COMPARISON OF INFUSIONS OF ALFENTANIL OR PETHIDINE FOR SEDATION OF VENTILATED PATIENTS ON THE ITU

P. M. YATE, D. THOMAS, S. M. SHORT, P. S. SEBEL AND J. MORTON

The ideal agent with which to sedate patients in the intensive care unit should provide cardiovascular stability, respiratory depression, reduction of intracranial pressure and analgesia. Ideally, it should have a pharmacokinetic profile which promotes its use by infusion. In addition, there should be minimal immunological or metabolic effects, a high therapeutic ratio and absence of active metabolites.

The withdrawal of Althesin, reports of cortisol suppression with etomidate (Lambert et al., 1983) and disordered pharmacokinetics with midazolam (Byatt et al., 1984), and a general dissatisfaction with some of the more traditional agents (Gast, Fisher and Sear, 1984) have necessitated a search for new agents in this field.

Alfentanil, a new short acting opioid, would appear to fulfil many of the above criteria. These include good cardiovascular stability even in high dose (Sebel, Bovill and van der Haven, 1982) and a short elimination half-life of approximately 90 min (Bovill et al., 1982) which has led to its successful use by infusion both during surgery (Ausems, Hug and de Lange, 1983) and to provide postoperative analgesia (Andrews et al., 1983; O'Connor, Escarpa and Prys-Roberts, 1983). A pilot study (Yate, Thomas and Sebel, 1984) suggested that alfentanil could be useful when given by infusion in the ITU.

The purpose of the present study was to investigate the suitability of alfentanil by infusion in a comparison with pethidine. Dose requirements, adequacy of sedation, quality of recovery, metabolic effects and pharmacokinetics have been assessed.

PATIENTS AND METHODS
Thirty patients requiring postoperative ventilation after open heart surgery were studied. All patients gave informed consent and the study had the approval of the local Ethics Committee. The patients were randomly allocated, using a computer-generated randomization code, to one of two groups: alfentanil (A) or pethidine (P). A standard anaesthetic technique was used: premedication was with lorazepam 2–4 mg by mouth 2 h before surgery and promethazine 25–50 mg plus...
papaveretum 15–20 mg i.m. 1 h later. Anaesthesia was provided with thiopentone, nitrous oxide in oxygen, halothane, midazolam (up to 10 mg) and fentanyl (up to 1000 μg). After surgery the patients were transferred to the intensive therapy unit and artificial ventilation (to normocapnia) continued until 8.00 a.m. the next day. Once in the intensive care unit, patients were not sedated until they had awoken from the anaesthetic—defined as the time when they could open their eyes and move all four limbs to command.

Patients in group A received midazolam 2.5 mg and alfentanil 15 μg kg$^{-1}$ i.v. followed by alfentanil 0.4 μg kg$^{-1}$ min$^{-1}$ by infusion. Patients in group P received midazolam 2.5 mg followed by an infusion of pethidine 10 mg h$^{-1}$. The injection of midazolam was given 3 min after the administration of the bolus of alfentanil, as earlier experience had shown that the simultaneous administration of alfentanil and midazolam could result in severe hypotension. The infusion rates in both groups were then adjusted by the ITU staff to provide optimal sedation. In addition, staff were given the option of incremental doses (alfentanil 15 μg kg$^{-1}$ or pethidine 10 mg) of opioid if the patient became unsettled, or of midazolam 2.5 mg i.v. if the patient was considered to be pain free and accepting IPPV, but too aware. After preliminary experience it was decided to give electively midazolam 2.5 mg to all the patients in the evening, to induce sleep.

The quality of sedation was assessed hourly by the nursing staff using a four point sedation score: 1 = Patient asleep or awake but needing no more analgesia. 2 = Mildly restless, but answers "no" when asked if more analgesia required. 3 = Mildly restless, answering "yes" to above. 4 = Restless, difficult to ventilate or in obvious pain.

As sedation was scored by a variety of nurses, an observer reliability study was conducted on similar patients using the method of Gelfand and Hartmann (1975).

The infusions were stopped at 8.00 a.m. the next day. Regular attempts were made to initiate satisfactory spontaneous ventilation (as judged by a ventilatory rate >12 b.p.m.). The trachea was extubated after approximately a further 15 min if the $P_{a\text{CO}_2}$ was less than 6.0 kPa. The hourly ventilatory rate and arterial $P_{\text{CO}_2}$ were recorded for 6 h after the cessation of the infusion in the spontaneously breathing patients, as were the times to spontaneous ventilation and extubation, and the first demand for further analgesic. As it is the practice in this unit to give prophylactic analgesics before removal of the chest drain, all patients were given pre-mixed 50% nitrous oxide in oxygen to breathe during this procedure. The degree of drowsiness following the end of the infusion was assessed hourly for 6 h using an assessment scale:

1 = Asleep and unrousable. 
2 = Asleep but rousable. 
3 = Awake but drowsy. 
4 = Wide awake and alert.

