Plasma Concentrations of Alfentanil Required to Supplement Nitrous Oxide Anesthesia for General Surgery

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To design an efficient infusion regimen from pharmacokinetic data, it is necessary to know the alfentanil plasma concentrations required for satisfactory anesthesia. In 37 patients about to undergo lower abdominal gynecologic, upper abdominal, or breast surgery, anesthesia was induced with alfentanil 150 μg/kg iv and 66% N2O in oxygen. Thereafter, N2O anesthesia was supplemented with a continuous infusion of alfentanil that was varied between 25 and 150 μg·kg⁻¹·h⁻¹, as indicated by the patient’s responses to surgical stimulation. Small bolus doses of alfentanil 7 or 14 μg/kg were administered and the infusion rate increased to suppress precisely defined somatic, autonomic, and hemodynamic responses. Arterial plasma concentrations of alfentanil were measured during the operation when the patient did and did not respond to noxious stimulation. Logistic regression was used to determine plasma concentration–effect curves for different stimuli. Plasma alfentanil concentrations required along with 66% N2O to obtain responses to single episodes of stimulation in 50% of the 37 patients (Cp90 ± SE) were: 475 ± 28 ng/ml for tracheal intubation, 279 ± 20 ng/ml for skin incision, and 150 ± 23 ng/ml for skin closure. Between skin incision and closure, multiple determinations of response/no response were made for each patient and an individual Cp90 was estimated. The Cp90 (mean ± SD) for the three surgical procedures were: breast, 270 ± 63 ng/ml (n = 12); lower abdominal, 309 ± 44 ng/ml (n = 14); and upper abdominal, 412 ± 135 ng/ml (n = 11). The Cp90 for satisfactory spontaneous ventilation after discontinuation of N2O was 223 ± 13 ng/ml. These data demonstrate that different perioperative stimuli require different alfentanil concentrations to suppress undesirable responses. Thus, the alfentanil infusion rate should be varied according to the patient’s responsiveness to stimulation in order to maintain satisfactory anesthetic and operative conditions and to provide rapid recovery of consciousness and spontaneous ventilation. (Key words: Anesthetic, intravenous: alfentanil. Anesthetic techniques: intravenous infusion. Pharmacodynamics: alfentanil. Pharmacokinetics: alfentanil. Potency, anesthetic: alfentanil; plasma concentration–effect curves. Surgery: breast; gynecologic; lower abdominal; upper abdominal.)

ALFENTANIL IS A NEW synthetic opioid that has a different pharmacokinetic profile than fentanyl.¹,² It has a shorter terminal elimination half-life, reflecting its smaller steady-state distribution volume relative to that of fentanyl. Alfentanil also differs from fentanyl in its more rapid equilibration between blood and brain; the half-time of blood:brain equilibration is 1–2 min for alfentanil versus 5–7 min for fentanyl.³

These pharmacokinetic differences translate into clinically important pharmacologic differences. The rapid blood:brain equilibration results in an extremely rapid onset of alfentanil’s narcotic effects. Alfentanil’s rapid redistribution from brain to other tissues and short terminal elimination half-life result in a short duration of action. Alfentanil has been used in single or multiple doses for minor, short surgical procedures.¹ For longer surgical procedures, very frequent iv injections of alfentanil have been required.⁴ Because rapidly and continuously fluctuating plasma concentrations are unlikely to provide optimal anesthetic conditions, administration of alfentanil by infusion at a constant rate will provide a more stable effect. However, the intensity of stimulation varies during anesthetic and operative procedures. Maintenance of an alfentanil concentration at the level required to suppress responses to the most intense stimulus may result in prolonged postoperative ventilatory depression. Ideally, the infusion rate should be adjusted in each patient according to the intensity of stimulation and the plasma concentrations maintained at or slightly above the minimum level required to maintain satisfactory anesthetic conditions in order to allow rapid recovery of consciousness and spontaneous ventilation at the end of the operation.⁴–⁶

The purpose of this study is to determine the plasma concentrations required to suppress responses to noxious stimuli of different intensities encountered during general surgical procedures. This information provides a rational basis for the future design of alfentanil infusion schemes.

Methods

Thirty-seven patients (ASA Physical Status I or II) were divided into three groups as follows:
1. Breast group: 12 female patients, aged 27–51 yr, undergoing a modified radical mastectomy. None of these patients had detectable metastases.

2. Lower abdominal group: 14 female patients, aged 25–49 yr, undergoing lower abdominal gynecologic surgery (four hysterectomies, four salpingostomies with lysis of adhesions, and six segmental resections and reanastomosis of the fallopian tube). Some of the data for this group of patients have been reported previously. 6,8

3. Upper abdominal group: 11 patients (four female, seven male), aged 23–54 yr, undergoing upper abdominal surgery (five Billroth II gastric resections, four cholecystectomies, and two highly selective vagotomies).

All patients consented to the clinical investigation as approved by the Medical Ethics Committee of the University of Leiden. The patients were premedicated with 10 mg diazepam orally 2 h before and 0.5 mg atropine im 30 min before the induction of anesthesia.

