Original Article

Postoperative Patient-Controlled Analgesia with Alfentanil: Analgesic Efficacy and Minimum Effective Concentrations

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Abstract
Forty ASA I-III patients recovering from major abdominal or orthopedic operations were investigated in an open clinical study to evaluate analgesic efficacy and threshold plasma concentrations of alfentanil during the early postoperative period using patient-controlled analgesia (PCA) by means of the On-Demand Analgesia Computer. Alfentanil demand dose was 212 μg, continuous infusion rate 25 μg/hr, hourly maximum dose 1.5 mg/hr; the lockout time was set to 1 min. The duration of PCA was 18.1 ± 5.2 hr (mean, SD) during which time 23.8 ± 14.2 demands per patient were recorded, resulting in an average alfentanil consumption of 4.99 ± 3.03 μg/kg/hr. Patient acceptance of PCA was high. Side effects were only of minor intensity and never gave rise to concern. Based on our own earlier PCA experience with other opiate analgesics, alfentanil proved to be about 1/12th as potent an analgesic as fentanyl and about 6-7 times more potent than morphine if both intensity and duration of effect were considered. Minimum effective alfentanil plasma concentration (MEC) varied greatly and could be best described by a lognormal distribution (range 0.6–99.2 ng/mL, median 14.9 ng/mL). Intraindividual MEC variability was consistently lower than intersubject variability (37.0% vs 65.2%). J Pain Symptom Manage 1990;5:249–258.

Key Words
Narcotic analgesics, alfentanil, pain treatment, postoperative, patient-controlled, pharmacokinetics, analgesic threshold concentrations

Introduction
Alfentanil has now found its place in anesthesia as one of the shortest-acting opiate analgesics, used to supplement balanced or total intravenous anesthesia with either continuous infusions or repetitive bolus, to maintain analgesia during the last few minutes of surgical interventions, or to treat short-lived pain periods, e.g., for changing of wound dressings or to facilitate postoperative mobilization. Its pharmacokinetic and pharmacodynamic effects are well defined. There is, however, only limited knowledge about “analgesic” blood concentrations.

It was the aim of this study to investigate alfentanil during the early postoperative period,
using intravenous patient-controlled analgesia (PCA) to define analgesic efficacy and side effects, and to determine those alfentanil plasma concentrations at which analgesia begins to subside.

**Patients and Methods**

Forty patients (ASA I–III) recovering from elective major abdominal or orthopedic surgery (mostly gastric and bowel surgery, hip and knee endoprotheses) under balanced anesthesia of at least 90-min duration were examined after institutional approval. They were informed in detail about the purpose of the study the evening preceding the operation and gave oral consent. Exclusion criteria were drug dependence, pregnancy, and manifest disease of the respiratory or excretory organs.

**Anesthesia and Postoperative Patient-Controlled Analgesia**

Premedication consisted of diazepam 10 mg by mouth on the evening before surgery and 2 mL Thalamonal intramuscularly (0.1 mg fentanyl, 5 mg droperidol) ~60 min prior to anesthesia. For induction alcuronium 2 mg, diazepam 0.15 mg/kg, hexobarbital 3 mg/kg, nitrous oxide in oxygen (1:1, 8 L/min) and fentanyl 4 μg/kg were used. Endotracheal intubation was performed after succinylcholine 1 mg/kg, and neuromuscular blockade was continued with alcuronium 5–8 mg. Controlled normoventilation was maintained with nitrous oxide in oxygen (2:1). At signs of insufficient anesthetic depth, additional fentanyl bolus doses of 0.1–0.2 mg or enfurane (0.5–1 vol. %) were administered. Neuromuscular blockade was antagonized after the operation using neostigmine 1 mg/atropine 0.5 mg. Opioid antagonists were never necessary.

Patient-controlled analgesia (PCA) was provided by means of the On-Demand Analgesia Computer (ODAC). The demand dose was alfentanil 212 μg, the continuous infusion 25 μg/hr (fixed rate, in order to prevent catheter obstruction), and the maximum hourly dose 1.5 mg/hr with a lockout time of 1 min. As soon as possible after extubation, patients were connected to the ODAC and monitored until they were fully orientated. After the procedure had been explained to them again, they were transferred to routine wards and observed until the following morning; sedatives and additional analgesics were not permitted.

