Patient-maintained remifentanil target-controlled infusion for the transition to early postoperative analgesia

S. SCHRAAG, G. N. KENNY, U. MOHL AND M. GEORGIEFF

Summary
We studied 30 male patients in the early postoperative period to assess the efficacy, safety and feasibility of a patient-demand, target-controlled infusion (TCI) of remifentanil. All patients received the same TCI-based propofol-remifentanil anaesthetic for elective orthopaedic surgery. At the end of surgery, infusion of remifentanil was reduced progressively until patients were breathing spontaneously. After extubation and transfer to the post-anaesthesia care unit, patients were given control of a handset and were able to increase the target remifentanil blood concentration by increments of 0.2 ng ml⁻¹. If there were no demands, the TCI controller automatically reduced the target concentration. Mean time to onset of satisfactory analgesia (VAS ≤3, out of 10) was 18.9 (95% confidence interval (CI) 15.8–21.9) min at a mean target remifentanil concentration of 2.02 (CI 1.87–2.16) ng ml⁻¹. There were no episodes of hypoxaemia and the lowest ventilatory frequency was 9 bpm. Nausea occurred in 26.6% of patients and 10% vomited. The majority of patients were only slightly sedated. These results imply an effective tool without respiratory side effects in the early postoperative period after anaesthesia using remifentanil as the analgesic component. (Br. J. Anaesth. 1998; 81: 365–368).

Keywords: analgesia, patient-controlled; analgesic techniques, infusion; analgesics opioid, remifentanil; pain, postoperative

Remifentanil is a novel, short-acting μ receptor opioid agonist, which has been introduced recently into clinical anaesthetic practice in most European countries and the USA. Its unique metabolism offers a favourable pharmacokinetic profile which results in rapid offset of drug effect, even after long infusions, expressed as a context-sensitive half-time of approximately 3 min, regardless of the duration of infusion.¹ These properties should confer ease of titration for changing intraoperative conditions. However, a major disadvantage of remifentanil is the appropriate transition to postoperative pain control, as the rapid offset of action has been shown to produce inadequate immediate postoperative analgesia,² which may adversely affect patient recovery and outcome.

In contrast, alfentanil, whose context-sensitive half-time is duration-dependent, has been shown to provide good quality analgesia after major surgery when administered as a target-controlled infusion (TCI) based on a three-compartment pharmacokinetic model.³ In this study we have assessed the efficacy, safety and feasibility of a patient-demand TCI for remifentanil for the transition to the early postoperative phase.

Patients and methods
After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied 30 consecutive male patients, ASA I and II, undergoing elective orthopaedic surgery. These procedures (table 1) have been shown to produce moderate to severe postoperative pain with comparable analgesic requirements at our institution. Patients older than 65 yr or with a known history of chronic drug or alcohol abuse were excluded, as were those suffering from obesity, expressed as a body mass index > 30 kg (m²)⁻¹. During the pre-anaesthetic visit, patients were instructed in the principles of patient-controlled analgesia (PCA) and after arrival at the preoperative preparation area the use of a PCA handset was demonstrated.