The patients breathed 100% oxygen and received pancuronium 20 μg/kg iv 3 min before induction of anesthesia. Alfenatal 150 μg/kg was injected iv in exactly 30 s, and 66% nitrous oxide in oxygen was administered by mask to induce general anesthesia; then succinylcholine 1 mg/kg was given iv to facilitate tracheal intubation within 1.5–2.5 min after the injection of alfenatal. Immediately after the induction dose of alfenatal, a continuous infusion of alfenatal 50 μg·kg⁻¹·h⁻¹ was started, using a calibrated infusion pump (WTI®, SP1002, Adequipment, Woerden, The Netherlands). The infusion rate was adjusted in steps of 25 μg·kg⁻¹·h⁻¹ between 25 and 150 μg·kg⁻¹·h⁻¹ and bolus doses of 7 or 14 μg/kg iv were given to suppress rapidly any responses indicating inadequate anesthesia (see following).

After endotracheal intubation the lungs were ventilated mechanically with 66% nitrous oxide in oxygen at an end-tidal carbon dioxide concentration (continuously recorded from a Datascop 500® CO₂ analyzer) between 4 and 5 vol% (29–36 mmHg) for the entire procedure. The electrocardiogram was recorded continuously, and the ventilatory pressures, respiratory minute volume, nasopharyngeal temperature, and blood loss were measured every 15 min. The following clinical criteria were used to categorize a "response":

1. Increase of systemic arterial systolic pressure greater than 15 mmHg above "normal." The "normal" systolic blood pressure for each patient was determined from measurements made at the time of admission to the hospital, in the ward, just before premedication, and on arrival in the anesthesia induction room. "Normal" was defined as the lowest or the most prevalent pressure during three or more determinations.

2. A heart rate exceeding 90 beats/min in the absence of hypovolemia. Fluid balance was evaluated every 15 min, and the objective was to maintain a positive balance. Each patient received 500 ml of iv fluids to start and 300–400 ml/h thereafter. Blood loss was minimal in most of the operations, and when it occurred, the blood loss was immediately replaced.

3. Somatic responses including bodily movements, swallowing, coughing, grimacing, or eye opening. Pancuronium was used only when absolutely necessary to facilitate the operation and only in the smallest dose that was needed (see "Results"). The degree of muscular blockade was estimated every 5–15 min by percutaneous stimulation of the facial nerve (train-of-four method).

4. Other autonomic signs of inadequate anesthesia, such as lacrimation, flushing, or sweating.

Arterial blood pressure and heart rate were continuously recorded and displayed to facilitate the identification of a response. Somatic and autonomic responses were identified by the attending anesthesiologist (M.E.A.) and verified by the assistant anesthesiologist. It should be noted that both anesthesiologists were completely familiar with the strict definition of responses and were continuously looking for any hint of light anesthesia. They were also continuously aware of the surgeons' actions and were able to recognize each lack of responsiveness. The nature of each response, the time of its occurrence, the alfenatal infusion rate, and the time of blood sampling were recorded for each response and each stimulus. The anesthesiologists were not blinded to the alfenatal dose—rate because they had a strict protocol to follow in reducing the rate and strict criteria to meet before increasing the dose—rate. Both were blinded to the alfenatal concentration in plasma, which was analyzed after completion of the operation.

An alfenatal bolus dose (7 μg/kg; or 14 μg/kg if the response was extreme, as defined in the following) was administered to suppress any response. The infusion rate was then increased by 25 μg·kg⁻¹·h⁻¹ to a maximum of 150 μg·kg⁻¹·h⁻¹ if a response was extreme (increase in systolic pressure greater than 25 mmHg or strong movement) or recurred quickly after a bolus dose. If a patient did not respond over a 15-min period of constant infusion, the alfenatal infuson rate was decreased by 25 μg·kg⁻¹·h⁻¹ to a minimum rate of 25 μg·kg⁻¹·h⁻¹. The goal was to use the lowest infusion rate necessary to maintain satisfactory anesthetic conditions. The alfenatal infusion was discontinued 15 min before the anticipated completion of surgery (based on our experience with the surgeon), and the nitrous oxide was discontinued at the end of the operation. If a patient did not regain consciousness and adequate spontaneous ventilation (tidal volume ≥ 7 ml/kg, frequency ≥ 10 beats/min, end-tidal carbon dioxide ≤ 6.5 vol% or ≤ 46 mmHg) within 10
Table 1. Details of Patients Studied

<table>
<thead>
<tr>
<th>Group</th>
<th>Breast (mean ± SD)</th>
<th>Lower Abdominal (mean ± SD)</th>
<th>Upper Abdominal (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12 F</td>
<td>14 F</td>
<td>11 (4 F, 7 M)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>41 ± 7</td>
<td>35 ± 10</td>
<td>44 ± 11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63 ± 8</td>
<td>61 ± 15</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>“Normal” SBP (mmHg)</td>
<td>118 ± 8†</td>
<td>126 ± 9</td>
<td>124 ± 8</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>157 ± 38</td>
<td>198 ± 67</td>
<td>194 ± 45</td>
</tr>
<tr>
<td>Dose–rate of alfentanil (µg · kg⁻¹ · min⁻¹)</td>
<td>1.24 ± 0.39</td>
<td>1.43 ± 0.55</td>
<td>1.99 ± 0.55*</td>
</tr>
<tr>
<td>Normal train of four (%)</td>
<td>92 ± 12*</td>
<td>78 ± 15*</td>
<td>59 ± 18*</td>
</tr>
</tbody>
</table>

N = number of patients; F = female; M = male.