**Blood Samples and Alfentanil Analysis**

Venous blood samples (3 mL) were taken immediately preceding each alfentanil bolus dose from an indwelling catheter in a contralateral forearm vein, starting with the second demand. The maximum number of samples was restricted to 15 per patient.

Plasma was prepared by heparinization and centrifugation and frozen at −20°C until analysis. Plasma alfentanil concentrations were determined in duplicate by radioimmunoassay, the detection limit being 0.5 ng/mL. The coefficient of variation for the radioimmunoassays were 3.0% within assays and 4.6% between assays.

**Documentation of Patient-Controlled Analgesia**

All valid demands were registered with the exact time of day. From these data, hourly or cumulative dosages were calculated and evaluated as a function of time. Blood pressure, pulse rate and respiratory frequency were documented hourly. Blood gas analyses from arterialized capillary blood were performed at 1 and 4 hr after start of PCA. On the following day, patients were interviewed using a standard protocol in order to gain information on side effects and patients' acceptance, and a retrospective pain score for the treatment period was assigned from a 6-point scale (0, no pain at all; 1, sometimes moderate; 2, always moderate; 3, sometimes severe; 4, always moderate, sometimes severe pain; and 5, discontinuation because of inefficacy).

**Statistics**

Means, standard deviations (SD), standard errors of the mean (SEM), and medians were calculated for statistical analyses. Intra- and interindividual variability of alfentanil minimum effective concentrations (MEC) were calculated according to methods described in detail in a previous publication. In short, a patient's mean MEC (MEC$_p$) and the corresponding coefficient of variation (CV$_p$) was averaged from his individual MEC values at the respective times (MEC$_t$). The mean of all MEC was used to get a group mean (MEC$_g$) and the respective
CV_i, the mean of all CV_i was calculated to give an average CV_m. CV_m can be considered the measure of intersubject variability, while CV_a is the measure of intrasubject variability. A linear regression analysis of MEC_i (in ng/mL) on time (in minutes) was performed for each patient from which the slopes (a), intercepts (b), and absolute coefficients of correlation (r/A) were then averaged.

Subgroups (males/females or abdominal/orthopedic procedures) were compared by means of Student’s t test for unpaired values or the Mann–Whitney Wilcoxon test for independent samples. Levels of significance were set to p ≤ 0.05.

Results

Patients and Anesthesia

Demographic data of the 21 male and 19 female patients are listed in Table 1. Comparing subgroups, there were statistically significant differences only for the sexes (age, weight).

Postoperative Patient-Controlled Analgesia

Patients were connected to the ODAC within 29.8 ± 18.2 min after extubation (mean and SD; median, 30 min). The time interval between extubation and complete understanding of the apparatus was 134.1 ± 159.8 min (median 97 min). Duration of treatment, number of individual demands, alfentanil consumption, and retrospective pain scores are listed in Table 2.

Among the subgroups, there were no statistically significant differences for either variable. Excellent to sufficient pain relief was possible in all but four patients (three males and one female from the abdominal surgery group, ASA II–III, where PCA had to be cancelled because of inefficacy after 4.3–6.8 hr, during which time cumulative alfentanil dosages of 2.35–5.64 mg had been demanded).

Figure 1 displays cumulative dose-time plots for all 40 patients. Figures 2 and 3 show mean hourly alfentanil consumptions as well as the mean cumulative alfentanil dosage.

Postoperative circulation was always normal, as was respiration. Figure 4 displays respiratory rates, and Table 3 gives the results of the blood gas analyses. There were no statistically significant differences between the subgroups with respect to either circulatory or respiratory parameter.