This assessment was performed by one person, a research nurse, who was unaware which sedative had been prescribed.

Blood was taken for the measurement of serum cortisol concentration at 17.00 h on the day before surgery, 17.00 h and 20.00 h in the ITU on the day of surgery (during the infusion) and at 17.00 h on the first day after operation. Samples to permit measurement of the concentration of alfentanil (group A) were taken before commencing the infusion of alfentanil at 1 h, 6 h, 12 h, immediately before the cessation of the infusion, and then at 2, 5, 10, 15, 30, 60, 120, 360, 400, 600 and 960 min after the discontinuation of the infusion. Samples were frozen and assayed at a later date, cortisol by a standard radioimmunoassay (Amerlex) and alfentanil by gas chromatography (Woestenborghs, Michielsen and Heykants, 1981).

The distribution and elimination half-lives for alfentanil were calculated using the plasma concentrations obtained after stopping the infusion of alfentanil. These were fitted to single and bi-exponential curves by non-linear regression (BMDP3R A Statistical Package, copyright Regents of the University of California). The clearance of alfentanil was calculated from the area under the curve as measured by the trapezoid rule. The volume of distribution was calculated from clearance x elimination half-life/0.693. Statistical analyses were performed using analysis of variance, Student's $t$ test, Mann-Whitney and Chi Square tests, where appropriate. Results were considered significant at $P < 0.05$ and are expressed as mean ± SEM.

RESULTS

Thirty patients were studied; one patient was excluded as a clinical decision was made not to ventilate the patient overnight. The demographic
TABLE I. Details of patients studied (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Group A (alfentanil) (n = 14)</th>
<th>Group P (pethidine) (n = 15)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>58.3 ± 1.76</td>
<td>57.4 ± 1.65</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.0 ± 2.34</td>
<td>73.1 ± 3.87</td>
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<tr>
<td>Bypass time (min)</td>
<td>119 ± 11</td>
<td>115 ± 12</td>
</tr>
<tr>
<td>Fentanyl dose (µg)</td>
<td>817 ± 56</td>
<td>825 ± 35</td>
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data, surgical and anaesthetic details were similar between the two groups (table I). All patients had normal preoperative hepatic and renal function as determined by routine biochemical screening.

The mean durations of the infusion in both groups were not significantly different: 17.2 ± 0.56 (range 11.25–19.75) h in group A and 17.8 ± 0.45 (range 15–21.8) h in group P. The dose of midazolam 6.16 ± 2.6 mg in group P was larger, but not significantly so, than in group A, 4.28 ± 0.56 mg. The mean infusion rates of alfentanil and pethidine were 0.46 ± 0.028 µg kg⁻¹ min⁻¹ and 0.3 ± 0.02 mg kg⁻¹ h⁻¹, respectively. The total dose of drug administered was 0.48 ± 0.036 mg kg⁻¹ of alfentanil and 5.3 ± 0.43 mg kg⁻¹ of pethidine. In group A, 22 extra incremental doses of alfentanil were given and the infusion rate had to be adjusted 14 times; in group P 10 incremental doses of pethidine were given and the rate had to be adjusted 56 times—significantly (P < 0.05) more often than in group A.

The mean infusion rates for the two groups are shown in figure 1. There was no significant increase in the infusion rate with time in either group; the initial increase in rate in the pethidine group, although not significant, possibly reflects an inadequate starting rate in some patients. Conversely, the mean plasma concentrations of alfentanil showed a significant increase (P < 0.05) during the infusion of that drug.

There was no statistically significant difference in the sedation scores between the two groups (fig. 2). On only 2% of the hourly assessments was the sedation considered totally unsatisfactory, in both groups. No clear relationship between the plasma concentrations of alfentanil and the sedation score could be found. The reliability of the nurse assessment score was 90%.

