ED\textsubscript{50} of Alfentanil for Induction of Anesthesia in Unpremedicated Young Adults

Thomas E. McDonnell, M.D., * Richard R. Bartkowski, M.D., Ph.D., † Jay J. Williams, M.D., Ph.D. †

This study determined the $\text{ED}_{50}$ and $\text{ED}_{90}$ of alfentanil for unconsciousness and anesthesia. A bolus of alfentanil was given to 28 healthy unpremedicated adults undergoing gynecologic or orthopedic procedures in one of four dosages: 100, 150, 200, or 250 µg/kg. Three indicators of induction were assessed 90 s later: eyelid reflex, response to verbal commands to breathe, and response to placement of a nasopharyngeal airway. Succinylcholine, given at 90 s, was followed by tracheal intubation 1 min later.

From probit analysis, the $\text{ED}_{50}$ and $\text{ED}_{90}$ for loss of voice response were 92 and 111 µg/kg, respectively, and for loss of nasopharyngeal airway response, 111 and 169 µg/kg. A high incidence of chest wall rigidity (75%) and movements of the limbs (54%) or eyes (25%) was seen. There were statistically significant increases of the heart rate prior to stimulation and of both the heart rate (21% rise) and systolic blood pressure (16% rise) from control to the peak value following intubation. Differences between alfentanil doses were not significant. Naloxone was required in 36% of patients for end-tidal P\textsubscript{CO\textsubscript{2}} greater than 48 mmHg at emergence from anesthesia; no patient required additional naloxone. Nausea or vomiting occurred in 39% of all subjects. Two patients recalled placement of the nasopharyngeal airway.

We conclude that alfentanil is an anesthetic, and its $\text{ED}_{50}$ (analogous to MAC of inhalational agents) is 111 µg/kg. The blood pressure and heart rate responses to laryngoscopy and intubation were modest after doses that allowed for extubation as early as 51 min after induction. (Key words: Analgesics: alfentanil. Anesthetics, intravenous: alfentanil. Blood pressure: hypertension. Heart: pulse rate. Potency, anesthetic: $\text{ED}_{50}$ alfentanil.)

ALFENTANIL is a new, short-acting opioid structurally related to fentanyl. In experimental animals, it has approximately one-third of fentanyl's potency and duration of action.¹ Alfentanil by infusion has been used as the sole agent for induction² and maintenance³ for general anesthesia. Its rapid onset of action and modest effects on hemodynamics suggest it may be useful for the several clinical situations that require both a rapid induction of anesthesia and maintenance of cardiovascular stability.

This investigation evaluated the ability of a bolus of alfentanil to induce anesthesia in unpremedicated young adults. The dose requirements of alfentanil were determined using two common indicators of anesthetic induction, the loss of eyelid reflex and response to voice, and an indicator of anesthesia, the lack of movement after placement of a nasopharyngeal airway. Additional characteristics were evaluated, including the effect of alfentanil on the blood pressure and heart rate response to tracheal intubation and the incidence of side effects.

Materials and Methods

The protocol was approved by the University of Pennsylvania Committee on Studies Involving Human Beings. Informed written consent was obtained from each patient the day before surgery.

Twenty-eight ASA physical status I patients, ages 18 to 41 yr, were studied and assigned randomly to receive one of the following doses of alfentanil: 100 µg/kg, 150 µg/kg, 200 µg/kg, or 250 µg/kg. No premedication or anticholinergic drug was administered. Patients were monitored with a blood pressure cuff (Riva–Rocci method), electrocardiogram, and capnometer (Hewlett Packard model 47210A), with an infrared CO\textsubscript{2} sensor located in the Y-piece of the anesthetic circle. After placement of an intravenous catheter, 500 crystalloid solution was infused and d-tubocurarine 3 mg was given. Baseline blood pressure and heart rate were recorded while the patients breathed 100% oxygen by mask for 3 min. The selected dose of alfentanil then was injected rapidly (less than 10 s) into a rapidly flowing intravenous infusion via the port nearest the intravenous catheter. Ventilation was assisted or controlled as necessary with 100% oxygen by mask. Chest wall rigidity was diagnosed when ventilation was impossible by mask and muscle contraction was evident in the neck. Limb movements and any other reactions were recorded when present. An aide, assigned to this task, read and recorded blood pressure and heart rate every 30 s until 2 min following intubation.