Side effects that occurred during the treatment period were nausea (30%), vomiting (15%), sweating (30%), and sedation (30%).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Sex (m/f)</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Duration of Surgery (min)</th>
<th>Intraoperative Fentanyl (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>40</td>
<td>21/19</td>
<td>50.8 ± 17.3</td>
<td>71.1 ± 11.7</td>
<td>163.3 ± 53.3</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>10/11</td>
<td>44.7 ± 13.6</td>
<td>75.9 ± 8.8</td>
<td>166.9 ± 53.3</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>11/10</td>
<td>57.5 ± 18.7</td>
<td>65.7 ± 12.4</td>
<td>159.2 ± 53.3</td>
</tr>
<tr>
<td>Abdom.</td>
<td>20</td>
<td>10/10</td>
<td>51.5 ± 18.1</td>
<td>71.6 ± 11.7</td>
<td>158.8 ± 65.7</td>
</tr>
<tr>
<td>Orthop.</td>
<td>20</td>
<td>11/9</td>
<td>50.4 ± 17.0</td>
<td>70.6 ± 12.0</td>
<td>167.8 ± 38.4</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th></th>
<th>PCA (hr)</th>
<th>Demands per Patient</th>
<th>Alfentanil Intake (mg)</th>
<th>(µg/kg/h)</th>
<th>Retrospective Pain Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>18.1 ± 5.2</td>
<td>23.8 ± 14.2</td>
<td>5.9 ± 3.3</td>
<td>4.99 ± 3.03</td>
<td>1.38 ± 1.48</td>
</tr>
<tr>
<td>Male</td>
<td>17.6 ± 5.5</td>
<td>27.4 ± 14.6</td>
<td>6.7 ± 3.4</td>
<td>5.45 ± 2.81</td>
<td>1.62 ± 1.72</td>
</tr>
<tr>
<td>Female</td>
<td>18.6 ± 4.9</td>
<td>19.7 ± 12.9</td>
<td>5.0 ± 3.9</td>
<td>4.40 ± 3.26</td>
<td>1.11 ± 1.15</td>
</tr>
<tr>
<td>Abdom.</td>
<td>17.1 ± 6.5</td>
<td>22.7 ± 14.2</td>
<td>5.6 ± 3.3</td>
<td>5.29 ± 3.27</td>
<td>1.85 ± 1.79</td>
</tr>
<tr>
<td>Orthop.</td>
<td>19.1 ± 3.3</td>
<td>24.8 ± 14.5</td>
<td>6.2 ± 3.3</td>
<td>4.69 ± 2.83</td>
<td>0.90 ± 0.91</td>
</tr>
</tbody>
</table>
Four patients (10%) showed signs of euphoria, whereas two patients (5%) were considered to feel sometimes dysphoric. There were no significant differences with respect to these side effects among the subgroups.

During the final interview on the first day after the operation, the retrospective pain score was given as 1.38 ± 1.48 (Table 2). Although pain relief was judged better in the orthopedic compared with the abdominal group, the difference was not statistically significant (Mann–Whitney Wilcoxon test, p = 0.0564). Of the patients who had former experience with conventional postoperative pain treatment (n = 15), 80% judged PCA to be superior; 68% of all patients would have preferred to remain connected to the ODAC on the next morning; 15% expressed a preference for the injections by the nursing staff to self-administration with a machine.
Minimum Effective Alfentanil Plasma Concentrations

Figure 5 describes 387 values of postoperative MEC\textsubscript{1} from the 40 patients, based on the duration of PCA treatment. Taking together both dependent and independent concentrations (i.e., concentrations within and between patients), the minimum effective concentrations could be best described by a log-normal distribution (median 14.89 ng/mL, range 0.57–99.2 ng/mL).

Table 4 lists the statistical measures resulting from intra- and interindividual calculations (see Patients and Methods). Subgroups were not significantly different.

The slopes of the individual regression lines (a) indicate that minimum effective alfentanil plasma concentrations rose gradually during the PCA treatment period (not significantly different from 0). This is also reflected by comparing the first and the corresponding last MEC\textsubscript{1} (9.22 ± 5.73 vs. 19.47 ± 15.52 ng/mL; n = 40; Student's t test for paired values p ≤ 0.05).

