Alfentanil’s Analgesic, Respiratory, and Cardiovascular Actions in Relation to Dose and Plasma Concentration in Unanesthetized Dogs

Joachim O. Arndt, M.D.,* Birgitt Bednarski,† Chandra Parasher, M.D.‡

Relationships between plasma concentrations of alfentanil and its analgesic, respiratory, and cardiovascular effects were determined in dogs. To avoid drug interaction, trained, unanesthetized, spontaneously breathing dogs were used. After a control period in the awake state, alfentanil was injected in increasing amounts (10, 20, 80, 160, and 320 µg/kg) at 5-min intervals to a total dose of 590 µg/kg administered over 20 min. The effects were observed on pain responses (heart rate and blood pressure changes and somatic reactions to tail clamping), respiration (respiratory rate, oxygen consumption [\(\dot{V}_O_2\)], blood gas tensions) and circulation (heart rate and blood pressure). The plasma concentration-effect curves, derived by relating the changes in multiple variables from the awake state to the corresponding plasma concentrations (range 8–5079 ng/mL), plateaued at and around 200 ng/mL during the injection period but were displaced in parallel to two-fold higher concentrations during recovery, which resembles acute tolerance. At maximally effective analgesic concentrations, which precipitated profound cardiorespiratory slowing with conspicuous hypoxemia, the \(\dot{V}_O_2\) of 4.4 ± 0.3 ml·kg\(^{-1}\)·min\(^{-1}\) corresponded with the calculated metabolic rate but increased to 6.3 ± 1.6 ml·kg\(^{-1}\)·min\(^{-1}\) during recovery. The analgesic action of alfentanil, which cannot be separated from its depressant cardiorespiratory effects and maximally effective analgesic concentrations (between 200 and 400 ng/mL), apparently does not jeopardize the adequacy of tissue oxygenation in dogs. (Key words: Analgesics: alfentanil. Blood pressure: drug effects. Heart rate: Metabolism: oxygen consumption. Ventilation: frequency; gas exchange.)

ALFENTANIL, a new opioid analgesic, acts faster, shorter, and appears to accumulate to a lesser extent than its structurally related predecessor fentanyl,§ because of its advantageous pharmacokinetic properties.² ³ According to dose-response studies in animals§ and also in man,⁷ the alfentanil–fentanyl potency ratios range between 3:1 and 6:1; however, according to plasma concentration-effect data, potency ratios of 40:1⁸ and even of 75:1 were reported for humans.⁹ These discrepancies have been attributed to drug-specific differences in the temporal relationship between concentration and effect and/or to differences in the shapes of the concentration-response relationship of the various measures of opiate action.⁹ However, the last alternative can hardly be reconciled with recent observations¹⁰ showing that fentanyl exerts its cardiovascular, respiratory, and also its analgesic actions in unanesthetized dogs at plasma concentrations that also produce electroencephalogram (EEG) slowing in unpremedicated humans.⁹ Whether alfentanil differs from fentanyl in this respect is uncertain at present. So far, only alfentanil’s analgesic plasma concentration has been determined in premedicated patients during surgery with artificial ventilation⁹,¹¹,¹² and/or after resumption of spontaneous breathing in the postoperative period.⁴,⁸,¹² These data do not allow construction of concentration-effect curves for different measures of opiate action that, in the absence of other drugs, should show also the maximum or ceiling effects. With the last stipulation in mind, plasma concentration-effect relationships for alfentanil’s cardiovascular, respiratory, and analgesic actions were derived in unanesthetized, spontaneously breathing dogs. We found that all these effects attained a maximum in the same range of plasma concentrations.

Materials and Methods

The data derive from six experiments on six healthy dogs (body weight 23.2 kg ± 2.6 SE). The dogs, which were awake during the controls, were trained to lie quietly without restraint in the lateral, horizontal position throughout the experiments. By previous operations, their common carotid arteries had been exteriorized in skin loops for blood sampling and blood pressure recording. The experimental protocol followed that of a recent study with fentanyl,¹¹ and we also used, except for one, the same dogs.