The anaesthetic technique was standardized. After premedication with oral clorazepate dipotassium 0.25 mg kg⁻¹, 1 h before surgery, anaesthesia was induced and maintained with 1% propofol and remifentanil 1 mg/50 ml (20 μg ml⁻¹) using TCI. TCI systems are designed to rapidly achieve and maintain predefined drug concentrations based on microcomputer-generated pharmacokinetic algorithms.⁴ They were programmed with pooled pharmacokinetic data for propofol⁵ and remifentanil⁶ and adjusted for patient age and weight. The TCI controller, which contains the microcomputer and a display showing, the calculated target plasma and effect site concentrations, was connected via a serial link to a Graseby 3400 syringe pump (Graseby Medical Inc., Watford, UK) to administer the anaesthetic drug. Beginning with a target concentration of 2.5 μg ml⁻¹, propofol TCI was titrated until loss of consciousness, expressed as a loss of response to verbal commands and loss of the eyelash reflex (Cₜᵣ₉ = target plasma concentration).
centration; nomenclature according to Glass and colleagues). Thereafter, remifentanil TCI was started to achieve an initial $C_{TP}$ of 4 ng ml$^{-1}$. Neuromuscular block was facilitated with vecuronium 0.1 mg kg$^{-1}$, the trachea was intubated and the lungs ventilated with 70% nitrous oxide in oxygen. Vecuronium was given only for tracheal intubation, and recovery of neuromuscular block was monitored by train-of-four counts. No antagonism of drug was necessary. End-tidal carbon dioxide tension was kept in the normocapnic range (4.6–5.8 kPa). Respiratory and cardiovascular monitoring were performed according to our institution’s standard practice and consisted of electrocardiogram, non-invasive arterial pressure and pulse oximetry. For maintenance of anaesthesia, propofol TCI was continued at the induction target at which unconsciousness occurred, while the remifentanil target was increased in steps of 0.5 ng ml$^{-1}$ when signs of inadequate anaesthesia developed. This was defined by one or more of the following criteria: increase in systolic arterial pressure by more than 20 mm Hg above pre-intubation values; heart rate greater than 90 beat min$^{-1}$ in the absence of hypovolaemia; autonomic signs, such as sweating or flushing; and somatic responses, such as movement, swallowing or coughing.

Approximately 10 min before the anticipated end of surgery, infusion of propofol was stopped and the target concentration of remifentanil was reduced progressively in decrements of 0.1 ng ml$^{-1}$ until patients were breathing spontaneously at a ventilatory frequency of ≥10 bpm. The target concentration of remifentanil at which each individual patient regained consciousness and tracheal extubation occurred was maintained until they were transferred to the post-anaesthesia care unit (PACU). A handset was connected to the TCI controller and the patient was given control. By pushing the demand button twice within 1 s when pain relief was required, the patient was able to increase the target concentration of remifentanil. The target concentration of remifentanil was increased by 0.2 ng ml$^{-1}$ after every successful demand. We chose a double push for every demand to ensure a minimum of alertness of the patient. There was a lockout time of 2 min after each increase in target concentration. In the absence of a demand within a 30-min period, the target concentration was automatically reduced by 0.2 ng ml$^{-1}$ during the first 4 h and further reductions of 0.2 ng ml$^{-1}$ were made every 45 min during the following 4 h.

After arrival in the PACU all patients were observed for the next 6 h and ventilatory frequency, oxygen saturation, pain and level of sedation were monitored. No additional oxygen was given unless $S_{\text{aO}_2}$ decreased to less than 95%. Assessments and observations started with initiation of the handset controller and were made every 3 min until adequate analgesia was provided and every 15 min thereafter.

### Table 1

**Orthopaedic procedures (n=30)**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroscopic knee joint surgery (not diagnostic)</td>
<td>7</td>
</tr>
<tr>
<td>Open repair of anterior cruciate ligament</td>
<td>9</td>
</tr>
<tr>
<td>Partial knee replacement</td>
<td>9</td>
</tr>
<tr>
<td>Shoulder arthroscopy and surgery</td>
<td>3</td>
</tr>
<tr>
<td>Fracture of the talus</td>
<td>2</td>
</tr>
</tbody>
</table>

Pain on movement was assessed using an 11-point (0–10) visual analogue scale (VAS) with 0 = no pain and 10 = worst pain imaginable. Patient rating scores of 3 or less were defined as adequate analgesia. The degree of sedation was recorded using the six-point scale described by Ramsay and colleagues. Every episode of nausea or vomiting was documented. After matching the “adequate analgesia” criteria (VAS ≤3), rectal diclofenac 100 mg was administered for further analgesia to every patient, except those with underlying renal impairment or a history of gastric ulcer. Remifentanil TCI was terminated after the observation period of 6 h by tapering off the infusion within 15–20 min. I.v. piritramide or standard morphine PCA was prescribed in patients with additional analgesic requirements.

### Statistical Analysis

Data are presented as mean, absolute range and 95% confidence intervals (CI). Patient values are given as mean (SEM). The relationships between target remifentanil concentration and ventilatory frequency and sedation score were investigated using regression analysis. Student’s $t$ test was used to compare target remifentanil concentrations for spontaneous ventilation and adequate analgesia, with $P<0.05$ considered significant. All analyses were performed using the StatView statistical software package (v.4.5, Abacus Concepts, Berkeley, CA, USA).

