Patient-maintained analgesia with target-controlled alfentanil infusion after cardiac surgery: a comparison with morphine PCA

M. R. Checketts, C. J. Gilhooly, G. N. C. Kenny

Summary
The performance of a patient-demand, target-controlled alfentanil infusion system was compared with that of a traditional morphine patient-controlled analgesia (PCA) pump in 120 adult patients after cardiac surgery. Patients were randomized to one of the two PCA systems for their postoperative analgesia in the intensive care unit and pain, nausea and sedation scores were recorded every 4 h for the first 24 h. Episodes of hypoxaemia, myocardial ischaemia and haemodynamic instability were also recorded. In patients using the alfentanil system the overall median visual analogue pain score was 2.3 (95% CI 2.3–2.8) compared with 3.0 (95% CI 2.7–3.2) in those using morphine PCA ($P < 0.05$), but both systems delivered high-quality analgesia. The two groups did not differ with respect to the overall sedation scores, the frequency of postoperative nausea and vomiting, haemodynamic instability, myocardial ischaemia or hypoxaemia. (Br. J. Anaesth. 1998; 80: 748–751)

Keywords: analgesia; patient-controlled target-controlled infusion; analgesics alfentanil morphine; surgery cardiac; pain postoperative

Postoperative pain may be managed poorly after cardiac surgery. This can contribute significantly to increased morbidity and mortality, because the haemodynamic consequences of postoperative pain increase myocardial oxygen demand and make myocardial ischaemia more likely. Furthermore, several studies have shown that high-quality analgesia can reduce the severity of episodes of myocardial ischaemia and facilitate early extubation with subsequent clearance of respiratory secretions after cardiac surgery. Use of patient-controlled analgesia (PCA) has markedly improved the control of postoperative pain, but the technique has not been used widely in cardiac surgical patients. One study compared PCA using morphine with nurse-controlled morphine infusions after cardiac surgery but failed to show any difference in postoperative pain scores or extubation times.

Morphine is the opioid analgesic most commonly used in PCA systems. When compared with alfentanil, it has a slower onset and offset of action after i.v. administration, which may lead to a delayed onset of analgesia and subsequent oversedation. Alfentanil is more than 100 times more lipid soluble than morphine and at pH 7.4 is about 90% un-ionized, whereas morphine is about 20% un-ionized. Therefore, alfentanil can diffuse from plasma to brain and back again more quickly than morphine, which explains its rapid onset and offset of analgesic activity. These physicochemical properties make alfentanil suitable for use in a phamaco-kinetically based patient-controlled analgesia infusion system. The present study compared a target-controlled infusion (TCI) of alfentanil, which was controlled by the patient as patient-maintained analgesia (PMA), with a morphine PCA system in the first 24 h after cardiac surgery. The effect of these two PCA systems on postoperative pain, sedation and nausea and vomiting, and on myocardial ischaemia and haemodynamic instability, was evaluated.

Patients and methods
After obtaining hospital Ethics Committee approval and written informed consent, we studied 120 adult patients scheduled for elective cardiac bypass surgery. A closed-envelope technique was used to allocate patients randomly to receive a morphine PCA system (group M) or a patient-maintained, target controlled alfentanil infusion (group A) for their postoperative analgesia. Exclusion criteria were poor ventricular function, as defined by an ejection fraction of less than 40% measured during coronary angiography, and hepatic or renal impairment identified after routine preoperative screening of blood biochemistry.

All patients were shown the relevant PCA handset at the preoperative visit and instructed on its use the day before surgery. A standardized anaesthetic technique was used for all patients. Oral premedication consisted of temazepam 30 mg, metoclopramide 10 mg and ranitidine 150 mg given 2 h before operation. Anaesthesia was induced and maintained with target-controlled infusions (TCI) of propofol and alfentanil. The TCI infusion systems are computer-controlled pumps programmed with pharmacokinetic models for propofol and alfentanil. When the age, sex and weight of the patient has been entered,
Use of alfentanil for patient-controlled analgesia

Table 1 Sedation score used in this study

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Agitated</td>
<td>No nausea or vomiting</td>
</tr>
<tr>
<td>1</td>
<td>Awake</td>
<td>Nausea only</td>
</tr>
<tr>
<td>2</td>
<td>Roused by voice</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>3</td>
<td>Roused by touch</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Unrousable</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Muscle relaxants</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Sleeping</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Patient characteristics and surgical data (mean (range)); no significant differences between groups. PMA = patient managed analgesia; PCA = patient controlled analgesia