Discussion

Although effective and safe methods are available, the treatment of postoperative pain still leaves much to be desired, as has been demonstrated in numerous critical reports throughout the world. Unfortunately, there is a lack of reliable, objective measurements for the quantification of acute clinical pain, but visual analog scales or verbal ratings seem appropriate for everyday practice. The measurement of analgesic...
consumption in patients who have virtually free access to the dose is another way to evaluate pain intensities, as well as the psychologic factors that undoubtedly influence them. Thus, PCA is not only suitable to establish and maintain adequate postoperative pain relief, but can also yield important information about pain behavior and clinical algesimetry. Comparing identical groups of patients who differ only with respect to the analgesic in use, PCA also allows conclusions on relative potencies and the incidence of side effects under adequate experimental conditions, i.e., optimum dosages and near optimum analgesic efficacy.

The most important goal of pharmacokinetics is to measure the time course of drug concentrations in blood or other body compartments, describe them mathematically, and predict them from suitable models. It is evident that blood levels alone are of only minor value unless the correlation between concentration and analgesia is also known. Comprehensive studies have now been done for most analgesics. Unfortunately, their value for clinical practice is rather controversial because the concentrations—analgesia relationship is extremely variable between patients. PCA not only overcomes such individual differences, but it also allows them to be quantified.

Alfentanil is one of the newer congeners of fentanyl and is characterized by a fast onset and a rather short duration of action. Hence, it was first recommended for short anesthetic procedures and—if applied by continuous infusion—for longer-lasting operations where fast recovery was desirable. For the same reason, alfentanil is also used as an analgesic component for sedation in intensive care units. There are only a few studies in which alfentanil was used for postoperative pain relief.
Table 4
Minimum Effective Concentrations (MEC) and Linear Regression Analysis (y = ax + b with y = MEC, in ng/mL and x = min); mean ± SD

<table>
<thead>
<tr>
<th>Samples/ Patient</th>
<th>MECa (ng/mL)</th>
<th>CVa %</th>
<th>CVb</th>
<th>a (ng/mL/min)</th>
<th>b (ng/mL)</th>
<th>r/b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9.7 ± 3.8</td>
<td>16.0 ± 10.4</td>
<td>37.0</td>
<td>65.2</td>
<td>1.85 ± 3.1</td>
<td>9.1 ± 9.3</td>
</tr>
<tr>
<td>Male</td>
<td>10.5 ± 4.4</td>
<td>14.9 ± 6.5</td>
<td>41.1</td>
<td>43.9</td>
<td>1.84 ± 2.5</td>
<td>7.2 ± 8.3</td>
</tr>
<tr>
<td>Female</td>
<td>8.7 ± 3.0</td>
<td>17.2 ± 13.5</td>
<td>32.9</td>
<td>78.5</td>
<td>1.87 ± 3.7</td>
<td>11.0 ± 10.0</td>
</tr>
<tr>
<td>Abdom.</td>
<td>9.3 ± 4.1</td>
<td>17.4 ± 13.2</td>
<td>38.1</td>
<td>75.8</td>
<td>2.60 ± 3.1</td>
<td>7.9 ± 9.6</td>
</tr>
<tr>
<td>Orthop.</td>
<td>10.1 ± 9.6</td>
<td>14.7 ± 7.0</td>
<td>35.8</td>
<td>47.9</td>
<td>1.78 ± 3.1</td>
<td>10.2 ± 9.1</td>
</tr>
</tbody>
</table>

MECa, group mean of individual mean MEC (MEC); CVa, intraindividual MEC variability; CVb, intersubject MEC variability; a, b, and r/b, coefficients of linear regression analyses; slopes (a) not significantly different from 0.

difference was not significant. There was also no significant difference in PCA use between the sexes.

Our results confirm the observation by Kay,11 who found in 21 abdominal surgical patients an alfentanil consumption of 8.1 µg/min (~6.9 µg/kg/hr), which fits well with the 5.3 µg/kg/hr reported here. Our figures are clearly lower than those reported by Welchew and Hosking,18 who found an average alfentanil consumption of ~8.9–12.8 µg/kg/hr in 20 patients recovering from upper abdominal surgery, using an ODAC adaptive rate (instead of a very low fixed rate) infusion.