“Normal” SBP = “normal” systemic arterial systolic blood pressure.

(See text for definition.)

Duration of anesthesia = time from the induction of anesthesia until the discontinuation of nitrous oxide.

Dose–rate of alfentanil = total dose of alfentanil required after the induction dose until discontinuation of the infusion divided by the duration of the infusion.

Normal train of four = total time of presence of four twitch responses to train-of-four stimulation of the facial nerve, expressed as a percentage of the duration of anesthesia.

* Significantly different (P < 0.05) from all other groups.
† Significantly different (P < 0.05) from lower abdominal group.

min after discontinuing nitrous oxide, the end-tidal CO₂ was maintained close to 8 vol% (58 mm/Hg) and naloxone (0.04 mg, iv) was administered every 1–2 min until the patient sustained adequate spontaneous ventilation without verbal encouragement.

Arterial blood samples were withdrawn from a radial arterial cannula (Teflon® 20-gauge) inserted before the induction of anesthesia. Samples were obtained before and 2, 5, and 10 min after the induction dose of alfentanil and, then, every 10 min until the first response indicating inadequate anesthesia. Additional samples of arterial blood were obtained at the time of such responses and 2, 5, and 15 min after any supplementary bolus dose and, then, every 5 min until the next sign of inadequate anesthesia appeared. Blood samples were also obtained at the discontinuation of nitrous oxide and when the patient regained satisfactory spontaneous ventilation or 10 min after the discontinuation of nitrous oxide if the patient did not meet the criteria of adequate spontaneous ventilation. Plasma was separated from blood and stored at −20° C until assayed. Alfentanil concentrations were determined by a radioimmunoassay specific for alfentanil.

Data Analysis

For the single events of intubation, skin incision, skin closure, and postoperative ventilation, each patient’s clinical state was categorized as “responsive” or “nonresponsive,” based on the criteria previously described. A single alfentanil plasma concentration at the time of the event was also available. The data for all patients in the three surgical groups were pooled for these single events, which were common to all patients regardless of the type of operation they underwent. The patients were similar in terms of age, body weight, and ASA Physical Status (table 1). None was taking medications preoperatively. The response–nonresponse data for each group overlapped that for the other groups for each of the single events. The clinical state of “responsive” or “nonresponsive” was related to the alfentanil concentration in plasma using the following version of the logistic equation:

\[
\text{Probability of no response} = \frac{\text{AFCp}^\gamma}{\text{CP50}^\gamma + \text{AFCp}^\gamma}
\]

where the probability of no response varies from 0 (response to noxious stimulation) to 1 (no response); AFCp is the measured alfentanil concentration in plasma; CP50 is the alfentanil plasma concentration that results in a 50% probability of a response; and \( \gamma \) is a dimensionless power function that determines the steepness of the slope of the probability versus concentration curve.

In the equation 1 model, the alfentanil plasma concentration and the associated response (0) or no response (1) are entered in an iterative, maximum likelihood (logistic regression) computer program (ELSFIT) that estimates the two parameters CP50 and \( \gamma \). CP50 is used to define the concentration versus response relationship in the same way as ED50 is used to characterize a quantal dose versus response relationship. It is analogous to the MAC value for inhalational anesthetics, except that a “response” included hemodynamic and other autonomic signs in addition to movement, the traditional end point for MAC.

The nonlinear regression data analysis for CP50 and \( \gamma \) generates a standard error that is a measure of the precision of the parameter estimate obtained from the one data set. In the case of each single-event stimulus (e.g., incision), the one data set includes 37 patients, and the CP50 of the single events were compared statistically by calculating the 95% confidence bounds for each parameter.

During the surgical operation itself, multiple measurements of alfentanil plasma concentrations were made for each patient during both “responsive” and “nonresponsive" periods. It was possible to characterize the CP50 and \( \gamma \) parameters for each patient using the data analysis described earlier and to average these parameters for all patients in each group in order to determine the mean value and its standard deviation for each type of surgical operation.

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Footnote:

One-way analysis of variance was used to determine if a significant difference ($P < 0.05$) existed between the mean values of $Cp_{90}$ and $Cp_{15}$ for the three surgical groups. If so, multiple two-tailed unpaired $t$-tests with the Bonferroni correction were performed to determine significant differences ($P < 0.05$) between groups.