### Results

A total of 30 patients, mean age 41.6 (range 18–65) yr and mean weight 72 kg (SEM 1.9) were included. Mean duration of surgery was 2.07 (SEM 0.12) h. The remifentanil TCI system functioned well and there were no technical problems during the study. Patients found it easy to use the handset and were satisfied with the PCA device. At the end of surgery, infusion of propofol was stopped at 4.2 (95% CI 2.2–5.1 CI) µg ml$^{-1}$ and the reduction in TCI remifentanil started with 4.8 (4.2–5.5) ng ml$^{-1}$. The mean target remifentanil concentration at which spontaneous ventilation was first noted after the end of surgery was 1.05 (0.97–1.14) ng ml$^{-1}$, significantly less ($P<0.0001$) than that required for adequate analgesia after operation, which was 2.02 (1.87–2.16) ng ml$^{-1}$. The variation between patients for these values was more than 200% (table 2). In contrast, the mean residual calculated target propofol concentration at the time of spontaneous ventilation was 1.2 (0.9–1.8) µg ml$^{-1}$.

Mean time to adequate analgesia (VAS <3) was 18.9 (15.89–21.91) min. With two exceptions, every patient achieved adequate analgesia within 30 min. There were no episodes of hypoxaemia (oxygen saturation <95%) or apnoea, and the lowest ventilatory frequency was 9 bpm (table 3). The majority of patients were only slightly sedated (median sedation score 2, out of a possible 6). The target concentration of remifentanil showed a linear correlation with slowing of ventilatory frequency ($r^2 = 0.7$) and level of sedation. The frequency of nausea and vomiting was 26.6% and 10%, respectively, and occurred predominantly in patients with relatively high and rapid increases in target concentrations of remifentanil.
**Patient-maintained remifentanil**

Table 2 Target remifentanil concentration (C<sub>TP</sub>) ng ml<sup>-1</sup> for sufficient spontaneous ventilation (T<sub>Csv</sub>) and adequate postoperative analgesia (T<sub>CVAS</sub>), in addition to time for adequate postoperative analgesia (VAS<3) (mean, range of absolute values and 95% confidence interval (CI))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (range)</th>
<th>95% lower</th>
<th>95% upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;Csv&lt;/sub&gt;</td>
<td>1.03 (0.6–1.6)</td>
<td>0.76</td>
<td>1.48</td>
</tr>
<tr>
<td>T&lt;sub&gt;CVAS&lt;/sub&gt;</td>
<td>2.02 (1.2–2.8)</td>
<td>1.43</td>
<td>2.69</td>
</tr>
<tr>
<td>VAS&lt;3 (min)</td>
<td>18.9 (8–45)</td>
<td>10.2</td>
<td>28.5</td>
</tr>
</tbody>
</table>

Table 3 Ventilatory frequency and oxygen saturation at the time of adequate analgesia (VAS<3) (mean, range of absolute values and 95% confidence interval (CI))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (range)</th>
<th>95% lower</th>
<th>95% upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilatory frequency (bpm)</td>
<td>16.5 (9–23)</td>
<td>14.9</td>
<td>18.1</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>98.2 (95–100)</td>
<td>97.5</td>
<td>98.8</td>
</tr>
</tbody>
</table>

Moderate postoperative shivering occurred in two patients but required no treatment.

**Discussion**

In this study, we have demonstrated that in 30 patients, infusion of remifentanil maintained by patient-controlled TCI was an effective and safe postoperative analgesic technique in the early period after remifentanil–propofol anaesthesia.