MEASUREMENTS

Circulatory Effects. Arterial blood pressure was recorded continuously (Statham 537® transducer) via a plastic can-
nula inserted into a carotid loop artery and heart rate with an ECG-triggered cardiotachometer.

Respiratory Effects. Respiratory rate (mercury-in-silastic gauge around the thorax) and oxygen consumption \( (V_{O_2}) \) standard temperature pressure dry (STPD) were measured continuously by passing air by means of a precision pump at 20 l/min through a transparent plastic hood placed over the animal’s head. The \( V_{O_2} \) was calculated from the air flow times \( O_2 \) difference (paramagnetic principle) between the inflowing and outflowing gas. The error of measurement amounts to less than 5%. Arterial blood gas tensions \( (P_{aO_2}, P_{aCO_2}) \) and \( pH \) were determined intermittently. A total of 100 ml of arterial blood was removed for blood gas analysis (1 ml each time) and alfentanil measurement (5 ml each time) and was replaced by saline.

Test for Pain Responses. Tail clamping with an arterial clamp (15 cm total length) was used as a pain stimulus. The jaws of the clamp were applied for their entire length (5 cm) to the base of the tail. The clamp was closed at the first notch for 1–2 s in the awake state, but up to 10 s with the ratchet fully closed (four notches) under the full action of alfentanil. Like in our previous study, the test was evaluated in terms of the provoked increase in heart rate and arterial pressure. The loss of somatic reactions (tail withdrawal, head raising, body movements, opening of the eyes) was also included in the protocol.

Determination of Alfentanil in Plasma. Plasma was separated by centrifugation and alfentanil extracted as described by Gillespie et al. Concentrations were measured with a Perkin-Elmer gas chromatograph F-22 equipped with a nitrogen-phosphorus detector with fentanyl as internal standard.

**Experimental Protocol**

The protocol aimed at establishing alfentanil plasma concentrations sufficiently high to reach maximum effects in all variables of interest. After setting up the recording system, the awake animals remained undisturbed in the lateral, horizontal position for at least 1 h. This period enabled the animals to calm down as evidenced by a low heart rate, blood pressure, and \( O_2 \) consumption.

The actual experiments started with the control period of 20 min. Alfentanil was then injected in increasing amounts (10, 20, 80, 160, and finally 320 \( \mu g/kg \)) in 5-min intervals so that a total of 590 \( \mu g/kg \) was given within 20 min. The injection time varied between 30 and 45 s.

Tail clamping and blood sampling for the determination of alfentanil and gas tensions were executed exactly during the last minute before the injection of the next dose of alfentanil and at 1, 2, 5, 10, 30, 80, and 140 min after the last injection, and blood sampling started after release of the clamp.

**Data Analysis**

The results are expressed as mean ± SE. Analysis of variance (repeated measure designs) with pairwise comparison was performed with \( P < 0.05 \) considered statistically significant.

**Results**

The time course of the actions of alfentanil is shown in figure 1. During the period of injection, the respiratory variables (figs. 1A and 1B) and also the heart rate (fig. 1C) changed in a dose-related manner but attained minima or maxima already after the fourth injection, i.e., after 270 \( \mu g/kg \) had been injected within 15 min. The fifth injection, adding to a total of 590 \( \mu g/kg \), had relatively few further effects. In the case of the arterial pressure, the dose relation is less clear. Following a transient increase, diastolic pressure returned to the controls after the fourth injection, whereas the systolic pressure remained slightly above the preinjection values.

Alfentanil also suppressed the cardiovascular responses to noxious stimulation (fig. 1D). The increase in heart rate and blood pressure that occurred in response to tail clamping decreased with increasing doses of alfentanil and finally were abolished after the fourth injection. When present, the strong clamping responses usually faded away within about 10 s after releasing the clamp and did not noticeably affect the measurements in panels 1A, 1B, and 1C. The measurements in 1C were always taken 5 min after the pain test.) Note also that repeated noxious stimulation during the control period always evoked the same increases in heart rate and blood pressure so that accommodation did not occur to a significant extent at least for the time intervals of 10 min.

