Influence of peroperative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanil TCI. A randomized, controlled study

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Background. Sufentanil and remifentanil are characterized by two different pharmacokinetic profiles. The aim of this study was to compare the effects of sufentanil and remifentanil administered using target-controlled infusion (TCI) on recovery and postoperative analgesia after major abdominal surgery.

Methods. Thirty adult patients scheduled for open colorectal surgery were included in a prospective, randomized study. Sufentanil TCI (sufentanil group) or remifentanil TCI (remifentanil group) was administered during surgery. In the remifentanil group, 30 min before the anticipated end of surgery, morphine 0.15 mg kg⁻¹ was administered i.v. In the sufentanil group, an effect-site concentration of 0.25 ng ml⁻¹ was targeted at extubation. In both groups, postoperative pain was controlled by titration of i.v. morphine and then patient-controlled analgesia with morphine.

Results. The extubation time was similar in the two groups (mean (SD) 13 (6) and 14 (6) min in the sufentanil and remifentanil groups respectively). Visual analogue scale scores were significantly greater during the first 2 h after tracheal extubation in the remifentanil group than in the sufentanil group. The time to first analgesic request in the postanaesthesia care unit was significantly longer in the sufentanil group than in the remifentanil group (55 (64) (range 2–240) vs 11 (7) (1–29) min; P<0.001). The cumulative morphine dose for titration was significantly greater in the remifentanil group (P<0.01). The cumulative morphine dose used during titration and patient-controlled analgesia was significantly greater in the remifentanil group 4, 12 and 24 h after extubation (P<0.05).

Conclusion. TCI sufentanil (0.25 ng ml⁻¹ effect-site concentration at extubation) is more effective than the intraoperative combination of remifentanil TCI infusion with morphine bolus (0.15 mg kg⁻¹) for postoperative pain relief after major abdominal surgery and does not compromise extubation and recovery.

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The quality of postoperative analgesia depends, in part, on the opioid infused during surgery.¹⁻³ Remifentanil is a potent and short-acting opioid with predictable and rapid recovery, which is relatively independent of the dose and the infusion duration.¹ Thus, it can be given in high dosages until skin closure with little risk of delayed postoperative recovery or respiratory depression. The consequence of its short action is that patients may experience considerable pain in the immediate postoperative period. Different protocols have been studied after remifentanil infusion to
reduce postoperative pain. After major surgery, morphine 0.15 mg kg\(^{-1}\) given 30 min before the end of surgery seems to provide acceptable pain relief.\(^4\) Despite this precaution, postoperative analgesic requirement is often increased when patients receive relatively large intraoperative doses of remifentanil.\(^1\)

Sufentanil is a more potent opioid than remifentanil and its analgesic effect lasts longer. The consequence of its long action is that sufentanil is not easy to infuse during a long period of time without risk of accumulation,\(^5\) delayed recovery and postoperative respiratory depression.

Computer-assisted target-controlled infusion (TCI) has been developed to rapidly achieve and maintain the target plasma or effect-site concentrations of i.v. anaesthetics deemed appropriate by the anaesthetist. As haemodynamic values vary widely because of the degree of surgical stress, the association of boluses with a variable opioid infusion rate allows a more stable haemodynamic profile with a satisfactory anaesthetic state.\(^6\)\(^-\)\(^7\) As sufentanil has a long context-sensitive half-time (25 min after a 3-h infusion), TCI will prevent long-acting opioid-induced peroperative accumulation and will allow rapid recovery from anaesthesia.

Furthermore, TCI would target an extubation concentration associated with good analgesia without delaying tracheal extubation or causing postoperative respiratory depression. Several pharmacokinetic models have been validated to predict sufentanil concentration.\(^8\)\(^-\)\(^10\)

TCI has also been used for remifentanil. As it has a short context-sensitive half-time (3.2 (0.9) min after a 3-h infusion),\(^11\) it does not accumulate during prolonged infusion. Only one pharmacokinetic model has been developed for this agent.\(^12\)

The goals of this study were to compare remifentanil and sufentanil with respect to recovery and postoperative analgesia when given by TCI after abdominal surgery. We tested the hypothesis that postoperative analgesia procured by a fixed residual concentration of sufentanil at extubation (0.25 ng ml\(^{-1}\)) is better than TCI remifentanil and morphine i.v. given 30 min before the end of surgery.

**Methods**

After approval by the Human Ethics Committee of our hospital and after we had obtained written informed consent, 30 adult patients were included in a prospective, randomized study. Patients were scheduled for open colorectal surgery for neoplasia or inflammatory disease planned to last at least 1 h and requiring morphine for postoperative analgesia. All patients were ASA physical status class I–III.

