Comparison of Alfentanil with Fentanyl for Outpatient Anesthesia

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Alfentanil (Alfenta®) is a new, rapid and short-acting synthetic analog of fentanyl that may offer advantages over the parent compound in the outpatient surgery setting. Previous authors have described the use of this new opioid compound by either repeated injection or continuous administration as a supplement to nitrous oxide.

The administration of ketamine or fentanyl by continuous infusion provided for more precise regulation of anesthetic or analgesic dose, and hence drug effect, when compared with conventional intermittent injection techniques. The continuous infusion technique lessened the total amount of drug administered and thereby decreased recovery times for outpatients. The present study was designed to compare the clinical effects and therapeutic concentration ranges for alfentanil and fentanyl when administered with nitrous oxide for maintenance of anesthesia during brief outpatient surgical procedures; and 2) to determine whether a continuous infusion of alfentanil (or fentanyl) would offer any advantages over the traditional intermittent injection technique.

MATERIALS AND METHODS

After informed consent was obtained, 100 healthy (ASA physical status I or II) young women presenting for midtrimester therapeutic abortion by dilatation and extraction were randomly assigned to one of four treatment groups: Group 1—fentanyl bolus (FB), n = 25; Group 2—fentanyl infusion (FI), n = 25; Group 3—alfentanil bolus (AB), n = 25; Group 4—alfentanil infusion (AI), n = 25.

This double-blind, open-parallel protocol was approved by the local institutional review board. The surgeon, anesthesiologist monitoring the patient, physician—observer, and patient were unaware of which analgesic drug was being administered. The four groups were comparable (mean ± SEM) with respect to age (25 ± 3 yr), weight (63 ± 4 kg), and gestation (16 ± 1 week). Before surgery, patients were asked to complete a baseline Trieger test (used to measure psychomotor function) and a series of analog scales (Appendix 1), which were used to assess the degree of pain and sedation.

These unpremedicated outpatients were taken to the operating room, where an 18-gauge intravenous catheter was inserted into a forearm vein and routine monitoring devices were applied (e.g., Dinamap® blood pressure cuff, precordial stethoscope, and ECG). All patients were administered droperidol, 0.625 mg iv. In addition, Groups 1 and 2 received fentanyl, 100 μg iv, and Groups 3 and 4 were given alfentanil, 500 μg iv, as a loading dose 2–3 min before induction of anesthesia.

In all groups, anesthesia was induced with thiopental, 4 mg/kg iv (over 30–60 s), and when the patient became unresponsive (i.e., loss of eyelid reflex), nitrous oxide (N₂O) 70% in O₂ was administered via a tight-fitting face mask with the use of conventional circle absorber system. When the patient resumed spontaneous ventilation, a maintenance infusion of fentanyl (Group 2) or alfentanil

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Received from the Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305. Accepted for publication August 20, 1985.

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Key words: Anesthetic technique: continuous infusion. Anesthetics, intravenous: alfentanil; fentanyl. Surgery: outpatient.

§ The opioid solutions were prepared so that the anesthesiologist administering the drugs used similar volumes for the bolus injections (e.g., fentanyl 50 μg/ml or alfentanil 250 μg/ml) and the maintenance infusions (e.g., fentanyl 2 μg/ml or alfentanil 10 μg/ml).
(Group 4) was started at a rate of 10 μg/min or 50 μg/min, respectively. End-tidal carbon dioxide (CO₂) was measured with a capnograph. The end of the CO₂ sampling catheter was located in the elbow connector for the face mask. End-tidal CO₂ values were considered valid only if an expiratory plateau phase was identified on the CO₂ tracing. Average end-tidal CO₂ values for patients from the infusion groups were obtained at 1-min intervals during the maintenance period. Determining the need for additional analgesic medication was based on a clinical assessment of the depth of anesthesia (e.g., changes in muscle tone or movement; alterations in the respiratory rate, arterial blood pressure, or heart rate in response to surgical stimulation).