Alfentanil also affected the behavior of the animals. With increasing doses, the animals appeared sedated and finally showed sleep-like behavior, usually after the fourth injection. Most important, the somatic responses to tail clamping, such as head raising, tail withdrawal, and body movements, were also abolished after the fourth injection.

In the postinjection period, the pain responses fully recovered, awareness was regained within 30 min after the last injection, and, except for \( V_{O_2} \) and blood pressure (which both increased more than the controls) the other variables returned to their preinjection values (half-lives given in table 1).

The alfentanil concentrations for these experiments listed in table 2 are both time- and dose-dependent. After the last dose, the plasma concentrations decreased most quickly to about one-twelfth (408 ± 29 \( \mu g/ml \)) of their peak (5079 ± 258 \( \mu g/ml \)) within 5 min after injection but then decreased less quickly to a final 16 ± 1 \( \mu g/ml \) in the following 115 min. Nonetheless, the plasma con-
AFLENTANIL CONCENTRATION VERSUS ITS EFFECTS IN DOGS

**FIG. 1.** Respiratory, cardiovascular, and analgesic effects of alfentanil in unanesthetized, spontaneously breathing dogs (means ± SE) from six experiments on six dogs. Increasing doses of alfentanil (10, 20, 80, 160, and 320 μg/kg) were injected at 5-min intervals as indicated by the numerals. The data-points at the time of injection (marked by arrows) reflect the effects of the previous dose. The increase in heart rate and blood pressure to tail clamping with a hemostat was defined as a pain response. X = P < 0.05 and XX = P < 0.01 for differences from the awake controls. Except for P<sub>0</sub>, all effects reached maxima after the fourth injection. Most variables returned to their preinjection values within 20–40 min after the last injection.

Concentrations measured at 5-min intervals increased proportionally with each incremental dose.

The concentration-effect curves in figure 2 relate the variable changes from the awake state to the plasma concentrations measured within 25 min after the first injection. For this part of the protocol, i.e., the incremental doses, the first noticeable effects occurred at about 8 ng/ml and then increased proportionally with concentration until a plateau was reached at around 200 ng/ml, a concentration sufficient also to abolish the heart and blood pressure increases as well as the bodily movements to tail clamping.

However, for decreasing plasma concentration during recovery after the last injection, all the concentration-effect curves except P<sub>ACO2</sub> shown in figure 3 were displaced in parallel to higher concentration. For the same effects, about twice the concentration apparently was

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alfentanil (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O&lt;sub&gt;2&lt;/sub&gt; consumption</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>15</td>
</tr>
<tr>
<td>P&lt;sub&gt;ACO2&lt;/sub&gt;</td>
<td>15</td>
</tr>
<tr>
<td>P&lt;sub&gt;ACO2&lt;/sub&gt;</td>
<td>25</td>
</tr>
<tr>
<td>pH&lt;sub&gt;ACO2&lt;/sub&gt;</td>
<td>30</td>
</tr>
<tr>
<td>Heart rate</td>
<td>15</td>
</tr>
<tr>
<td>Pain response</td>
<td>10</td>
</tr>
</tbody>
</table>

**TABLE 1.** Half-lives of Recovery for Various Parameters Following the Last Injection of Alfentanil
Table 2. Alfentanil Plasma Concentrations (Mean ± SE) from Six Experiments on Six Unanesthetized Dogs