The mean times to extubation, spontaneous ventilation and first demand for analgesia are shown in table II. In both groups 80% of patients were breathing spontaneously in 30 min and in 70% the trachea was extubated within 1 h of stopping the infusion. The prolonged recovery
TABLE II. Recovery times (median and range)

<table>
<thead>
<tr>
<th></th>
<th>Group A (alfentanil)</th>
<th>Group P (pethidine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time end of infusion to spontaneous ventilation (min)</td>
<td>15.5 (5-230)</td>
<td>10 (1-60)</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>40 (25-231)</td>
<td>36 (1-110)</td>
</tr>
<tr>
<td>Time to first demand for analgesic (min)</td>
<td>180</td>
<td>210</td>
</tr>
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times in group A were attributable to one patient (No. 15) and, if she is excluded, the mean times to spontaneous ventilation and extubation were, respectively, 16.7 ± 11.4 min and 51 ± 24 min in group A and 16.8 ± 5.2 min and 49.5 ± 7.8 min in group P. This patient behaved quite differently to the others in the group; extubation was not possible until 230 min after the cessation of the infusion and then only after naloxone 0.3 mg i.v. Respiratory rate and arterial $P_{\text{CO}} _2$ were satisfactory for a further 420 min when she suddenly had a
respiratory arrest which was treated with a further naloxone 0.4 mg i.v. and i.m. Subsequently, she made a good recovery. Examination of the patient's records could not identify any special features apart from her general physical state, which was poor, and that she was one of only two patients in the trial to receive erythromycin.

There was a wide range in post-infusion demands for analgesia: two patients in group A and three in group P did not require any in the first 10 h after infusion.

The mean arterial $P_{\text{CO}}$ and ventilatory rate in the first 6 h in the spontaneously breathing patients are shown in figures 3 and 4. There were no significant differences between the two groups. In addition, no difference was detected in the degree of postoperative drowsiness between the two groups (fig. 5); no patient was classified as unrousable at any time.

Cortisol concentration

These results are shown in figure 6. There were no significant differences between the groups in the preoperative cortisol values or in those

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**FIG. 4.** Mean ventilatory rate (± SEM) for 6 h after cessation of the infusion in those patients breathing spontaneously.

**FIG. 5.** Results of assessment scale of drowsiness in the post-infusion period. This is expressed as a percentage of the total number of hourly assessments at each score.
obtained on the first day after operation. A marked response to the stress of surgery was seen in both groups. However, the mean cortisol concentrations at 20.00 h during the infusion were significantly lower in the patients receiving alfentanil ($P < 0.01$). The mean duration of the infusion at this time was similar in both groups.

**Pharmacokinetics**

Thirteen complete sets of plasma concentrations were collected, of which 12 could be fitted to single and bi-exponential curves. However, in all 12 a better fit, as judged by smaller residuals, was found with a bi-exponential decay. The derived pharmacokinetic variables are shown in table III. No curve could be fitted to the results from patient No. 15. The mean values of the 12 patients are plotted in figure 1; the results from patient 15 are shown separately. This patient can be seen to have kinetics markedly different from those of the other 12 patients, with a greatly prolonged half-life which was estimated at 720 min and a clearance,
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FIG. 7. Mean (± SEM) plasma decay curve in the 12 patients (B) and a separate plot of the post-infusion plasma concentrations in patient No. 15 (A).

DISCUSSION

Alfentanil has many theoretical advantages over other opioids in view of its high therapeutic ratio and previously published pharmacokinetic profile (Bovill et al., 1982). Concern has been expressed about pethidine on account of its potential cardiotoxicity (de Castro et al., 1979) and neurotoxicity related to nor-pethidine (Miller and Jick, 1978). Morphine has been reported to have unsatisfactory kinetics in renal failure (McQuay and Moore, 1984), a common problem in the ITU. There is little experience of the use of other opioids by infusion, most having a pharmacokinetic profile unsuited to prolonged administration by infusion.

We have compared an infusion of alfentanil with one of pethidine, both supplemented with a very small dose of midazolam. Pethidine was chosen for comparison on account of its regular use in this unit. Moreover, infusions of pethidine for postoperative analgesia have been extensively studied (Church, 1979; Stapleton, Austin and Mather, 1979). The group of patients chosen for this study, although not typical of the patients in a general ITU (40% of the patients in our ITU) provided a homogeneous group for study.

The design of this study was to use variable infusion rates to provide good sedation and rapid recovery. We were able to provide comparable sedation with both groups. However, it is suggested by the significant increase in the number of changes in rate with the pethidine group that the sedation was easier to achieve with alfentanil. The infusion rates of alfentanil required were in the range 0.4–0.5 µg kg⁻¹ min⁻¹—similar to those reported previously (Yate, Thomas and Sebel, 1984) with unsupplemented alfentanil, although supplemented with midazolam in the present study. Although the previous report suggested that alfentanil could be used as the sole agent, midazolam had to be added in the pethidine group for satisfactory sedation, and in an effort to maintain comparability between the groups midazolam was given to the alfentanil
patients as well. The mean infusion rate of pethidine was comparable with that previously reported for postoperative pain relief in non-ventilated patients (Stapleton, Austin and Mather, 1979).