The criteria used to indicate an increase in analgesic dosage included a change in respiratory rate, heart rate, or mean arterial blood pressure exceeding 20% of the value that prevailed immediately before surgical stimulation. However, the earliest clinical signs of "light" anesthesia were increasing muscle tone and/or purposeful movement. Patients manifesting clinical signs of inadequate analgesia received either a single injection of fentanyl 50 μg iv (Group 1) or alfentanil 250 μg iv (Group 3), or the rate of the maintenance infusion of fentanyl (Group 2) or alfentanil (Group 4) was increased. If repeated supplemental injections of the analgesics or increases in the maintenance opiate infusion rate were unable to suppress signs of light anesthesia, small doses of thiopental 25–50 mg iv were administered. No other anesthetic or analgesic agents were administered during the maintenance period. The fentanyl or alfentanil infusion rates were decreased if the patient manifested evidence of excessive narcotic effect (e.g., progressive slowing of respiratory rate). In general, fentanyl and alfentanil infusion rates varied between 2–25 μg/min and 10–150 μg/min, respectively. Ventilation was assisted when the respiratory rate decreased below 5 breaths/min and during prolonged periods of apnea (>30 s). If increased muscle tone (e.g., rigidity) precluded adequate ventilation after insertion of a nasal airway, succinylcholine, 5–10 mg iv, was given.

At the end of surgery, the opiate infusion and N₂O were discontinued. The averaged dose of opioid analgesic (μg·kg⁻¹·min⁻¹) for each patient was calculated by dividing the total narcotic dose (μg) by body weight (kg) and then dividing this value (μg/kg) by the duration of anesthesia (min). Recovery times were recorded by a physician–observer as follows: awakening time (time from discontinuation of N₂O until the patient was responsive to simple commands); orientation time (time until the patient was oriented to person and place); and ambulation time (time until the patient could walk unassisted).

Postoperatively, a physician–observer administered psychometric tests at 30-min intervals and recorded side effects in the recovery room. The Trieger tests were scored by the absolute number of dots missed and the total distance (mm) from the missed dots to the nearest line. Pain and sedation analog scales were 100-mm lines, and patients were instructed to place a perpendicular mark through the analog scale at the point which reflected the degree of pain or wakefulness they were experiencing at that time, respectively (Appendix 1). A score of 100 on the pain or sedation scale represented maximal discomfort or sedation, while a score of zero was no pain or sedation. Patients were discharged from the recovery room when they were able to empty their bladder and ambulate without assistance.

Venous blood samples were obtained at 2–5-min intervals during the maintenance infusion period from patients in Groups 2 and 4 through a 19-gauge "butterfly" needle placed in the arm contralateral to the arm receiving the opiate infusion. Serum alfentanil and fentanyl concentrations were analyzed using a modification of the alfentanil and fentanyl radioimmunoassay methods described by Michiels et al. The standard curves for alfentanil and fentanyl were linear over concentration ranges from 10 to 500 ng/ml and 0.2 to 20 ng/ml, respectively.

Data were analyzed as follows: continuous variables were analyzed using Statistical Analysis System (SAS), one-way analysis of variance, and Duncan's multiple range test (P < 0.05). Categoric variables were evaluated with SAS chi-square analysis (P < 0.05). All data are expressed as mean values ± S.E.M. Trieger tests were scored in terms of the number of dots missed (maximum 40) and the total distance from the missed dots to the nearest line (maximum 200 mm). Serum concentrations of alfentanil and fentanyl during the maintenance infusion period were averaged for each patient and reported as the mean effective (therapeutic) serum concentration.

RESULTS

The mean duration of anesthesia (22–27 min) did not differ significantly among the four groups. The number of supplemental injections of thiopental as well as the total doses of thiopental (4.1–4.5 mg/kg) were similar in all four study groups. The intraoperative and postoperative effects of alfentanil and fentanyl when administered with nitrous oxide for maintenance of anesthesia are summarized in tables 1 and 2. Although neither opiate compound produced statistically significant changes in cardiovascular variables, alfentanil was associated more frequently with decreases in heart rate. The adjunctive use of fentanyl, and, to a lesser extent, alfentanil, was associated with significant respiratory depression.
TABLE 1. Narcotic Analgesic Requirements and Incidences of Intraoperative Side Effects following the Use of either Fentanyl or Alfentanil as a Supplement to Nitrous Oxide

