- or post-operative complications apart from isolated instances of transient nausea (no statistically significant difference between groups).

Groups were similar in age, weight, duration of surgery and time spent in the recovery room after operation (table 3).
All anaesthetic agents and induction combinations studied previously with respect to haemodynamic stability have been shown to have disadvantages. When added to thiopental, nitroprusside, hydralazine and isosorbide dinitrate help to maintain stable AP after intubation but do not prevent (and may even cause) tachycardia. Propranolol and esmolol can prevent tachycardia after intubation but not hypertension, and can exacerbate bronchospasm and depress cardiac function. Labetalol can provide control of both HR and AP, but at the risk of cardiac depression and bronchospasm. Lidocaine (lignocaine), whether i.v. or topical, has been shown to provide little protection against tachycardia or hypertension. Both fentanyl and alfentanil can cause chest wall rigidity, in addition to bradycardia and hypotension when given in doses sufficient to induce anaesthesia. Ketamine provides rapid onset and profound analgesia, but has been associated with hallucinations and catecholamine release, commonly resulting in both tachycardia and hypertension.

Despite the recent increase in the popularity of propofol, thiopental is still the most common induction agent in all institutions of which we have personal knowledge. However, thiopental causes cardiac depression and venodilation. Our previous study, performed in a patient population identical to that in Table 1, showed that all groups had similar heart rate and arterial pressure changes after intubation. However, there were significant differences in the maximum changes in heart rate and arterial pressure between the groups, as shown in Table 2 and Figure 1.
the current study, showed that thiopental, when given as the sole induction agent, typically resulted in large variations in both HR and AP. Thiopental does not result in direct release of catecholamines. However, HR and AP values after intubation following induction with thiopental proved to be no different from those achieved with ketamine, presumably because the lack of analgesia with this agent provided no protection against catecholamine release commonly caused by a noxious stimulus such as tracheal intubation. Thiopental with fentanyl provided partial protection against tachycardia and hypertension subsequent to intubation, but at the cost of both bradycardia and hypotension before intubation. Ketamine with fentanyl resulted in significant obtundation of tachycardia and hypertension after intubation, with little or no change in HR or AP before intubation.

The goal of our study was to determine if alfentanil in combination with ketamine could provide haemodynamically stable induction of anaesthesia, and to determine the optimum dose of alfentanil that would be required. We chose to evaluate ketamine with doses of alfentanil ranging from 1 to 40 \( \mu \text{g kg}^{-1} \) as this is the dose range of alfentanil that has been found previously to be at least partially effective in obtruding the haemodynamic response to tracheal intubation when combined with thiopental. Ketamine is commonly administered for induction of anaesthesia in doses of 1–2 mg kg\(^{-1}\). Previous studies have shown that catecholamine release and subsequent increases in HR and AP do not increase with increasing doses of ketamine but are constant within the range 0.5–1.5 mg kg\(^{-1}\). We chose to use ketamine 1 mg kg\(^{-1}\) for all patients in the hope that a lower dose would lead to a shorter duration of action, which would result in a lowered incidence of postoperative hallucinations and emergence delirium.

Our study clearly demonstrated that alfentanil, combined with ketamine, significantly obtunded the increase in HR and AP after intubation usually associated with ketamine alone, and greatly reduced the duration, without resulting in a decrease in HR and AP before intubation and causing only a small decrease in HR and AP within 5 min of intubation (alfentanil 40 \( \mu \text{g kg}^{-1} \) only). It must be noted, however, that statistically significant results are not necessarily clinically significant. Some patients with severe cardiac or cerebrovascular disease can tolerate little or no haemodynamic instability, while a reduction in the increase in HR and AP after intubation of approximately 14 beat min\(^{-1}\) and 20 mm Hg, respectively, combined with rapid return to baseline levels might mean a clinically significant difference in outcome for other patients. Changes in HR and AP responses with ketamine and alfentanil 30–40 \( \mu \text{g kg}^{-1} \) were comparable with those found in our previous study with either ketamine–fentanyl or thiopental–fentanyl. The combination of thiopental–fentanyl is commonly administered and has been studied often. As the onset times of both ketamine and alfentanil are 30–60 s, in circumstances where a rapid onset of action with relative haemodynamic stability is required (i.e. rapid sequence induction in an elderly or debilitated patient), ketamine–alfentanil would seem to be a viable alternative to more traditional techniques.

Induction of anaesthesia with ketamine alone results in an increase in AP and HR after intubation that could be deleterious in patients with cardiac or cerebrovascular disease. We restricted our study to patients without cardiac or cerebrovascular disease, as we did not feel it medically safe to use ketamine as the sole induction agent in such patients. Consequently, we cannot say with absolute certainty that ketamine with alfentanil could provide superior haemodynamic stability in the more debilitated population; however, results obtained in previous studies with thiopental, ketamine and thiopental–fentanyl showed little difference in haemodynamic response between healthy patients and those with cardiac disease.

Therefore, it seems likely that this would also be the case for ketamine–alfentanil.

Benzodiazepines, barbiturates, potent inhalation anaesthetic agents and fentanyl reduce or eliminate the incidence of hallucinations and delirium caused by ketamine. We do not find it surprising, therefore, that our study, which included potent

### Table 3: Age, weight, duration of surgery and recovery room time in the five groups (mean (SD or range)). No significant differences

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine alone</td>
<td>Ketamine + alfentanil 10 ( \mu \text{g kg}^{-1} )</td>
<td>Ketamine + alfentanil 20 ( \mu \text{g kg}^{-1} )</td>
<td>Ketamine + alfentanil 30 ( \mu \text{g kg}^{-1} )</td>
<td>Ketamine + alfentanil 40 ( \mu \text{g kg}^{-1} )</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>41.4(18–80)</td>
<td>40.0(19–80)</td>
<td>46.3(18–78)</td>
<td>43.8(21–68)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.6(13.4)</td>
<td>72.6(16.0)</td>
<td>74.3(17.0)</td>
<td>80.0(15.2)</td>
</tr>
<tr>
<td>Case duration (min)</td>
<td>160(79.9)</td>
<td>186(117)</td>
<td>168(94.2)</td>
<td>162(82.3)</td>
</tr>
<tr>
<td>Recovery room (min)</td>
<td>122(36.8)</td>
<td>135(95.8)</td>
<td>131(60.3)</td>
<td>121(38.2)</td>
</tr>
</tbody>
</table>
inhalation agents in every case and alfentanil in most, showed no incidence of hallucinations, dysphoria or postoperative delirium.

In summary, induction of anaesthesia with ketamine and alfentanil 30–40 μg kg⁻¹ provided haemodynamic stability superior to that obtained with ketamine alone and comparable with that seen in previous studies with either thiopental–fentanyl or ketamine–fentanyl, with little or no postoperative dysphoria or emergence delirium and no patient complaints regarding anaesthesia.

References


27. Tweed WA, Mymuin D. Myocardial force-velocity relations during ketamine anaesthesia at constant heart rate. Anesthesiology 1974; 41: 49–52.