Results

The patients were comparable in their age, body weight, ASA classification of physical status, and duration of anesthesia (table 1). There was a slight but statistically significant difference in the mean “normal” systolic blood pressure between the breast group and the lower abdominal group. The average dose-rate of alfentanil required after the induction of anesthesia was significantly higher in the upper abdominal group and lowest in the breast group; the dose-rate required for the lower abdominal group was intermediate but not statistically different from the breast group.

The induction of anesthesia with alfentanil was associated with some side effects. Twenty-three of the 37 patients developed muscular rigidity of the trunk and extremities at approximately the same time they lost consciousness. The muscular rigidity was relieved by succinylcholine (1 mg/kg iv) and did not recur. Fifteen patients had a short period of hypotension (defined as a systolic blood pressure more than 25 mmHg below their “normal” pressure) immediately after the induction dose of alfentanil. However, the systolic blood pressure did not fall below 85 mmHg in any patient and was never below 100 mmHg for longer than 10 min. This hypotensive period was longer in the lower abdominal group than in the other groups, perhaps for the following reasons: 1) The first ten patients of the 14 in the lower abdominal group did not receive 500 ml of intravenous fluids prior to the induction of anesthesia; all the other 27 patients in the study did. 2) There was a longer interval between anesthetic induction and the start of surgery in the lower abdominal group than in the other two groups; this delay resulted from the need to prepare and drape both the abdominal and perineal areas. One patient in each group had bradycardia (<50 beats/min) after the alfentanil induction. In each case, atropine 0.25 mg iv restored the heart rate to the preinduction value. During the maintenance of anesthesia, six patients had brief episodes of clinically insignificant bradycardia (i.e., between 50–60 beats/min without hypotension or changes in the ST segment on the ECG). Overall, the hemodynamic conditions were satisfactory during most of the anesthetic period (table 2).

The incidence of somatic, hemodynamic, and other autonomic responses to noxious surgical stimuli in the three groups are shown in table 3. The incidence of heart-rate responses was low in the breast group; consequently, the average total duration of tachycardia (expressed as a percentage of the duration of anesthesia) was also lowest in this group (see table 2). It is likely that the incidence of somatic responses was influenced by the different degrees of muscular relaxation required to facilitate surgery in each group. However, our regular testing of muscular relaxation by train-of-four nerve stimulation indicated that the patients should have been able to show muscular

### Table 2. Cardiovascular Variables during Anesthesia and Surgery

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Lower Abdominal</th>
<th>Upper Abdominal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above normal + 15 mmHg</td>
<td>5.4 ± 3.5</td>
<td>5.4 ± 3.5</td>
<td>5.4 ± 3.5</td>
</tr>
<tr>
<td>Normal + 15 mmHg</td>
<td>91.4 ± 4.3</td>
<td>91.4 ± 4.3</td>
<td>91.4 ± 4.3</td>
</tr>
<tr>
<td>Below normal – 15 mmHg</td>
<td>3.1 ± 2.4</td>
<td>3.1 ± 2.4</td>
<td>3.1 ± 2.4</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above 90 beats/min</td>
<td>0.7 ± 0.9</td>
<td>0.7 ± 0.9</td>
<td>0.7 ± 0.9</td>
</tr>
<tr>
<td>Between 50–90 beats/min</td>
<td>99.3 ± 0.9</td>
<td>99.3 ± 0.9</td>
<td>99.3 ± 0.9</td>
</tr>
</tbody>
</table>

* The total accumulated time that each hemodynamic condition existed in each patient was determined and expressed as a per cent of the duration of anesthesia (induction to discontinuation of nitrous oxide). The mean value ± SD for each condition is shown for each group of patients.

† The duration of “hypotension” after the induction dose of alfentanil was significantly longer ($P < 0.05$) and the total time of “normal” blood pressure less in the lower abdominal group than in the breast group. (See text.)

‡ Significantly different ($P < 0.05$) from upper abdominal group.

### Table 3. Incidence of Responses to Intraoperative Noxious Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Lower Abdominal</th>
<th>Upper Abdominal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>12</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Hemodynamic responses</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>SBP &gt; normal + 15 mmHg</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &lt; 90 beats/min</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Somatic responses</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Other autonomic responses</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are presented as the median number of response episodes per patient; the range of numbers of episodes among the patients in each group is shown in parentheses. See “Methods” for definitions of responses.

**SBP** = systemic arterial systolic blood pressure.
TABLE 4. \( C_{90\%} \) and Slopes (\( \gamma \)) of the Alfentanil Plasma Concentration-Effect Curves for Single Short-duration Events

<table>
<thead>
<tr>
<th>Event</th>
<th>( C_{90%}) ± SE ng/ml</th>
<th>95% Confidence Limits ng/ml</th>
<th>( \gamma ) ± SE</th>
<th>( N )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation</td>
<td>475 ± 28</td>
<td>532 to 418*</td>
<td>9.7 ± 5.1</td>
<td>37</td>
</tr>
<tr>
<td>Skin incision</td>
<td>279 ± 20</td>
<td>320 to 238†</td>
<td>6.6 ± 3.3</td>
<td>37</td>
</tr>
<tr>
<td>Skin closure</td>
<td>150 ± 23</td>
<td>196 to 163†</td>
<td>4.4 ± 1.9</td>
<td>37</td>
</tr>
<tr>
<td>Spontaneous ventilation</td>
<td>223 ± 13</td>
<td>249 to 197†</td>
<td>9.2 ± 3.9</td>
<td>37</td>
</tr>
</tbody>
</table>

\( C_{90\%} \) = alfentanil plasma concentration at which there is 50% chance of a response.
\( \gamma \) = dimensionless exponent that determines the slope of the plasma concentration-effect curve.
SE = standard error of the parameter estimated by nonlinear regression.
95% confidence limits = 95% confidence limits defined as \( C_{90\%} ± 1.96 \times SE \).
* Significantly different from all other events.
† Significantly different from intubation and skin closure.