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Analgesic Dose*</th>
<th>Respiratory depression</th>
<th>Muscular Rigidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg</td>
<td>µg·kg⁻¹·min⁻¹</td>
<td>Mild†</td>
</tr>
<tr>
<td>FB</td>
<td>432 ± 38</td>
<td>0.20 ± 0.03</td>
<td>32</td>
</tr>
<tr>
<td>FI</td>
<td>280 ± 20†</td>
<td>0.11 ± 0.01†</td>
<td>40</td>
</tr>
<tr>
<td>AB</td>
<td>2.447 ± 202</td>
<td>1.30 ± 0.16</td>
<td>40</td>
</tr>
<tr>
<td>AI</td>
<td>1.649 ± 100†‡</td>
<td>0.77 ± 0.07†</td>
<td>28</td>
</tr>
</tbody>
</table>

* Mean values ± SEM.
† Percentage with 15–25% decrease in respiratory rate from post-induction value.
‡ Percentage requiring ventilatory assistance (i.e., respiratory rate <5 breaths/min).
§ Percentage requiring administration of succinylcholine 5–10 mg iv boluses.

The total narcotic analgesic requirements in the AI and FI groups were significantly decreased compared with the AB and FB groups, respectively (table 1). When continuous (vs. intermittent) administration techniques were used, the averaged maintenance dose requirements for alfentanil and fentanyl were decreased by 41% and 45%, respectively. In addition, the times to awakening were significantly decreased in the infusion (vs. repeated injection) groups. Based on the administered dose, fentanyl was found to be six to eight times more potent than alfentanil, irrespective of the administration technique. Intraoperative side effects (e.g., respiratory depression, apnea, and chest wall rigidity) were less frequent with alfentanil. Although prolonged periods of apnea requiring assisted ventilation were not reported in either infusion group, they occurred in 34% of the patients in Group 1 (FB) and 4% of the patients in Group 3 (AB). The averaged end-tidal CO₂ values (mean values ± SEM) for patients in the alfentanil and fentanyl infusion groups were 39 ± 2 mmHg and 46 ± 3 mmHg, respectively. Since end-tidal CO₂ measurements obtained at the level of the face mask underestimate the arterial CO₂ content, these data would indicate that varying degrees of hypercarbia occurred when the patients receiving the opioid infusions were allowed to ventilate spontaneously. Within 5 min of discontinuing the nitrous oxide, however, all patients had end-tidal CO₂ values in the normal range (35–40 mmHg).

No clinically significant respiratory depression was evident during the postoperative recovery period.

The average infusion rates for alfentanil and fentanyl were 0.8 and 0.1 µg·kg⁻¹·min⁻¹, respectively. Examples of the relationship between the changes in the fentanyl or alfentanil infusion rates and the resultant serum concentrations are shown in figures 1 and 2, respectively. The mean serum levels of alfentanil or fentanyl (±SEM) when administered as a supplement to thiopental and nitrous oxide were 99 ± 7 ng/ml (range: 59–191 ng/ml) or 2.4 ± 0.2 ng/ml (range: 1.2–4.0 ng/ml), respectively. For individual patients, fentanyl and alfentanil levels varied over a threefold to sixfold range during these brief operations (figs. 3 and 4, respectively). Yet, the mean serum narcotic levels required to suppress clinical responses to the surgical stimulus (e.g., uterine dilatation and extraction) remained relatively stable during the operation. Comparing the potency ratio based on serum concentrations required to produce adequate analgesia would suggest that alfentanil is approximately one-fortieth as potent as fentanyl.