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>Time after First Injection (min)</th>
<th>Plasma Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>5</td>
<td>8 ± 0.2</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>17 ± 1</td>
</tr>
<tr>
<td>80</td>
<td>15</td>
<td>79 ± 4</td>
</tr>
<tr>
<td>160</td>
<td>20</td>
<td>172 ± 7</td>
</tr>
<tr>
<td>320</td>
<td>21</td>
<td>5079 ± 258</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>771 ± 10</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>408 ± 29</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>169 ± 3</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>35 ± 4</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>24 ± 1</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>16 ± 1</td>
</tr>
</tbody>
</table>

needed during recovery than during the incremental dose phase. Alternatively, at a given concentration, alfentanil has lost up to 20% of its initial effectiveness. In fact, most of the variables had returned to their preinjection values of the awake state within 115 min after the last injection, when plasma concentrations were still twice (16 ± 1 ng/ml) the initial plasma concentrations (8 ng/ml), which were found to produce the first noticeable effects. However, V̇O₂, which decreased least during the injection, increased conspicuously during recovery and was still well above the controls (5.4 ± 0.9) at the end of the recording period 6.3 ± 1.6 ml·kg⁻¹·min⁻¹.

Discussion

In awake dogs, the alfentanil plasma concentration-effect curves for multiple measures of action reached plateaus (maximum or ceiling effects) at the same plasma concentrations during the initial injection phase. Like in our previous experiments with fentanyl, which yielded the same results in every aspect addressed in the present study, increasing doses of alfentanil were injected every 5 min. These injection intervals were in all likelihood suf-

![Fig. 2. Plasma alfentanil concentration-effect relationships of the respiratory, cardiovascular, and analgesic action in unanesthetized, spontaneously breathing dogs. Changes from the preinjection values in the awake state with the curves drawn by eye. Alfentanil (10, 20, 80, 160, and 320 µg/kg) was injected intravenously every 5 min. The increase in heart rate and blood pressure to tail clamping with a hemostat was taken as a pain response. X = P < 0.05 and XX = P < 0.01 for differences of effects between one concentration to the next. All curves are in the same concentration range with maxima or minima at concentrations at and around 200 ng/ml.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931401/ on 11/26/2018)
FIG. 3. Alfentanil plasma concentration-effect curves for increasing and decreasing concentrations in unanesthetized dogs. Data for increasing concentrations (circles) represent those for cumulative doses injected at 5 min intervals, for decreasing concentrations (dots) those during recovery after the last injection with the direction of change indicated by arrows. Effects in per cent of the maximum changes (Δmax) from the awake state with the curves drawn by eye. Means ± SE. For the recovery phase, the data—except for PaCO₂—are displaced to higher concentrations. Note also the strong and sustained increase in oxygen consumption per minute (V̇O₂).

Sufficiently long to reach a concentration equilibrium between the brain and plasma because indirect evidence suggests that alfentanil enters the brain faster than fentanyl. Yet, even though we cannot exclude with certainty some lag between the brain and plasma concentrations for the period immediately after the last injection when the alfentanil plasma concentration quickly decreased to only a fraction of its initial peak (see table 2), it appears nevertheless justifiable to presume that all other alfentanil concentrations measured in this study by and large reflect those in the brain.