Each patient was examined at 30, 60, and 90 s after injection of alfentanil for the presence of an eyelid reflex (ER), defined as an immediate blink after brushing either lash with a finger tip, and voice response (VR), defined as a breath within 10 s of three consecutive voice commands to breathe. At 90 s after injection, a lubricated 5 Fr rubber nasopharyngeal airway was placed. A positive response (NAR) consisted of movement of the head, neck, or limbs. Facial movements in the absence of the above were not considered as a positive response. Those who responded to any of the three stimuli at 90 s received an additional dose of alfentanil 50 µg/kg.

Succinylcholine 1.5 mg/kg was given to all patients at 90 s, followed 1 min later by tracheal intubation. Tri-
methaphan (3 mg/min) and ephedrine (5–10 mg iv) were
given for increases or decreases, respectively, of systolic
blood pressure from more than 25% of the control value.
Each patient received 100% oxygen until 2 min after
intubation, when inhalation anesthesia was begun. No
opioids or other intravenous sedatives were given after
induction. Neuromuscular blocking agents were used
when clinically indicated. All observations, including
blood pressure determinations, were made by individuals
who were unaware of the alfentanil dose and not involved
in the study.

At the termination of anesthesia, neuromuscular
blockade was reversed and inhalational anesthesia was
discontinued. After 5 min, naloxone in increments of
0.05 mg was given every 2 min if end-tidal \( P_{CO_2} \) exceeded
48 mmHg while the patient had spontaneous ventilation
of 100% \( O_2 \). Patients who received naloxone had an end-
tidal \( P_{CO_2} \) determination 30 min after extubation. All
patients were questioned on the first and thirtieth post-
operative days regarding their sensations and last rec-
collections during induction.

Statistical analyses were performed using probit anal-
ysis\(^1\) for the dose response data, analysis of variance
(nested design)\(^5\) with Newman–Keuls tests\(^6\) and the Bon-
feronni procedure for the hemodynamic data, analysis
of variance for the group age and weight comparisons,
chi-square tests for rigidity and emetic symptom data,
and the Wilcoxon rank–sum test for the relationship be-
tween the use of naloxone and the duration of anesthesia.
\( P < 0.05 \) was accepted as significant. Data are presented
as mean ± SD.

**Results**

There were no significant differences in the ages and
weights among the four groups (table 1). The median
duration of anesthesia for the 24 gynecologic and four
orthopedic procedures was 81 min (range: 51 to
304 min).

The patient responses for voice and nasal stimulation
at the four dose levels are presented in table 1 and figure
1. The reflexes were suppressed maximally 90 s after
alfentanil; only one voice response changed between 60
and 90 s, and there was a substantial suppression even
at 30 s (table 2). Therefore, only results for 90 s were
analyzed. Only two patients, both in the 100 \( \mu g/kg \) group,
were responsive to voice at 90 s. No patient who received
200 or 250 \( \mu g/kg \) moved in response to placement of
the nasal airway. In each of the two lower dose groups,
two patients who were unresponsive to voice moved after
placement of the airway. Eyelid reflex was not abolished
completely in any dose group. The \( ED_{90} \) and \( ED_{90} \) for
the suppression of response to voice and nasopharyngeal
airway are listed in table 3.

A high incidence of chest wall rigidity was observed
(table 4), which frequently rendered ventilation impos-
sible. There was no significant difference in the incidence
of rigidity among the four dose groups. Purposeless limb
movements were observed frequently (table 4); most
commonly, these consisted of clenching of one or both
fists. Patients also manifested varying degrees of wrist
and forearm flexion. Unlike chest wall rigidity, there was
a statistically significant trend toward a higher incidence
of purposeless limb movements with higher doses of
alfentanil. Random blinking of the eyes (not in response
to stimulation, but often making assessment of eyelid
reflex difficult) or roving movements of the eyes were seen

| Table 1. Group Profiles and Response Suppression at 90 s Following Intravenous Alfentanil |
|-----------------|-----------------|-----------------|-----------------|
| Dose \( \mu g/kg \) | Age* yr ± SD | Weight* kg ± SD | N | Voice | Nazal |
| 100 | 31 ± 6.2 | 66 ± 6.9 | 7 | 5 | 3 |
| 150 | 31 ± 5.1 | 57 ± 7.3 | 7 | 7 | 5 |
| 200 | 31 ± 6.0 | 67 ± 12.1 | 7 | 7 | 7 |
| 250 | 31 ± 7.9 | 60 ± 14.6 | 7 | 7 | 7 |