To overcome the disadvantage of immediate painful conditions after stopping infusion of remifentanil, which occurs significantly earlier compared with other opioids, several studies examined the feasibility of a manually controlled remifentanil infusion. Bowdle and co-workers compared different infusion rates (0.05–0.15 µg kg<sup>-1</sup> min<sup>-1</sup>) and the effect of incremental bolus doses in a multicentre study. They found adequate analgesia in 78% of patients within 30 min, but adverse respiratory effects were a notable problem (29% of patients, 7% apnoea). In another multicentre study comparing remifentanil with alfentanil for major abdominal surgery, Schüttler and colleagues titrated a manual infusion beginning with 0.1 µg kg<sup>-1</sup> min<sup>-1</sup>. They found that rapid changes in remifentanil blood concentration by bolus administrations or increases in infusion rate resulted in a high frequency of muscle rigidity, respiratory depression and apnoea. An editorial comment to this article stated that using remifentanil in the manner described was unacceptable. Similar results were reported recently by Yarmush and co-workers. They conducted a double-blind comparison of manually controlled remifentanil infusion (median rate 0.125 µg kg<sup>-1</sup>min<sup>-1</sup>) with morphine boluses during the first 25 min after the end of surgery. Transient respiratory depression, apnoea or both (14%) were the most frequent adverse effects in the remifentanil group. The incidence of nausea and vomiting seemed to be highly variable in these studies. There was no significant difference in the frequency of vomiting in our study compared with that of Bowdle and colleagues (approximately 10%), but Schüttler and co-workers reported that 47% of patients in the remifentanil group suffered nausea, which is almost twice that seen in our patients (26%). In contrast, the study of Yarmush and colleagues described an incidence of 17% nausea in the remifentanil group compared with 6% in the morphine group. This suggests a dose-dependent adverse effect which may be aggravated by incremental manual bolus doses.

A theoretical advantage of remifentanil TCI, which increases the blood concentration by a controlled stepwise titration of only small boluses, is the avoidance of an uncontrolled overshoot in blood concentration associated with manual bolus administration. As remifentanil has a fast effect site equilibration (T<sub>1/2</sub> k<sub>eo</sub> = 1.6 min), every new target results in rapid onset and rapid achievement of a stable level of drug effect. In fact, none of our patients experienced significant respiratory depression, and sufficient analgesia was achieved in a reasonable time.

Alfentanil, which has a comparable effect site equilibration to remifentanil, has been shown by van den Nieuwenhuyzen and colleagues to be significantly faster in onset of analgesia compared with morphine when used as TCI. With a mean time of 20 min from the start of therapy to onset of sufficient analgesia, their results were similar to our finding of 18 min with remifentanil. Similar results have been reported by Irwin and co-workers using patient-controlled alfentanil TCI, which was as safe and effective as standard morphine PCA after orthopaedic surgery. Our finding, that the mean remifentanil target concentration for recovery of spontaneous ventilation at the end of surgery was approximately 50% of that for adequate pain control thereafter, was probably because of a residual anaesthetic effect of propofol and reflects a possible pharmacodynamic interaction of the two drugs.

We did not measure remifentanil blood concentrations and therefore we could not estimate the performance of the remifentanil TCI. However, the pharmacokinetic data used to programme the TCI controller have been shown to be sufficiently reliable. Pharmacokinetic bias and precision, expressed as relative and absolute percent performance error, are reported to be 26% and 19% respectively, which are comparable with data obtained for alfentanil and sufentanil TCI–PCA. Even if we knew the actual blood concentrations of remifentanil, this would be only a minor contribution as the pharmacodynamic variance of the required target concentrations between individual patients (approximately 200%) exceeds the expected pharmacokinetic error.

Another possible source of inaccuracy could be the physical performance of the infusion pump and dilution of the drug. A remifentanil concentration of 50 µg ml<sup>-1</sup> has been reported to be associated with a high incidence of opioid-induced adverse effects when used as a manual infusion. The choice of i.v. tubing, deadspace of taps or three-way valves, and changes in flow rates of additional fluids may substantially influence moment-to-moment delivery, resulting in varying drug concentrations. Therefore, we used a low concentration of remifentanil (20 µg ml<sup>-1</sup>) which was connected to the proximal port of the i.v. cannula, flushed by a constant infusion of Ringer’s lactate. Even taking these precautions into account, our preliminary experience does not yet
support the use of this system without adequate supervision and monitoring.

We conclude that patient-demand target-controlled infusion of remifentanil was a convenient and effective tool for the transition to sufficient analgesia in the early postoperative period. As our preliminary experience was limited to 30 patients, the safety of the system and lack of respiratory side effects have to be discussed with caution. To validate this technique against standard PCA bolus therapy, further controlled studies are needed.

References