To attain the maximally effective alfentanil plasma concentration, a cumulative dose of only 270 µg/kg was sufficient with the injection intervals of 5 min, whereas, for example, a three-fold higher cumulative dose of 788 µg/kg was needed to produce the same maximal changes in various cardiovascular and respiratory variables in awake dogs, when injection intervals were extended to 10 min. Obviously, dose-effect studies with alfentanil, which has the highest elimination rate of all opiates currently in use, may yield ambiguous potencies unless the injection protocol takes the drug-specific difference in the time concentrations after injection into account. Nevertheless, to evoke the maximum intensity of alfentanil's various components of actions in awake dogs, dose and injection intervals or infusion rates must be such that plasma concentrations of approximately 200 ng/ml are established.
<table>
<thead>
<tr>
<th>Species</th>
<th>Number</th>
<th>Plasma concentrations (ng·mL⁻¹)</th>
<th>Test Criteria</th>
<th>Drug Administration</th>
<th>Other Drugs Administered</th>
<th>Ventilation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>human</td>
<td>7</td>
<td>122 ± 18 100</td>
<td>Awareness with adequate breathing</td>
<td>Single dose injection</td>
<td>Promethazine Thiopental Atropine Lorazepam Atropine Pancuronium</td>
<td>SB</td>
<td>Schütter and Stockel 1982</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>1760 ± 460 270 ± 130</td>
<td>Blood pressure during &quot;maximal sternal spread&quot;; Awareness after anesthesia</td>
<td>Variable-rate infusion</td>
<td>CV</td>
<td>de Lange and de Bruijn, 1983</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>350/225 160 ± 37 160 ± 37</td>
<td>Blood pressure during intraabdominal stimulation or closing the abdomen; Awareness with adequate breathing at extubation</td>
<td>Variable-rate infusion plus single doses</td>
<td>N₂O Diazepam Atropine Pancuronium</td>
<td>CV</td>
<td>Ausems and Hug, 1983</td>
</tr>
<tr>
<td>human</td>
<td>16</td>
<td>167/219 108 ± 37 108 ± 37</td>
<td>Blood pressure during body-surface surgery; CO₂ responsiveness, Pao₂, Pco₂, postoperative pain scoring; EEG slowing: 50% effect</td>
<td>Constant-rate infusion (50–100 µg·kg⁻¹·min⁻¹)</td>
<td>N₂O Methohexital Pancuronium</td>
<td>SB</td>
<td>O'Connor et al., 1983</td>
</tr>
<tr>
<td>human</td>
<td>6</td>
<td>520 ± 163 167 ± 219</td>
<td>Maximum effects for multiple variables at increasing/decreasing concentrations</td>
<td>Constant-rate infusion (20 µg·kg⁻¹·min⁻¹) Constant-rate infusion for several minutes during induction</td>
<td>AV</td>
<td>Scott et al., 1985</td>
<td></td>
</tr>
<tr>
<td>dogs</td>
<td>6</td>
<td>200/400 200/400 200/400</td>
<td>Maximum effects for multiple variables at increasing/decreasing concentrations</td>
<td>Multiple-dose injections</td>
<td>SB</td>
<td>Author's observation</td>
<td></td>
</tr>
</tbody>
</table>

SB = spontaneous breathing; CV = controlled ventilation; AV = assisted ventilation.

Curiously, during recovery, the effects (except for the PaCO₂) were less for a given plasma concentration than during the incremental-dose phase, and it appeared that about twice the plasma concentration would have been needed to maintain the initially attained effects. This loss of effectiveness resembles acute tolerance, which was manifested here as an in-parallel shift of the concentration-effect curves to higher concentrations. In fact, most of the variables had returned to their preinjection values within 115 min after the last injection, even though the alfentanil concentration in the plasma (16 ± 1 ng/ml) was still two-fold higher than that which had produced the first noticeable effects initially. \( \dot{V}_{\text{O}_2} \), however, increased substantially, and this increase lasted during recovery. During the cumulative-dose phase, the minimal \( \dot{V}_{\text{O}_2} \) (4.4 \( \pm \) 0.3 ml·kg⁻¹·min⁻¹) corresponded with the calculated basal metabolic rate (Brody's formula; i.e., \( \dot{V}_{\text{O}_2} = 10.15 \cdot \text{kg}^{0.72} \)) and decreased in spite of the conspicuous decrease in respiratory rate, heart rate, and Pao₂ by 62%, 46%, and 35%, respectively, but was 17% lower than in the awake state (not measured under basal conditions). However, early during recovery, \( \dot{V}_{\text{O}_2} \) increased above the controls and remained at its elevated level (6.3 ± 1.6 ml·kg⁻¹·min⁻¹) until the end of the experiment. Whether this sustained increase in metabolism with its accompanying hypercarbia, which was also observed in ventilated dogs, is either an early manifestation of tolerance or merely the response to the regain of awareness is impossible to tell from our data. The first alternative is attractive because \( \dot{V}_{\text{O}_2} \) increased in dogs during 24 h deep pentobarbital anesthesia and likewise in cultured glial cells kept at constant barbiturate concentrations for 2 weeks. It is, therefore, at least likely that the increase in metabolism in our study may also be an early sign of tolerance.