* No significant difference among the groups.

| Table 2. Number of Patients Not Responding to Voice at 30, 60, and 90 s Following Alfentanil |
|-----------------|-----------------|-----------------|
| Dose \( \mu g/kg \) | N | 30 | 60 | 90 |
| 100 | 7 | 5 | 5 |
| 150 | 7 | 7 | 7 |
| 200 | 7 | 7 | 7 |
| 250 | 7 | 6 | 6 | 6 |

Fig. 1. Dose–response curves for loss of response to voice and
nasopharyngeal airway, 90 s following alfentanil in unpremedicated
adults. Curves are the best fit lines as given by probit analysis.
in 25\% of patients. Apnea occurred in all patients, except in three who received 100 \( \mu g/kg \). One patient in each group received trimethaphan for a 25\% rise in systolic blood pressure above control: the two patients in the 100 and 250 \( \mu g/kg \) groups had an increase of systolic blood pressures prior to succinylcholine administration and laryngoscopy, while the two patients in the 150 and 200 \( \mu g/kg \) groups had a hypertensive response following intubation. Two patients received ephedrine, both for decreases in systolic blood pressure following supplemental alfentanil given at 90 s.

Two-way analysis of variance (nested design) tested the differences of the systolic and diastolic blood pressures and heart rate for each initial alfentanil dose and three times: control, 90 s after drug, and in the 2 min period (peak value) following intubation. There were no significant differences related to the dose. Repeat analysis for the systolic, diastolic pressures and heart rate in terms of total dose, initial plus supplemental, also failed to yield a dose-dependent effect. Heart rate and both pressures had significant changes with time. Heart rate increased from the control of 81 \( \pm 19 \) beats/min (mean \( \pm \) SD) to 92 \( \pm 25 \) beats/min at 90 s (\( P < 0.05 \)). The peak heart rate following intubation, 98 \( \pm 22 \) beats/min, was significantly greater than control but not the 90 s value. The change in systolic blood pressure from control, 123 \( \pm 15 \) mmHg, to the 90 s value of 117 \( \pm 23 \) mmHg, was not statistically significant, but there was a significant increase after intubation to 136 \( \pm 29 \) mmHg. There was a significant increase in diastolic blood pressure from the 90 s value of 74 \( \pm 12 \) mmHg to the peak after intubation, 84 \( \pm 17 \) mmHg (table 5).

The increase in end-tidal \( P_{CO_2} \) from control to immediately after intubation (mean change \( \pm \) SD: 4.0 \( \pm \) 5.5 mmHg) was significant (\( P < 0.01 \)). The greatest increase was 20 mmHg, from 36 to 59 mmHg occurring over 3 min in a patient who also manifested profound limb and chest wall rigidity; all other patients maintained end-tidal \( P_{CO_2} \) less than 48 mmHg.

Naloxone was required in 35\% of all patients, and its use was independent of the total alfentanil dose. The total doses of naloxone were 0.05 mg (\( n = 1 \)), 0.1 mg (\( n = 8 \)), and 0.15 mg (\( n = 1 \)). The association of naloxone use with shorter procedures approached but did not reach statistical significance (\( P = 0.11 \)). A relationship between naloxone use and procedure length or alfentanil dose may have been masked by the varying duration and concentration of supplemental inhalational anesthesia (halothane in two patients, enflurane in 11, and isoflurane in 14). All patients in the study were extubated in the operating room. The end-tidal \( P_{CO_2} \) determination in the recovery room was lower than that at extubation for each patient receiving naloxone, and no additional naloxone was given to any patient.

Thirty-nine per cent of all patients experienced wretching or vomiting in the recovery period. There was no significant association between the incidence of emetic symptoms and the magnitude of the alfentanil dose or the use of naloxone.

Two patients recalled placement of the nasopharyngeal airway. The first patient (100 \( \mu g/kg \) group) had moved with its placement, though she did not remember the stimulus as uncomfortable. The second (150 \( \mu g/kg \) group) showed no response to airway placement but recalled a painful nasal stimulus. No patient recalled difficulty with breathing, chest or limb tightness, or tracheal intubation. Two patients recalled euphoria upon induction, and another dizziness.