Common postoperative side effects produced by alfentanil and fentanyl included nausea (52–68%), vomiting (36–60%), and dizziness (24–52%). Although there were no statistically significant differences between the groups with respect to these postoperative side effects, times to awakening, orientation, and ambulation were significantly

TABLE 2. Postoperative Recovery Times and Side Effects Following the Use of either Fentanyl or Alfentanil as an Adjuvant to Nitrous Oxide

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Recovery times (min)*</th>
<th>Side Effects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Awake</td>
<td>Oriented</td>
</tr>
<tr>
<td>FB</td>
<td>5.2 ± 0.9</td>
<td>7.7 ± 1.1</td>
</tr>
<tr>
<td>FI</td>
<td>3.7 ± 0.8†</td>
<td>6.1 ± 1.2</td>
</tr>
<tr>
<td>AB</td>
<td>2.5 ± 0.3‡</td>
<td>3.5 ± 0.4‡</td>
</tr>
<tr>
<td>AI</td>
<td>1.2 ± 0.1†‡</td>
<td>2.6 ± 0.3‡</td>
</tr>
</tbody>
</table>

* Mean values ± SEM.
† AI or FI group significantly different from AB or FB group (P < 0.05), respectively.
‡ AB or AI group significantly different from FB or FI group (P < 0.05), respectively.
shorter with alfentanil (table 2). Compared with fentanyl, recovery of psychomotor function also was more rapid and postoperative drowsiness and sedation was less with alfentanil (fig. 5; table 2). Postoperatively, Trieger scores differed significantly between the fentanyl and alfentanil groups (e.g., 13 ± 2 mm vs. 9 ± 2 mm at 30 min; 9 ± 2 mm vs. 2 ± 1 mm at 60 min, respectively). However, a significantly higher percentage of patients in the alfentanil (vs. fentanyl) groups complained of pain during the recovery period (table 3). Finally, even though their Trieger scores returned to baseline within 60 min, residual sedation was noted in the alfentanil infusion group at the time of discharge from the outpatient unit (fig. 5).

**DISCUSSION**

The ideal anesthetic technique for outpatient surgery would provide for a rapid and pleasant loss of consciousness, adequate depth of anesthesia without significant cardiorespiratory changes, and rapid recovery without side effects. Volatile anesthetics generally are considered to be superior to iv anesthetics for outpatients because they are controlled more easily. However, for some outpatient procedures (e.g., mid-trimester abortions) it is desirable to avoid inhaled anesthetics. Given the pharmacokinetic characteristics of alfentanil, one would predict that when it is used to supplement nitrous oxide for maintenance of anesthesia that a shorter recovery time would result as compared with fentanyl. Analogous to our previous findings, the continuous infusion of alfentanil (and fentanyl) resulted in significant decreases in maintenance drug dosages and recovery times compared with the "conventional" incremental injection technique.

Recently, several brief reports have described the use of alfentanil during outpatient anesthesia. Depending on the amount of drug administered, recovery

**FIG. 1.** Examples of the relationship between changes in the maintenance fentanyl infusion rate ( ) and the resultant serum fentanyl concentration ( ).

**FIG. 2.** Examples of the relationship between changes in the maintenance alfentanil infusion rate ( ) and the resultant serum alfentanil concentration ( ).

**FIG. 3.** Serum fentanyl concentration curves for individual patients as a function of time following the loading dose. Average serum fentanyl concentrations ( ) for all patients in Group 2 as a function of time during the maintenance infusion (mean values ± SEM).

**FIG. 4.** Serum alfentanil concentration curves for individual patients as a function of time following the loading dose. Average serum alfentanil concentrations ( ) for all patients in Group 4 as a function of time during the maintenance infusion (mean values ± SEM).
times following alfentanil were either similar\textsuperscript{15,20,21} or shorter\textsuperscript{16-19,22,23} than those reported following the use of either fentanyl\textsuperscript{15-21,23} or halothane.\textsuperscript{22} The incidences of side effects associated with alfentanil were reported to be similar to those produced by fentanyl\textsuperscript{15-17,19} Unfortunately, even when minimally effective doses of these opioid compounds are administered (i.e., using continuous infusion), the incidence of postoperative side effects may be unacceptably high for some outpatients (table 2).