<table>
<thead>
<tr>
<th></th>
<th>Alfentanil</th>
<th>Morphine</th>
<th>PMA patients</th>
<th>PCA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>58 (39–70)</td>
<td>61 (38–74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (56–114)</td>
<td>76 (43–120)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>39/13</td>
<td>41/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>79 (31–150)</td>
<td>86 (50–177)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic crossclamp time (min)</td>
<td>51 (15–92)</td>
<td>55 (28–132)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

the pumps can achieve and maintain any calculated plasma concentration selected. The lungs were ventilated with an air/oxygen mixture. Patients were cooled to 28°C during cardiopulmonary bypass and the selected target concentration of alfentanil was reduced. At the start of rewarming the TCI alfentanil infusion was stopped in group M patients, who received a 30 mg bolus dose of morphine followed by an infusion of 2 mg h⁻¹ that was continued into the early postoperative period in the cardiac intensive care unit (CICU). Group A patients continued to receive the TCI alfentanil infusion and returned to the CICU after surgery with an initial predicted target concentration set at an appropriate level. The TCI propofol infusion was discontinued in both groups on arrival in the CICU. In both groups, patients were judged to be able to use a PCA handset when they opened their eyes and obeyed simple commands. At this point, the background infusion was stopped in group M patients and the PCA pump reprogrammed to deliver a 1 mg bolus with a 3-min lockout. In group A patients, a PCA handset was plugged into the alfentanil TCI system. When the patient successfully pushed the PCA button to request pain relief, the target concentration of alfentanil delivered was increased by 5 ng ml⁻¹ with a lock-out time of 2 min. If analgesia was not requested for 30 min, the target concentration was automatically reduced by 5 ng ml⁻¹. If the button was subsequently not pressed the target concentration was further reduced in steps of 5 ng ml⁻¹ every 30 min for the first 4 h of use, every 45 min for the next 4 h and every 60 min thereafter. The system was programmed to deliver a minimum plasma concentration of 15 ng ml⁻¹ and a maximum of 150 ng ml⁻¹.

The patients were extubated in the CICU when the following criteria were met: core temperature > 36.5°C; patient obeys simple commands; haemodynamic stability (systolic arterial pressure > 80 and < 170 mm Hg, heart rate > 50 and < 120 beats min⁻¹); satisfactory arterial blood gases (PaO₂ > 12 kPa with PaCO₂ < 0.6; PaCO₂ < 7 kPa when breathing spontaneously); urine output > 1 ml kg⁻¹ min⁻¹; chest drain blood losses < 30 ml h⁻¹. The elapsed time from CICU admission to extubation was recorded. Monitoring included 5-lead electrocardiography with continuous 3-lead ST segment analysis, intra-arterial pressure and continuous pulse oximetry. At 4-h intervals the nausea and sedation scores (table 1) and the visual analogue pain score (VAPS) were recorded and a blood gas sample drawn for measurement of PaO₂ and PaCO₂. A 12-lead ECG was also taken every 4 h. Patients were observed for the first 24 h after operation. Visual analogue pain scores (VAPS) were recorded with the patients at rest, by CICU nursing staff who had been trained in the technique by one of the authors (MRC). The VAPS system had been explained to all patients on the day before surgery. For patients who were intubated it was possible to obtain a VAPS score if they were awake and able to obey simple commands, otherwise no score was recorded.

Myocardial ischaemia was defined as ST segment changes (elevation or depression) of more than 2 mm in any ECG lead, haemodynamic instability as a fluctuation in mean arterial pressure or heart rate by more than ± 30% in the first 24 h (± 30% compared with baseline values recorded after admission to CICU) and hypoxaemia as an oxygen saturation measured by pulse oximeter of < 90%.

The assessors were not blinded because the two PCA systems were visually very different and cloaking them was impractical. At the end of the 24-hour study period, patients who had been randomized to the alfentanil PMA system received the morphine PCA pump for the next 2–3 days until simple oral analgesics were adequate.

All patients were visited by one of the authors on day 4 or 5 after surgery and asked to classify the quality of their initial postoperative analgesia as excellent, good, satisfactory or poor. They were also invited to comment on the patient-controlled analgesia system they had used.

Student’s t tests were used to compare patient groups. We evaluated the VAPS by using the Mann–Whitney U test and comparing the 95% confidence intervals, as has been recommended.9 A chi-square test was used to compare nausea scores and Mann Whitney U tests for all other comparisons between the two groups, using Minitab for Windows software (version 9.2 running under Windows for Workgroups 3.11 on a Hi Grade LBC2 100 notebook computer). A P<0.05 was taken as statistically significant.

Results

One hundred and twenty patients were recruited into the study but 15 were withdrawn because of surgical...
complications that required reoperation or violation of the study protocol. A total of 105 patients were studied. There were no differences between groups in patient characteristics (table 2). The surgical procedures are listed in Table 3.

Mean time to tracheal extubation in the alfentanil analgesia group was 288 min (95% confidence interval 218–358) compared with 411 min in the morphine group (95% CI 331–491) \( (P < 0.05) \).