The alfentanil infusion was stopped 16.3 ± 5.0 min (mean ± SD) before the end of the operation. Twenty-five patients recovered consciousness and adequate spontaneous ventilation within 3.7 ± 2.0 min (mean ± SD, range 1–9 min) after the nitrous oxide was discontinued at the end of the operation. Naloxone 0.07 ± 0.04 mg (mean ± SD, range 0.04–0.2 mg) was administered to 12 patients because they did not recover or sustain adequate spontaneous ventilation within 10 min after the end of surgery. Nine of these 12 patients did show adequate spontaneous ventilation in the first 10 min after surgery when they were verbally or physically stimulated, but they did not sustain adequate ventilation without encouragement. In the subsequent recovery period, all patients sustained satisfactory spontaneous ventilation (without additional naloxone) and responded appropriately to standard questions asked at regular intervals. Twenty patients (five–eight in each group) requested analgesics within 2 h postoperatively, and 12 patients (three–five in each group) needed an antiemetic (domperidone [Motilium®]). When questioned on the first postoperative day, none of the patients remembered anything between the time of receiving the induction dose of alfentanil and the discontinuation of nitrous oxide. All patients recalled blurring of their vision before induction (due to pancuronium 20 \( \mu \)g/kg), and most remembered tracheal extubation or conversation in the operating or recovery rooms.

The relationships between the alfentanil plasma concentrations and nonresponsiveness to four specific events of short duration in all patients (i.e., endotracheal intubation, skin incision, skin closure, and recovery of spontaneous ventilation) are summarized in figures 1 and 2 and table 4. Only one measurement of alfentanil plasma concentration and one observation of response or nonresponse were made for each of these single events in each patient. The relationships between the alfentanil plasma concentration and the response or nonresponse status of all patients are summarized for each event in the diagrams shown in the upper part of the figures. In each response–no-response diagram, three areas can be distinguished. For example, in figure 1 there is an alfentanil plasma concentration below which all patients spontaneously regained and maintained adequate spontaneous ventilation, and there is a plasma concentration above which all patients required naloxone. There is also a range of overlapping plasma concentrations in which there were patients that did and patients that did not require naloxone. Plotted below the response–no-response diagrams in figures 1 and 2 are the continuous probability curves of nonresponse versus the alfentanil plasma concentration obtained from the logistic regression analysis.

There were significant differences between the \( C_{90\%} \) for intubation, skin incision, and skin closure (table 4). The \( C_{90\%} \) of skin closure was significantly lower than that of the endotracheal intubation.

![Graph showing relationship between alfentanil plasma concentration and the probability of needing naloxone](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931396/)

Fig. 1. Relationship between the alfentanil plasma concentration and the probability of needing naloxone to restore adequate spontaneous ventilation. The diagram at the upper part of the figure shows the alfentanil plasma concentrations of the patients who required naloxone to maintain adequate spontaneous ventilation (upward deflections) and those of the patients who did not need naloxone (downward deflections). The plasma concentration–effect curve (lower part) was defined from the quantal data shown in the diagram using logistic regression. † indicates ±SE of \( C_{90\%} \) (see table 4).
for the recovery of spontaneous ventilation after the discontinuation of nitrous oxide. There was no significant difference in the slopes ($\gamma$) of the plasma concentration–effect curves for these four single events.

Multiple observations in each patient (responses and nonresponses) were made during the actual breast surgery and during the intraabdominal part of the upper and lower abdominal surgery. This made it possible to study the quantal responses to stimulation for each patient. The bars in figure 3 represent the range of plasma concentrations in which there were and were not responses to noxious stimulation in each patient. At plasma concentrations below those indicated by the bar, there was never a response. Visual inspection revealed no relationship between the position or the width of the bars for the individual patients in each group and the type of operation within each group (i.e., cholecystectomy vs. Billroth II resection or hysterectomy vs. salpingostomy). Nor was there a relationship between gender and the position or width of the bars for the patients in the upper abdominal group. There appeared to be less variability in the alfentanil requirements among the patients undergoing lower abdominal operations. Nine of the 14 patients in this group were operated on by the same surgeons, whereas six different surgeons performed the 12 breast biopsies and nine different surgeons were involved in the 11 upper abdominal procedures.
Table 5 shows the $C_p$ and slopes ($\gamma$) of the plasma concentration versus probability of no-response curves as determined by logistic regression for each patient. The variability of the plasma concentrations required to block responses to these stimuli in each patient was relatively small, as indicated by the width of the bars in figure 3 and the steepness of the individual plasma concentration-effect curves in figure 4. There was a 1.6–3.3-fold range of concentrations among the patients within each group (fig. 4); consequently, the standard deviation of the mean $C_p$ for each group was relatively large (fig. 5; table 5). The $C_p$ for the upper abdominal group was significantly higher than the $C_p$ for the breast and lower abdominal groups, which were not statistically different. The steepness of the plasma concentration-effect curves was less in the upper abdominal group—a consequence of a relatively larger variability of the alfentanil requirements within individual patients—but the slopes ($\gamma$) of the mean curves were not significantly different (table 5).