The high incidence of nausea and vomiting is particularly troublesome, since all patients in our study were premedicated with droperidol (0.625 mg iv), a potent antiemetic. The incidences of nausea and vomiting might have been lower if larger doses of droperidol had been administered; however, Cohen \textit{et al.}\textsuperscript{24} reported that even a small dose of droperidol, 1 mg iv, could significantly delay awakening following brief outpatient procedures. Alternatively, the use of metoclopramide (a gastrointestinal agent with antiemetic properties) might decrease the incidence of opioid-induced nausea and vomiting without prolonging recovery.\textsuperscript{24} Although the adjunctive use of opioid analgesics during outpatient anesthesia might be limited because of side effects, preinduction doses of narcotic analgesics (e.g., fentanyl 1–2 \textmu g/kg, iv) can decrease the maintenance anesthetic requirement and thereby shorten recovery times without significantly increasing the incidence of postanesthetic side effects in the outpatient setting.\textsuperscript{25-27}

Our observation that an equianalgesic dose of alfentanil may be associated with less respiratory depression than fentanyl would support the findings of Scamman \textit{et al.}\textsuperscript{28} These investigators reported that equianalgesic doses of fentanyl produced longer-lasting and more intense respiratory depression than alfentanil. Andrews \textit{et al.}\textsuperscript{29} reported that the ventilatory response to carbon dioxide was depressed to a lesser extent during the infusion of alfentanil compared with fentanyl. We would postulate that alfentanil's more rapid onset of action (\textit{vs.} fentanyl)\textsuperscript{30} allowed for more precise titration of the drug during these short surgical procedures; and therefore, its use was associated with fewer intraoperative side effects (e.g., respiratory depression, muscular rigidity) and more rapid recovery times. In spite of surgical stimulation, however, maintenance infusions of both opioid analgesics were associated with significant respiratory depression (since our end-tidal P\textsubscript{CO\textsubscript{2}} values would be expected to underestimate the actual arterial P\textsubscript{CO\textsubscript{2}} values). Thus, hypercarbia would be expected in spontaneously breathing patients receiving an opioid infusion in combination with nitrous oxide.

Recent studies have determined the optimal alfentanil infusion rates and plasma concentrations required to supplement nitrous oxide for a variety of surgical procedures.\textsuperscript{31-33} Depending on the type of surgical stimulus, the mean effective maintenance infusion rate can vary from 0.25 to 2.5 \textmu g kg\textsuperscript{-1} min\textsuperscript{-1} and is associated with alfentanil concentrations ranging from 100 to 500 ng/ml\textsuperscript{32,33}. Because the duration of anesthesia was short, full loading doses were not administered in our outpatient study and, therefore, the serum levels were lower than might be predicted based on the average infusion rates (due to the presence of both redistributional and metabolic processes). Our studies and others\textsuperscript{3} have demonstrated the feasibility of maintaining an adequate state of surgical anesthesia with a continuous alfentanil infusion and ni-

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{Upper panel: Change in sedation analog scores (sum of five 100 mm analog scales, with 0 [no sedation] to 100 [maximal sedation] for each scale) as a function of time after awakening from anesthesia (mean values ± SEM). Lower panel: Change in Trier scores (number of dots missed) as a function of time after awakening from anesthesia. Asterisk indicates significant differences (P < 0.05) between fentanyl (O ----- O) and alfentanil (O --- O) infusion groups at the indicated time intervals.}
\end{figure}
TABLE 3. Pain Analog Scores and Percentage of Patients Complaining of Pain (cramping) before and after the Operation*  

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Preoperative baseline</th>
<th>30 min</th>
<th>Postoperative 60 min</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score†</td>
<td>%</td>
<td>Score†</td>
<td>%</td>
</tr>
<tr>
<td>FB</td>
<td>19 ± 4</td>
<td>16</td>
<td>11 ± 3</td>
<td>16</td>
</tr>
<tr>
<td>PI</td>
<td>24 ± 4</td>
<td>16</td>
<td>18 ± 4</td>
<td>16</td>
</tr>
<tr>
<td>AB</td>
<td>21 ± 4</td>
<td>8</td>
<td>20 ± 4</td>
<td>12</td>
</tr>
<tr>
<td>AI</td>
<td>21 ± 4</td>
<td>12</td>
<td>31 ± 5‡</td>
<td>36‡</td>
</tr>
</tbody>
</table>

* Insertion of desiccated seaweed (laminera) on the day before surgery can produce lower abdominal discomfort, while administration of oxytocin (or meperidine) frequently causes postoperative pain.