To calculate relative equipotent doses of opiate analgesics, most authorities have so far used only drug consumption, corrected for duration of treatment and/or for patients' weights, not taking into account that the quality of pain relief may have differed between the test drugs. Table 5 combines data from the present alfentanil study with similar PCA investigations by our team, where the product from analgesic consumption (µg/kg/hr) and retrospective pain assessment has been tried for equipotency comparison. It appears from this table that alfentanil is ~48th as potent as fentanyl if one takes into account both intensity and duration of effect, or ~6–7 times more potent than morphine. The authors are well aware that "historical" equipotency comparisons as shown in Table 5 cannot be considered as firm as those obtained in a randomized trial, since they fail to take into account minor differences in anesthetic and surgical techniques, patient selection, etc. On the whole, however, the figures com-

Table 5
Equipotency Calculations

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Demand-Dose (µg)</th>
<th>Consumption (µg/kg/hr)</th>
<th>Retrospec. Pain Score (0–5)</th>
<th>Relative Equipotent Dose (Product)</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>34</td>
<td>0.46</td>
<td>1.07</td>
<td>0.01</td>
<td>2</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>40</td>
<td>0.63</td>
<td>1.57</td>
<td>0.02</td>
<td>8</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>212</td>
<td>4.96</td>
<td>1.37</td>
<td>0.15</td>
<td>9</td>
</tr>
<tr>
<td>l-Methadone</td>
<td>1145</td>
<td>14.20</td>
<td>1.60</td>
<td>0.50</td>
<td>38</td>
</tr>
<tr>
<td>Piritramid</td>
<td>1990</td>
<td>30.44</td>
<td>1.42</td>
<td>0.96</td>
<td>39</td>
</tr>
<tr>
<td>Morphine</td>
<td>1920</td>
<td>29.60</td>
<td>1.52</td>
<td>1.00</td>
<td>40</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>3846</td>
<td>117.52</td>
<td>1.82</td>
<td>4.75</td>
<td>41</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>7980</td>
<td>155.57</td>
<td>1.60</td>
<td>4.82</td>
<td>42</td>
</tr>
<tr>
<td>Pethidine</td>
<td>9615</td>
<td>175.10</td>
<td>2.22</td>
<td>8.63</td>
<td>43</td>
</tr>
<tr>
<td>Tramadol</td>
<td>9615</td>
<td>203.12</td>
<td>2.27</td>
<td>10.24</td>
<td>43</td>
</tr>
</tbody>
</table>

Comparison of alfentanil data from the present investigation with results for other drugs in identical PCA conditions. Relative equipotent doses are based on the product of mean analgesic consumption (µg/kg/hr) and retrospective pain score (morphine = 1).
pare favorably with the literature: White and colleagues found a dose ratio of 1:6 to 1:40 when examining fentanyl and alfentanil for short outpatient procedures; Sold and Weisz reported a ratio of 1:11 for longer lasting anesthesia, and Hynynen and colleagues obtained a ratio of 1:13 during coronary artery surgery. In his postoperative PCA study with fentanyl and alfentanil, Kay reported on a ratio of about 1:9.

The side effects during alfentanil PCA were of only minor intensity and corresponded in type and incidence to those that are usually found postoperatively. It should be mentioned in particular that clinically relevant respiratory depression was never observed, which is in agreement with the hypothesis that opiate-induced respiratory depression will occur only after overdosage, whereas relatively high-opiate doses that are needed for effective pain relief do not mean overdosage. As in previous PCA studies, patients' acceptance of PCA was extraordinarily high.

There are several reports in the literature in which opiate blood concentrations measured under PCA are compared with underlying pharmacokinetic models, as well as with pain relief achieved. Using pethidine during labor, e.g., Hogg and Rosen found a rather bad correlation between calculated and measured blood levels. Tamsen and his colleagues, on the other hand, reported on a close correlation only if individual pharmacokinetic variables derived from intraoperative analysis were used for comparison with postoperative data of the same patient; intersubject variability, however, was found to be very high for all analgesics studied. Quite apart from the fact that such time-consuming analytic techniques appear so far unrealistic for clinical practice (concentrations are mostly available only days later), these results suggest that generalization of pharmacokinetic parameters is not justified: every patient may have different analgesic requirements.