**Discussion**

The primary objective of this study is to define the alfentanil concentrations required along with 66% nitrous oxide to provide a satisfactory state of general anesthesia. A basic premise underlying this study is that alfentanil equilibrates rapidly between plasma and its sites of action within the brain. Scott et al. have shown an extremely close correlation of the rise and decline of alfentanil concentrations in plasma with the onset and recovery of EEG changes indicative of narcotic effect. Further support for this premise comes from the present study in which the alfentanil concentration versus effect curves were very steep for the individual patients. This steep relationship

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**Fig. 3.** Relationships of alfentanil plasma concentrations to responsiveness of patients during breast surgery (upper, left graph) and during the intraabdominal part of lower (upper, right graph) and upper (lower graph) abdominal surgery. Each bar represents the highest concentration associated with a response and the lowest concentration at which there was no response (see text).
is typical for anesthetics\textsuperscript{8} and for narcotic analgesics\textsuperscript{9} and would not be found if there was significant delay between the abrupt change in plasma concentration after an intravenous bolus dose of alfentanil and the control of responses to noxious stimulation.

The multiple signs of inadequate anesthesia (e.g., increased blood pressure, movement) were chosen to represent the full spectrum of general anesthetic objectives. No one sign was consistent and sufficient to represent satisfactory anesthesia with alfentanil and nitrous oxide. To minimize investigator bias and also to allow quantal analysis of the data, the signs were precisely and rigidly defined. To preserve somatic signs, minimal degrees of skeletal muscle paralysis were used only when essential for the completion of the operative procedures. This was especially important in some patients who exhibited only somatic signs in response to noxious stimulation, without any hemodynamic or other autonomic sign.

Defining responses in a quantal manner (i.e., all or none, present or absent) is appropriate for the clinical management of anesthesia. Typically, the anesthesiologist does not use a single continuous variable to determine the

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>( C_{\text{pp}} ) (ng/ml)</th>
<th>( \gamma )</th>
<th>( C_{\text{pp}} ) (ng/ml)</th>
<th>( \gamma )</th>
<th>( C_{\text{pp}} ) (ng/ml)</th>
<th>( \gamma )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>212</td>
<td>7.1</td>
<td>279</td>
<td>10.0</td>
<td>450</td>
<td>7.2</td>
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* Significantly different \((P < 0.05)\) from the other two groups.

Fig. 4. Alfentanil plasma concentration vs. effect curves for each individual patient during breast surgery and during the intraabdominal part of lower and upper abdominal surgery. (Patients were also receiving 66% nitrous oxide in oxygen.) The \( C_{\text{pp}} \) and slope \( \gamma \) (see table 5) of these curves were defined from the quantal responses of the individual patients to these stimuli using logistic regression.
Fig. 5. Mean alfentanil plasma concentration–effect curves for the intraoperative period in each surgical group of patients during nitrous oxide anesthesia. The $C_{p50}$ and slope of these curves were determined by averaging the estimates of individual patients (see table 5). indicates SD of $C_{p50}$ (see table 5).

depth of anesthesia; rather, the overall status of each patient is assessed in reference to a series of criteria similar to those used in this study in order to reach a decision that the anesthetic state is or is not adequate. Also, some of the signs are not quantifiable; they are either present or not (e.g., tearing). Although trends in heart rate and blood pressure may be indicative of changing levels of an anesthetic drug, we defined hemodynamic responses in terms of absolute changes in heart rate and blood pressure in order to make the investigator’s decision to reduce or to increase drug administration as objective as possible. Thus, all of the signs of anesthetic state were of a quanital nature.