**Discussion**

Responses to various stimuli have been utilized to indicate adequate induction of anesthesia. The eyelid reflex has been used to indicate depth of anesthesia with agents such as ether,\(^7\) thiopental,\(^8\) and methohexital.\(^9\) Responsiveness to verbal command has been used to define the end points of fentanyl\(^10\) and alfentanil\(^5\) infusions for induction of anesthesia. We utilized these two indicators in addition to the response to placement of a nasopharyngeal airway, a stimulus that is both painful and reproducible. The dose range was chosen from pilot studies and reported infusion doses\(^5\) to provide a lower dose near the threshold for unconsciousness and extend beyond a twofold dose range.

In the present study, response to voice was lost at lower doses followed by response to the nasopharyngeal airway, while eyelid reflex was unpredictable. The \( ED_{50} \) and \( ED_{90} \) for loss of eyelid reflex, 115 and 382 \( \mu g/kg \), respectively,

### Table 3. \( ED_{50} \) and \( ED_{90} \) (95\% Confidence Limits) for Loss of Each Reflex

<table>
<thead>
<tr>
<th>Reflex</th>
<th>( ED_{50} ) (( \mu g/kg ))</th>
<th>( ED_{90} ) (( \mu g/kg ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voice Nasopharyngeal</td>
<td>92( \dagger )</td>
<td>111( * )</td>
</tr>
<tr>
<td></td>
<td>111 (59–137)</td>
<td>169 (137–383)</td>
</tr>
</tbody>
</table>

\( \dagger \) Extrapolated.

\( * \) Data insufficient to calculate 95\% confidence limits.

### Table 4. Number of Patients with Chest Wall Rigidity and Purposeless Limb Movements Following Induction of Anesthesia with Alfentanil

<table>
<thead>
<tr>
<th>Dose (( \mu g/kg ))</th>
<th>N</th>
<th>Rigidity( * )</th>
<th>Movement( \dagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>150</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>200</td>
<td>7</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>250</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

\( \dagger \) No significant difference among the groups.

\( * \) Significant difference among the groups, \( P < 0.05 \).
were unexpectedly high because of misinterpretation of random eye movements for eyelid reflexes. The unstimulated eye movements, roving and blinking, obscured the true reflex, making a reliable determination impossible.

The ability of the high-dose fentanyl technique to induce anesthesia in the absence of premedication has been questioned. Sebel et al.\textsuperscript{11} in evaluating the electroencephalographic effects of fentanyl 30–70 μg/kg, felt ethically obligated to premedicate all patients. We have demonstrated the ability of a bolus of alfentanil to induce anesthesia in young patients in the absence of premedication. One patient had postoperative recall for the nasopharyngeal airway; she had responded to its placement with head and neck movement. A second patient, who did not respond to its placement, recalled a painful nasal stimulus. As review of her record indicated the nasal airway was in place at her emergence from anesthesia, it is possible she recalled its removal rather than its insertion.

The incidence of chest wall rigidity was 75% for the entire study population. Its incidence during infusion of alfentanil for induction had varied from 22% to 50%.\textsuperscript{2,3} Rapid administration of other narcotics also has been reported to result in chest wall rigidity.\textsuperscript{12,13} Although premedication with benzodiazepines is thought by some investigators to decrease the incidence of this phenomenon,\textsuperscript{2} benzodiazepines lower the dose of narcotic required for induction and thus may decrease the incidence of rigidity only secondarily.

In previous investigations of alfentanil, upper limb stiffness was reported.\textsuperscript{2,3} In addition, we observed purposeless movements of the upper extremities characterized by finger, wrist or forearm flexion, and random blinking and roving movements of the eyes. The precise mechanism of narcotic-induced stimulation including chest and abdominal rigidity has not been elucidated.