The plasma concentrations of alfentanil required during the infusion were in the region 150–200 ng ml⁻¹, a concentration the same as that required for maintenance during nitrous oxide-supplemented alfentanil for lower abdominal surgery (Ausems and Hug, 1983).

The results for recovery (apart from patient No. 15) were acceptable in terms of lack of sedation and adequacy of respiratory rate and PaCO₂ and, in terms of Pco₂ and ventilatory rate, better than previously reported (Andrews et al., 1983) after a short infusion of alfentanil for postoperative analgesia. Although the post-infusion plasma concentrations obtained in this study have been associated with respiratory depression as measured by carbon dioxide response curves (O’Connor, Escarpa and Prys-Roberts, 1983), the mean plasma concentrations (excluding patient No. 15) of alfentanil after infusion had decreased to less than 150 ng ml⁻¹ by 30 min, a figure previously quoted (Ausems and Hug, 1983) for satisfactory spontaneous ventilation, a finding supported by the clinical results in this study.

Although this was not primarily a pharmacokinetic study, any planned administration of a drug by infusion for a long period should take into account the known pharmacokinetics of the drug in that particular situation. Most of the previously published pharmacokinetic data of alfentanil have been obtained after a single i.v. dose in healthy volunteers (Bower and Hull, 1982) or young healthy patients undergoing surgery (McDonnell et al., 1982; Fragen et al., 1983).

In one small study with patients undergoing open heart surgery (Hug, de Lange and Burm, 1983) in which the kinetics were studied before and after cardiopulmonary bypass, a prolonged elimination half-life was found after the post-bypass dose, as a result of an increase in the volume of distribution. There are no reports of the pharmacokinetics of alfentanil after prolonged infusions in the intensive care unit. The results obtained in the 12 patients with an acceptable bi-exponential fit show plasma half-lives similar to those obtained by Hug, de Lange and Burm (1983) in cardiac surgical patients, when a large dose was given after surgery. In that study the prolonged elimination half-life was attributable to an increase in the volume of distribution. In our study the total volume of distribution was smaller (0.59 litre kg⁻¹)—more like that seen in general surgical patients (Schuttler and Stoeckel, 1982), the prolonged elimination half-life of 162 min in our study being the result of the reduced rate of clearance, 2.66 ml kg⁻¹ min⁻¹.

The possible advantages of alfentanil are clouded by the potentially serious problem encountered in patient No. 15. Assuming the respiratory arrest was the result of the termination of the effect of the first dose of naloxone, the long duration of action of naloxone is surprising, although a wide variation in the half-life of naloxone has been reported (Aitkenhead et al., 1984). The plasma concentrations measured in this patient showed a greatly reduced clearance, leading to a very prolonged half-life. The reasons for this are unclear; there was no biochemical evidence of hepatic dysfunction, which might be expected to reduce clearance. This patient was receiving erythromycin, a drug that has been reported to interfere with drug excretion (Green and Clement, 1983). However, another patient in the trial (No. 7) was also receiving erythromycin and she had a normal clearance of 3.32 ml kg⁻¹ min⁻¹, although a rather prolonged elimination half-life (253 min). There have been other reports of prolonged elimination half-life of alfentanil as a result of a reduced clearance, although not in this order. Notably, McDonnell, Bartkowski and Kahn (1984) suggested that it may be caused by an abnormality of hepatic hydroxylation similar to that seen with debrisoquine and phenacetin—an abnormality found in approximately 10% of the population.

The introduction of any new drug to the ITU requires careful investigation of any metabolic effect. Previous studies of the metabolic effects of alfentanil have been confined to the effect of large doses administered before open-heart surgery. In one study (de Lange et al., 1983) alfentanil 42 μg kg⁻¹ given before surgery caused marked suppression of the metabolic responses to surgery, similar to that seen with sufentanil and fentanyl. In another study which investigated the metabolic effects of the administration of fentanyl 50 μg kg⁻¹ after surgical stimulus (Bent et al., 1984), it was suggested that, once established, the normal stress response could not be suppressed by opioids. In our study, a surprising finding was the marked difference between the two groups. The reason for this is unclear; it may be an effect, on a reduced
scale, similar to that seen with alfentanil during cardiac surgery, or a reflection of better sedation produced by alfentanil. If alfentanil is to be used for prolonged infusions in the ITU, further investigations of the metabolic effect are required.

In conclusion, we have shown that alfentanil at an infusion rate of 0.4–0.5 μg kg⁻¹ min⁻¹ or pethidine at a mean infusion rate of 0.3 mg kg⁻¹ h⁻¹ can be used as the main agent for sedation of ventilated patients in the ITU, with good recovery in the majority.

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REFERENCES