† Scale: 0 = no pain, to 100 = pain could not be worse (mean value ± SEM).
‡ AI group significantly different from FB group, P < 0.05.

Ethroid oxide (67–70%), providing the opioid infusion rate is varied according to clinical signs of "light anesthesia."

As reported in an earlier study, the average fentanyl concentration required to produce adequate analgesia in the presence of 70% NaNO during these brief gynecologic procedures varied over a wide range (1–5 ng/ml). Since the surgical stimulus was virtually identical for all patients, individual variability in serum levels presumably reflects differing individual sensitivities to the analgesic drugs. Alternatively, the differences among patients in their dosage requirements and resultant serum levels may relate to a lack of sensitivity of the methods, dictating an increase or decrease in drug administration. Despite the surgical stimulation, patients receiving a fentanyl infusion hypoventilated throughout the operation. Cartwright et al. reported that fentanyl concentrations in this range are associated with a 50% depression of CO2 responsiveness.

Mean alfentanil concentrations ranging from 60 to 190 ng/ml were required for these brief gynecologic operations with 70% nitrous oxide. The alfentanil levels required during these short outpatient surgical procedures were significantly lower than those required to supplement more invasive surgical procedures, yet higher than the levels needed to produce postoperative analgesia. Although fentanyl was "only" six to eight times more potent than alfentanil on the basis of dosage data, a comparison of the serum level data would indicate that fentanyl is approximately 40 times more potent than alfentanil. Andrews et al. also reported a fentanyl–alfentanil potency ratio of 8:1, based on comparable infusion rates. However, the ratio was closer to 40:1, based on the plasma concentrations required to achieve a similar pharmacodynamic (analgesic) effect. The explanation for the large discrepancy in potency between dosage data and serum concentration data is related in part to the small initial volume of distribution for alfentanil (11 l) compared with fentanyl (60 l). Because of this difference in the distribution volume, the administration of an alfentanil dose that is six to eight times larger than a given dose of fentanyl would be expected to achieve an initial serum concentration that is approximately 40 times higher. In addition, alfentanil's more rapid onset of action would be expected to minimize the lag time between changes in serum concentration and changes in narcotic effect (compared with fentanyl). The decreased hysteresis with alfentanil (vs. fentanyl) would be expected to result in an even greater apparent potency difference between the two opioid compounds. In fact, Scott et al. reported a fentanyl–alfentanil potency ratio of 75:1 when the opiate drug levels required to produce similar EEG changes were compared.

Based on the results of preliminary clinical studies, we assumed that fentanyl was approximately five times more potent than alfentanil. This study and others would indicate that the potency ratio based on administered dose may be closer to 8:1. Since the initial (loading) doses of fentanyl and alfentanil in our study were determined on the basis of a 5:1 potency ratio, we may have started with a relative overdose of fentanyl compared with alfentanil. In determining a true potency ratio for fentanyl and alfentanil, the narcotic effect should be studied at different drug dosages (or preferably, steady state concentrations). Since the slope of the dose–response curve for fentanyl or alfentanil might differ, the calculated potency ratio may differ at either higher or lower drug levels. The existence of hysteresis further complicates attempts at correlating serum narcotic concentrations with the intensity of the drug's effect on the central nervous system. The greater degree of hysteresis associated with fentanyl can have clinical implications as demonstrated in our study. Since the peak effect of a small supplemental injection of fentanyl will occur later than a comparable dose of alfentanil, it is necessary to give an injection of fentanyl earlier in order to prevent clinical responses to noxious stimulation. This practice might lead to a relative overdose with fentanyl, resulting in a higher incidence of side effects and more prolonged recovery times (vs. alfentanil).