Median overall visual analogue pain scores for the 24-h study period were lower in patients using alfentanil patient-maintained analgesia, at 2.3 (95% CI 2.3–2.8) compared with 3.0 (95% CI 2.7–3.2) in the morphine group \( (P < 0.05) \). However, there were no significant differences in the comparative VAPS at each of the 4-hourly assessments (fig. 1). Median 24-h consumption of alfentanil was 29.4 mg (range 11–59 mg, 95% CI 24–34 mg) and that of morphine was 45.5 mg (range 12–91 mg, 95% CI 39.9–51 mg). Mean predicted alfentanil target concentration at admission to the CICU was 96 ng ml\(^{-1}\) (95% CI 89–103 ng ml\(^{-1}\)). However, the predicted alfentanil concentrations requested by individual patients ranged from 15 ng ml\(^{-1}\) to the maximum permitted value of 150 ng ml\(^{-1}\).

There was no significant difference between the two groups in nausea or sedation scores. Twenty of 52 patients in the alfentanil and 24 of 53 in the morphine group had nausea scores greater than 1 in the first 24 h. Median sedation score in both groups was 52 patients in the alfentanil and 24 of 53 in the morphine group (mean duration 61 min) compared with 41% of patients in the morphine group (mean duration 71 min). These differences were not statistically significant. One patient, who was in the alfentanil group, required a sodium nitroprusside infusion to control hypertension following an aortic valve replacement.

In the first 24 h after operation, oxygen saturations of \(<90\%\) by pulse oximetry were recorded in nine (17%) of the alfentanil group (mean duration 21 min) and 14 (26%) patients in the morphine group (mean duration 39 min). These differences were not significant. There was no significant difference in the \( PaCO_2 \) values from blood gases in the two patient groups, the mean values being 5.5 (SD 0.836) in the alfentanil group and 5.6 (SD 1.43) in the morphine group.

Ninety-one percent of patients who used the alfentanil PMA system rated their postoperative analgesia as excellent or good while the remaining 9% felt it was only satisfactory or poor. The corresponding figures in patients in the morphine group were 82% and 18%. However, these differences were not statistically significant (fig. 2). Alfentanil plasma concentrations requested by patients who rated their analgesia as excellent or good did not differ from those in the group rating their analgesia as satisfactory or poor.

**Discussion**

The pharmacokinetic and pharmacodynamic profile of alfentanil make it suitable for use in a patient-maintained TCI system. It has a rapid onset of action and short elimination half life and has been shown to provide good-quality analgesia when administered by TCI after major vascular surgery. Morphine, which is the opioid most commonly used in PCA pumps in the UK, has a relatively slow onset of action and analgesia may be delayed.

Use of both alfentanil target-controlled, patient-maintained analgesia and morphine bolus PCA resulted in good quality analgesia in patients after cardiac surgery. Lower pain scores were recorded in the patients who received alfentanil, but although statistically significant, this difference is probably not clinically significant. The median pain scores of 2.3 in the alfentanil PMA group and 3.0 in the morphine PCA group were within the “zone of analgesic success” of VAPS < 3.0 postulated by Manthra. The present results compare favourably with a previously reported median pain score of 4.0 after cardic bypass surgery, when intravenous bolus doses of morphine were administered by nursing staff.

In the present study, patients who received alfentanil were extubated significantly sooner than those in the morphine group. The clinical impression was that the alfentanil patients were less sedated, particularly in the first 12 h after surgery, but this was not substantiated after statistical analysis of the sedation scores in the two groups. The Addenbrooke’s sedation score used in this study may not have been sensitive enough to identify genuine differences and scores were obtained only every 4 h. The different analgesic regimens that were used after cardiopulmonary bypass may have influenced the postoperative patient sedation levels, but again we were unable to...
show any significant differences. It was technically impractical to blind the PCA systems but a strict extubation protocol was used to facilitate comparisons between the two groups.

There was no significant difference in the frequency and duration of episodes of myocardial ischaemia, cardiovascular instability and hypoxaemia in the two groups and no patient had postoperative myocardial infarction. The fact that only one patient in the study required sodium nitroprusside in the postoperative period is encouraging, and a reduced requirement for antihypertensive medication has been reported previously in patients receiving high-quality analgesia.3 12 In the present study myocardial ischaemia was less frequent than in two uncontrolled previous studies, in which ischaemic events were reported in 48% and 40% of patients, respectively, after coronary artery bypass grafting.13 14 The 19% frequency of ischaemia in our patients using the alfentanil patient-maintained analgesia system is similar to the 15% reported by Liem and colleagues in CABG patients who received high thoracic extradural analgesia.3 However, it was significantly higher than the 4% frequency reported in another study that used prolonged high-dose opioid infusions in the postoperative period.15

Postoperative interviews with our patients before their discharge from hospital showed a high level of satisfaction with both patient-controlled analgesia systems. More patients in the alfentanil PMA group felt that their postoperative analgesia was excellent or good compared with those using the morphine PCA pump, but this difference was not significant. Patients had little difficulty in using the PCA handsets and this work has confirmed previous reports that PCA techniques can successfully be used by adult cardiac surgical patients in the immediate postoperative period.16

Acknowledgements
This work was supported by a grant from the Medical Research Council. The authors thank all the anaesthetists, cardiac surgeons and intensive care unit nursing staff at Health Care International for their help with the present study.

References