Anesthetic plasma concentrations of alfentanil have already been determined in several studies. Hynynen and colleagues found 750–900 ng/mL for aortocoronary surgery, from which patients awoke at ~70 ng/mL. According to Fragen and colleagues, alfentanil serum levels of 400–596 ng/mL seem sufficient for surgical analgesia when combined with 67% nitrous oxide; their patients awoke at 178–310 ng/mL. Similar results were obtained by Bovill and colleagues, Shafer and colleagues, and Chauvin and colleagues. Schütz and colleagues estimate that 290 ng/mL was acceptable for superficial pain and 480 ng/mL was required for intraabdominal stimulation. Lower concentrations (72–359 ng/mL in combination with general anesthesia) were reported by O'Connor and colleagues, where 110 ng/mL produced excellent postoperative analgesia. Yace and colleagues found in ventilated ICU patients a therapeutic window at ~150–250 ng/mL. So far, no alfentanil plasma levels have been reported under PCA conditions.

To determine analgesic “threshold” concentrations (minimum effective concentrations, MEC), venous blood samples were taken immediately before a patient demand, i.e., at a point in time when the patient was just becoming dissatisfied with analgesia. It is evident from Figure 5 and Table 4 that a generalizable threshold concentration does not exist. There were some patients with intraindividual stable MEC that, however, differed between subjects, while there were others who also showed remarkable intraindividual variations. Figure 5 underlines that MEC's are usually lognormally distributed and that the range is rather broad. Following proposals by Gourlay and colleagues, it could be shown for our own data that intraindividual variability in alfentanil MEC was consistently lower than the interindividual one (Table 4). These findings are in good agreement with previous PCA results for fentanyl and buprenorphine, as well as for sufentanil and tramadol (in preparation). It is interesting to note that the median fentanyl MEC was ~1 ng/mL in comparison to the 15 ng/mL of alfentanil, which again confirms the estimated potency relation of ~1:15 as stated earlier.

The data obtained in this study are not limited to statements about absolute alfentanil concentrations and their variance. By considering the time variable, it can also help to answer the questions of accumulation and tolerance. In contrast to previous fentanyl results, individual regression analyses (MEC vs time of MEC), as proposed by Tamsen and colleagues, resulted in slightly positive, although highly variable slopes (Table 4: 1.85 ± 3.18 ng/mL/min [mean ± SD]; median, 0.729; range, −0.96–13.16, slopes not significantly different from 0). That threshold concentrations gradually increase
with time must not be considered as accumulation but rather reflects the development of acute tolerance. Another explanation could be that the first alfentanil MECs were relatively low because of residual fentanyl effects from anesthesia, and that they had to be increased as soon as the fentany levels declined. Unfortunately, fentanyl concentrations were not determined in this study.

In summary, adequate analgesia was achieved with alfentanil in most patients. The favorable patient acceptance indicates that intravenous PCA is a promising method, not only for the treatment of acute pain but also for pharmacologic and algiesimetric investigations. Our findings confirm that "analgesic" threshold alfentanil concentrations vary considerably after surgery. To get into the therapeutic window for analgesia, plasma alfentanil concentrations of >15 ng/mL seem necessary. If one takes into account both peak intensity and duration of effect, alfentanil was found to be ~4,500 times as potent as an analgesic as fentanyl. Further investigations comparing the efficacy and side effects of alfentanil PCA to those of other opiates are required before postoperative pain treatment with alfentanil can be recommended on a more widespread basis.

Acknowledgments

Mrs. R. Lade was most helpful in organizational problems and performed the alfentanil radioimmunoassays. The authors are gratefully indebted to Janssen GmbH, West Germany, for valuable assistance throughout the study. The authors would like to express their thanks to all members of the medical and nursing staffs in their hospital for their interest and assistance, and to the patients for their patience and cooperation.

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