The use of the logistic equation with an iterative maximum likelihood approach to characterize the relationship between the alfentanil plasma concentration and the response–nonresponse condition represents a data analysis technique described by Waud. The statistical basis of this approach has been discussed by others. The logistic equation defines the probability of suppressing a response to a given stimulus at a given alfentanil plasma concentration. Two parameters characterize this relationship: the $C_{p50}$ and $\gamma$, the slope term. The $C_{p50}$ or plasma concentration that results in a 50% probability of nonresponse is a measure of alfentanil anesthetic requirement. With the iterative maximum likelihood (logistic regression) approach, one estimates the statistical confidence of this parameter, allowing the construction of 95% confidence bounds for statistical inference. The $\gamma$, or slope term, has less pharmacologic meaning than $C_{p50}$; rather, it is mathematically necessary to generate the sigmoid-shaped curve seen in figures 1, 2, and 4, and it enables the prediction of other points on the concentration versus response curve (e.g., $C_{p95}$). The magnitude of $\gamma$ reflects
the steepness of the alfentanil plasma concentration versus probability of nonresponse relationship; large values indicate a very steep curve. Incidentally, very steep concentration versus response relationships, similar to those we found for alfentanil, have been observed for inhalational anesthetics and for narcotic analgesics.\textsuperscript{5,8,9} The quantal analysis, concept, and applications of \( C_{P_{95}} \) for intravenous drugs are similar to those for MAC of inhalational anesthetics.\textsuperscript{12} There are some differences, however, and these are important in the interpretation of the data presented herein. In MAC determinations, a single stimulus (skin incision for patients) and a single end point of response (movement—MAC, plasma catecholamine elevation—MAC BAR) are used.\textsuperscript{15} In our study, the \( C_{P_{95}} \) for skin incision is based on any and all responses (somatic, autonomic, hemodynamic), and a variety of stimuli were studied and found to have different \( C_{P_{95}} \)s (tables 4 and 5). Nevertheless, it should be possible to compare intravenous and inhalational anesthetic potency and efficacy with these techniques. Determination of the \( C_{P_{95}} \) should also be useful in analyzing factors modifying the responses to intravenous anesthetics (e.g., age, drug interactions, tolerance).

Skin incision has been used as a standard "supramaximal" stimulus in most studies of concentration versus response relationships for the inhalational anesthetics.\textsuperscript{8} It has the disadvantages of: 1) allowing only one measurement per patient; and 2) possibly not being representative of all possible noxious stimuli encountered in surgical operations. Our study demonstrates that skin incision is clearly not the most intense stimulus encountered in the perioperative period, and therefore, it should not be used as the representative of all noxious stimuli associated with anesthetic and surgical procedures. As yet, no other anesthetic drugs have been evaluated against the spectrum of stimuli and according to the multitude of criteria used in the clinical practice of anesthesia.

We combined the data from all 37 patients for each of the four single-event stimuli because the stimulus was virtually identical in all three groups of patients. There are some points to be noted in the interpretation of these data. 1) Tracheal intubation occurred soon after beginning the administration of alfentanil and nitrous oxide, probably before complete equilibration of either drug between plasma and brain had occurred. Despite the high degree of consistency in the data (table 4), different alfentanil concentrations in plasma may have been found if laryngoscopy and intubation had occurred later relative to the start of drug administration. 2) The alfentanil requirements for skin incision (single event in 37 patients) were extremely close to those for breast surgery (multiple determinations in 12 patients). This finding supports the validity of the two methodologies and is suggestive of the alfentanil concentrations likely to be required for other types of superficial operations. 3) There is no certain explanation for the apparently different alfentanil requirements for skin incision and skin closure. Perhaps a rapid incision along a length of skin is more stimulating than the intermittent puncturing of the skin by a needle during closure. 4) The alfentanil requirements for skin closure in the presence of nitrous oxide were less than the alfentanil concentrations associated with satisfactory spontaneous ventilation in the absence of nitrous oxide. This is of obvious practical importance in assuring prompt recovery from a satisfactory state of general anesthesia. It reflects the positive interaction of alfentanil and nitrous oxide and the rapid elimination of nitrous oxide.\textsuperscript{14} The three types of surgical procedures were chosen to be representative of different intensities of stimulation with the assumption that different concentrations of alfentanil would be required for satisfactory anesthesia. The mean \( C_{P_{95}} \) values appear to support our assumption, but there is considerable overlap in the alfentanil requirements for the three groups (table 5). Among the variables to be considered in the interpretation of these data are: 1) the variability inherent in patients in their responses to premedicant and anesthetic drugs and to noxious stimulation; and 2) differences in the intensity of stimulation for the same operative procedure related to surgical technique (different surgeons, more or less difficult operations because of adhesions, etc.). In fact, the variability was greater for upper abdominal operations, which would be expected to involve the most variable intensity of stimulation during the intraabdominal portion of the procedure. This variability indicates the limitations of administering the same dose—rate of an anesthetic drug (without monitoring responses) to all patients when a prompt recovery is desirable.

The steepness of the concentration versus effect curves for most individual patients is suggestive of a clinical tactic to individualize anesthetic administration. That is, once the drug concentration is "on the patient's response curve," only small changes in drug concentration will be required to maintain a satisfactory depth of anesthesia.

There are at least two ways to approach the individual patient's concentration versus response curve. In all cases, the approach would have to be based on careful observation of the patient's response, or lack of response, to a stimulus. One approach would be to administer a loading dose and continuous infusion calculated to establish a plasma concentration near the \( C_{P_{95}} \) for all patients.\textsuperscript{15,16} In the absence of response to noxious stimuli, the infusion rate would be decreased in a stepwise fashion over time (e.g., every 15 min) until a response was observed, at which point a small bolus dose would be given and the infusion rate returned to the previous step. The limitations of this approach are related to the fact that the \( C_{P_{95}} \) level for a population of patients is much too high for extremely
sensitive patients and may produce drug toxicity (not a major problem with most narcotic analgesics intraoperatively) or a prolonged recovery, especially if the duration of the operation is too short to allow the step-wise decrements in the infusion rate to reach the patient’s concentration versus response curve.