The survey of the literature in table 3 shows that concentration-effect curves for various components of the action of alfentanil that should include the plateau of action and exclude interactions with other drugs either in humans or dogs are not yet available. In looking at the
cardiovascular responses to painful stimuli, most authors were concerned with alfentanil's analgesic properties during surgery in premedicated patients ventilated with oxygen alone or with oxygen/nitrous oxide or plasma concentrations were reported at which patients regained awareness and adequate spontaneous breathing in the postoperative period.

The use of different test criteria, uncertainties about the plateau of the concentration-effect relationship as a prerequisite for the derivation of meaningful 50%-effect concentrations, drug interactions, and, most importantly, differences in the mode of drug administration, along with uncertainties about the time of blood sampling, render a comparison of the available concentration-effect data almost impossible. Nonetheless, there is correspondence in results in that humans, much like dogs, appear to regain awareness with adequate spontaneous breathing at similar concentrations in the postinjection or postoperative period. Under these conditions, the slowly changing plasma concentrations are presumably in equilibrium with those in the brain. By contrast, a delayed equilibrium between brain concentrations (or effects) and plasma concentrations most likely explains the so much higher effective concentrations with rapid infusion for brief time periods, with variable-rate infusions or with constant-rate infusions that were supplemented with bolus injections.

Hysteresis, demonstrated for a special measure (spectral edge of the EEG) and special circumstances (rapid infusion of low doses), was most recently brought into debate. Scott et al. certainly raised important questions but, without knowledge of the brain concentrations, it appears to be premature to accept the reported IC₅₀ values and the extreme alfentanil–fentanyl potency ratio of 75 (see also Hug's editorial). In fact, hysteresis suggests alfentanil will gain effectiveness with decreasing concentrations, whereas acute tolerance, shown in the present study, suggests the opposite. Both hysteresis and acute tolerance certainly complicate the interpretation of plasma concentration-effect data that, at present, remain indispensable for pursuing clinical and pharmacologic studies as long as it is not feasible to relate drug effects to the concentrations in the brain or, even more precisely, at the site of drug action. Acute tolerance, which accounted for up to 20% loss of effectiveness in this study, must be accepted as a disturbing factor and taken into consideration when designing drug administration schemes. But hysteresis can be avoided by the appropriate study protocol, which should aim at establishing an equilibrium between the drug concentration in the plasma and at the site of action. In this case, maximally effective concentrations are at and around 200 ng/ml for alfentanil and 30 ng/ml for fentanyl with increasing concentrations in awake dogs but are about two-fold higher for decreasing concentrations. Thus the alfentanil–fentanyl potency ratio is approximately 7:1, which agrees by and large with the literature.

Therefore, both agents, which are known to compete for the same binding sites—the opiate receptors—are alike in their basic pharmacodynamic properties and, thus, their principle effects but differ in potency and duration of action.

Whether our observations can be extrapolated to humans may be debated. But in awake dogs in whom drug interactions were excluded, alfentanil, much like fentanyl, exerts its analgesic and cardiorespiratory actions in the same range of plasma concentrations. Contrary to the recently expressed view, the concentration–effect relationship for various components of opiate action are of similar shape and plateau in the same range of plasma concentrations; therefore, it is impossible to separate alfentanil's analgesic properties from its undesirable cardiorespiratory depressant effects. Curiously, in spite of profound cardiorespiratory depression and hypoxemia, spontaneous breathing with adequate oxygen supply was maintained at maximally effective analgesic concentrations in dogs. But a word of caution must be added: In our pharmacologic study, the plasma concentrations of alfentanil were increased to an extent as to saturate the involved binding sites and, thus, to produce maximum effects. Whether humans would resume spontaneous breathing under these extreme conditions is impossible to tell because the potential hazards of the accompanying profound hypoxemia certainly mandate ventilatory support.

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