A major limitation of our study design relates to the use of clinical (subjective) criteria for judging the "depth of anesthesia." Of primary importance for detection of an inadequate (or "light") level of anesthesia was the presence of increased muscle tone or gross motor activity (i.e., movement) by the patient. A change in the respiratory
pattern occurred before any changes were noted in the hemodynamic variables. On several occasions, patients moved in response to surgical stimulation without any apparent changes in their heart rate or mean arterial pressure. An attempt was made to minimize the amount of narcotic analgesic administered in all four study groups by insisting that additional injections or increases in the maintenance infusion rates be dependent upon predetermined signs of inadequate analgesia. The ability of the anesthetist to titrate the dose more closely when the indication for additional analgesic medication disappeared (i.e., to “abort” the increase in dose in the infusion groups but not in the bolus groups), represents one of the major advantages of the infusion technique over the incremental injection method. On the other hand, increases in drug concentrations may occur slowly with increases in the maintenance infusion rate (figs. 1 and 2) and, hence, administration of a small bolus dose may be more effective in preventing a response to transient noxious stimuli. Finally, when minimally effective doses of short-acting analgesics are administered during an operation, residual postoperative analgesia is less.

In conclusion, alfentanil appears to offer some clinically significant advantages over fentanyl as a supplement to thiopental and nitrous oxide during outpatient anesthesia. The use of a continuous infusion (vs. intermittent injection) of alfentanil allows the anesthetist to titrate the dose of drug with greater precision and thereby minimize the dosage requirement. Unfortunately, postoperative nausea and vomiting associated with the use of alfentanil (and fentanyl) could delay discharge from the outpatient facility. Further studies comparing alfentanil infusions with volatile analgesics (when used as adjuncts to nitrous oxide) are needed to define the role for this potent, rapid, and short-acting opioid analgesic in outpatient anesthesia.

The authors thank Dr. W. A. Dworsky (from the Department of Obstetrics and Gynecology) as well as the residents in the Department of Anesthesia at Stanford University School of Medicine for their assistance and cooperation during this investigation.

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Pulmonary Hypertension and Noncardiogenic Pulmonary Edema Following Cardiopulmonary Bypass Associated with an Antigranulocyte Antibody

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The syndrome of fulminating noncardiogenic pulmonary edema (NCPE) following cardiopulmonary bypass (CPB) has been described many times. The proposed causes are an anaphylactic or idiosyncratic reaction to protamine or some undefined reaction to blood products. Yet a specific mechanism was not established in the previously reported cases.¹,² The following is a case report of a patient in whom severe NCPE likewise developed with marked pulmonary hypertension following CPB. Follow-up investigations revealed the presence of an antigranulocyte antibody in the serum of one of the donors that specifically reacted with the recipient's granulocytes.

**REPORT OF A CASE**

A 50-year-old man with persistent exertional angina was scheduled for elective coronary artery bypass grafting. Medical history was significant for a 40 pack-year smoking history, but the patient denied any wheezing, chronic sputum production, or prior treatment for pulmonary disease. Aside from localized edema following a prior penicillin injection, he had no other known allergies to medications. He had previously received protamine 5 mg iv during cardiac catheterization without sequela. There was no history of prior blood transfusions or adverse reactions to general anesthetics.

Preoperative physical examination revealed clear lung fields and an S4 gallop. Chest roentgenogram showed slight cardiomegaly, but lung fields were clear and without evidence of pulmonary vascular engagement.

On the morning of surgery, the patient began to complain of angina shortly after arriving in the operating room area; these symptoms quickly resolved with the administration of nitroglycerin (sublingual, followed by 75 μg/min, iv) and propranolol, 2 mg, iv. Uneventful induction of general anesthesia with fentanyl, 50 μg/kg, iv and meperidine, 26 mg, iv, ensued. Baseline and subsequent hemodynamics, arterial blood gases, ventilator settings, and concomitant medications were obtained.

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Received from the Departments of Anesthesiology/Critical Care Medicine and Laboratory Medicine and Surgery, The Johns Hopkins Medical Institutions, 600 North Wolfe Street, Baltimore, Maryland 21205. Accepted for publication August 21, 1985. Presented in part at the 1985 Meeting of the Society of Cardiovascular Anesthesiologists.

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