Another way to approach an individual patient’s concentration versus response curve is quickly to achieve a stable drug concentration, evaluate the patient’s responsiveness, and then rapidly raise or lower the concentration to another stable level and reevaluate responsiveness. The key to this approach is not to know the drug concentration in plasma, but to be able quickly to produce proportional increments or decrements in the concentration and to home in on the individual patient’s needs by making progressively smaller increments and decrements. This approach is facilitated by the use of an infusion pump controlled by a computer programmed according to average pharmacokinetic parameters. The feasibility of this approach has been demonstrated.17–19

Regardless of the approach taken to intravenous anesthesia, the uses and limitations of concentration versus response data should be kept in mind. Such data define the range of concentrations that are likely to be useful (therapeutic window), indicate the variability likely to be encountered within and among patients, and facilitate comparisons of drugs and studies of factors influencing anesthetic drug requirements. Under certain conditions (e.g., narcotic anesthesia for cardiac surgery followed by ventilatory support overnight16), the Cp95 may serve as the target concentration to be maintained during the entire operation in the absence of drug toxicity. Obviously, such data are essential to the development of infusion schemes designed to produce and maintain drug concentrations within the therapeutic window. However, it must be emphasized that: 1) knowledge of the specific drug concentrations in plasma is not essential to the use of such infusion schemes, as long as the dose–rate can be titrated against the desired response; 2) measurements of drug concentrations in plasma are helpful in verifying the appropriateness of the infusion for a particular patient and in understanding abnormal or unexpected results (i.e., pharmacokinetic vs. pharmacodynamic variability); 3) maintenance of a constant drug concentration is desirable for many experimental purposes but is inappropriate for most clinical anesthesia in which the intensity of stimulation and drug requirements vary and a rapid recovery is desirable; and 4) certain pharmacokinetic characteristics of the drug facilitate a variable dose–rate titrated against the patient’s responses—these include rapid equilibration of the drug between plasma and the site of action, rapid redistribution of the drug from brain to nonresponsive tissues, and rapid elimination of the drug from the body, preferably without the formation of active metabolites.23

To achieve a prompt recovery at the conclusion of the operation (and also to avoid side effects and toxicity caused by excessive concentrations of some drugs), it is essential to aim for the minimum infusion rate for each patient. This was accomplished in this study by scheduling decrements in the infusion rate every 15 min until the patient exhibited a response indicative of inadequate anesthetic depth. The decrements were small, and the responses were easily controlled by a small bolus dose and return to the infusion rate that existed prior to the last decrement. In this way, we continually assessed the patient’s needs and verified that the alfentanil dose–rate was at or very slightly above the minimum required. This titration of dose–rate to the patient’s responses requires extremely close attention to signs of light anesthesia. If the anesthesiologist does not respond promptly, clinical experience has shown that larger doses and additional drugs may be required to regain control of the patient’s responses.

Small intravenous bolus doses are an efficient means of controlling responses to stimulation for two reasons.
1) They provide an immediate increase in plasma and brain concentrations of the drug, whereas it requires a long time (4 × T1/2) for the drug concentration to approach its new steady state after an increment in the infusion rate.20
2) Many surgical stimuli are of a transient nature, and the bolus dose produces a transient increase in drug concentration. Of course, in the face of frequent or continuous intense stimulation, the combination of a bolus dose and an increased infusion rate is appropriate.

As in the case of the potent inhalational anesthetics, it is crucial to prompt recovery for the anesthesiologist to anticipate the completion of the operation and to discontinue drug administration accordingly. This was relatively easy to do with alfentanil and nitrous oxide because the alfentanil concentrations required for skin closure in combination with nitrous oxide were lower than those concentrations associated with satisfactory spontaneous ventilation when nitrous oxide administration was discontinued. Of course, the rapid elimination of nitrous oxide, a substantial component of the anesthetic, was an important factor in the rapid recovery.

The ranges of alfentanil plasma concentrations reported by other investigators for satisfactory anesthetic conditions in the presence of other CNS depressants (i.e., premedication, hypnotics, N2O) are similar to those described in this article.21 Also, the alfentanil concentrations associated with mild ventilatory depression and analgesia in other studies are close to those we found at the end of anesthesia in patients breathing spontaneously.22–24

In summary, this study demonstrates a means to quantitate the anesthetic contribution of an intravenous drug. By defining signs of inadequate anesthesia and relating them to plasma concentrations of a drug that equilibrates rapidly between plasma and brain, concentration versus
response curves can be constructed for stimuli of different intensities. This information provides a scientific basis for administering the drug at a variable rate according to the responses of each patient, ensuring satisfactory anesthetic conditions and prompt recovery.

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References