In our unpremedicated patients, induction of anesthesia with alfentanil resulted in a significant increase in heart rate prior to stimulation. This is in contrast to the bradycardia (35% decrease from control) reported after alfentanil 160 μg/kg was administered to dogs.\textsuperscript{1} Bradycardia also has been observed after the use of morphine\textsuperscript{14} and fentanyl\textsuperscript{15,16} in humans. The concurrent increase in $P_{CO_2}$ could account for some of our findings. This is a strong possibility in the patient whose end-tidal $P_{CO_2}$ increased 23 mmHg (to 59 mmHg), since her pulse increased from 69 min to 118 beats/min. In the other patients, however, the end-tidal $P_{CO_2}$ increase averaged 3 mmHg and the highest value was 47 mmHg. This was a modest increase, consistent with 2 min of apnea. It appears to be unlikely that any heart rate response could be attributable to this small change in $P_{CO_2}$.

After induction with the bolus of alfentanil, intubation resulted in increases in heart rate and systolic blood pressure of 21% and 10%, respectively, from control. These data compare favorably with those of other techniques designed to blunt the hemodynamic response to intubation, including thiopental with intravenous or laryngotracheal lidocaine.\textsuperscript{17} While alfentanil hemodynamics were not found to be dose-dependent in this study, some dose-related effect still could be present. This might be seen with a wider dose range or a larger sample. The data also may be interpreted to suggest a limit to the degree of protection provided by alfentanil against sympathetic responses. Recent evidence indicates this to be true for high doses of fentanyl in patients undergoing coronary artery bypass procedures. Doses of fentanyl 50–60 μg/kg, approximately equipotent to alfentanil 150–200 μg/kg, did not block completely the hemodynamic response to noxious stimulation including intubation,\textsuperscript{18} and higher doses of fentanyl (100 μg/kg) did not protect the myocardium from ischemia upon sternotomy.\textsuperscript{19}

The doses of alfentanil used in this study allowed for extubation of all patients in the operating room. Of the patients who required naloxone at emergence from anesthesia, none demonstrated secondary respiratory depression. The incidence of emetic symptoms in this study was high, particularly in patients who underwent laparoscopy (8 of 17, or 47%). In a concurrent group of 110 patients undergoing laparoscopy in our hospital with a variety of anesthetic techniques, the incidence of nausea or vomiting was 31%, which agrees with data of other authors.\textsuperscript{32} In

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Table 5. Cardiovascular Responses during Induction with Alfentanil in 28 Patients} & & & & \\
\hline
\textbf{Heart rate} & \textbf{Control (n)} & \textbf{90 s after} & \textbf{Peak Value to 2 min} & \textbf{$P < 0.05^*$} \\
\textbf{(beats/min ± SD)} & \textbf{Alfentanil (n)} & \textbf{after Intubation (n)} & & \\
\hline
\textbf{Systolic blood pressure} & \textbf{81 ± 19} & \textbf{92 ± 25} & \textbf{98 ± 22} & \textbf{a, c} \\
\textbf{(mmHg ± SD)} & \textbf{123 ± 16} & \textbf{117 ± 23} & \textbf{136 ± 29} & \textbf{b, c} \\
\textbf{Diastolic blood pressure} & \textbf{79 ± 9} & \textbf{74 ± 12} & \textbf{84 ± 17} & \textbf{b} \\
\textbf{(mmHg ± SD)} & & & & \\
\hline
\end{tabular}
\end{table}

\begin{itemize}
\item $^*$ a = t\textsubscript{1} versus t\textsubscript{2}; b = t\textsubscript{2} versus t\textsubscript{3}; c = t\textsubscript{3} versus t\textsubscript{4}. Data were analyzed using two-way analysis of variance (nested design); differences were determined using the Newman–Keuls test.
\item $^\dagger$ Prior to painful stimulation or additional drug.
\end{itemize}
a group of 178 patients undergoing other gynecologic procedures at our institution, 11% had emetic symptoms. Analysis of contingency tables arranged for anesthetic and procedure revealed a trend (P = 0.07) toward an increased incidence of nausea and vomiting after an alfentanil induction.

In conclusion, alfentanil without supplementation is an anesthetic. Its ED₉₀ for suppression of a withdrawal response to a nasopharyngeal airway, analogous to the MAC of inhalational agents, is 111 µg/kg. The sympathetic responses to laryngoscopy and intubation are blunted after doses that allow for extubation of healthy patients after approximately 1 h. Muscle relaxants can eliminate chest wall rigidity and limb movements. Alfentanil, therefore, has promise as an induction agent in a dose near its ED₉₀ of 169 µg/kg when its rapid onset, short duration of action, and cardiovascular properties can be used to advantage.

References