Study exclusion criteria were: age <35 or >85 yr, ASA physical status class IV or V, history of chronic pain, regular use of analgesics or use of opioids within 12 h before surgery, chronic use of benzodiazepine or clonidine, a history of drug or alcohol abuse, a history of allergy to opioids or any other drug used in the study, contraindications to the self-administration of opioid (i.e. inability to understand the patient-controlled analgesia (PCA) system), psychiatric disorders, pregnancy, breastfeeding, the presence of hepatic, kidney or pulmonary dysfunction, and participation in another research project.

The evening before surgery, patients were instructed in the use of a 10-cm visual analogue scale (VAS) on which 0 cm represented no pain and 10 cm the worst imaginable pain. The use of a PCA system (Fresenius Vial, Brezins, France) was also explained at this time.

Patients were premedicated with hydroxyzine 1 mg kg\(^{-1}\) orally the night before surgery and 2 h before surgery. Heart rate, arterial pressure and pulse oximetry were noted before induction and repeated at regular intervals thereafter.

The anaesthetic technique was standardized and administered by the same anaesthetist (ND) throughout the study. After non-invasive monitor devices had been placed, a forearm vein was cannulated for administration of anaesthetics. Ringer’s lactate and saline solution were infused at 10 ml kg\(^{-1}\) h\(^{-1}\) in addition to fluid replacement as indicated clinically (hydroxyethyl starch or blood). Patients were preoxygenated for 3 min by mask with 100% oxygen.

Anaesthesia was induced with sufentanil or remifentanil using a TCI system and a bolus dose of propofol 2 mg kg\(^{-1}\) followed by rocuronium 0.6 mg kg\(^{-1}\) to facilitate orotracheal intubation. After tracheal intubation, the lungs were ventilated to maintain normocapnia (end-tidal carbon dioxide pressure between 4.6 and 5.8 kPa) with desflurane and nitrous oxide 50% in oxygen. An i.v. catheter was inserted in the contralateral arm. Rocuronium infusion was titrated to maintain one response at the corregator supercilli after supramaximal train-of-four stimulation at the facial nerve.\(^13\) A radial artery catheter was inserted for continuous blood pressure monitoring and blood sampling. Central temperature was recorded throughout the surgical procedure.

Opioid was infused in target effect-site mode from induction to the end of surgery using Stanpump software (January 1998; Dr Steven L. Shafer, Palo Alto, CA, USA). The pharmacokinetic sets used to calculate target effect-site concentrations of remifentanil and sufentanil were those published by Minto and colleagues\(^12\) and Gepts and colleagues\(^9\) respectively. A Pilot Anesthesy pump (Becton Dickinson, Brezins, France) was driven by a personal computer.

Randomization was by computer-generated codes maintained in sequentially numbered, opaque envelopes, which were opened before induction of general anaesthesia. Patients were divided into two groups. In one group (remifentanil group), induction of anaesthesia used remifentanil (50 µg ml\(^{-1}\)) at a target effect-site concentration of 4 ng ml\(^{-1}\) for intubation. Then the concentration was increased or decreased if inadequate anaesthesia was suspected (2–10 ng ml\(^{-1}\)). In the second group (sufentanil group), induction of anaesthesia used sufentanil (5 µg ml\(^{-1}\)) at a target effect-site concentration of 0.5 ng ml\(^{-1}\) for intubation. Then the concentration was adapted in the same
way as for remifentanil (0.2–1 ng ml\(^{-1}\)). If anaesthesia was inadequate despite the modification of the opioid concentration, the end-tidal desflurane concentration was adjusted (2–6% end-tidal concentration) in a similar fashion in the two groups.

Inadequate analgesia was defined as heart rate exceeding preinduction values by 15% and/or systolic arterial blood pressure exceeding baseline values by 20% for at least 1 min. Patient movements, coughing, weeping or sweating were also considered to be signs of inadequate anaesthesia. Hypotension, defined as a systolic arterial pressure <80 mm Hg or a mean arterial pressure <60 mm Hg, was treated by stepwise reduction in the designated study drugs. Additional i.v. fluids were given as deemed appropriate. Similarly, atropine or intermittent bolus doses of epinephrine were given as necessary to treat bradycardia or persistent hypotension.

In the remifentanil group, 30 min before the anticipated end of surgery, morphine 0.15 mg kg\(^{-1}\) was administered i.v. Remifentanil TCI infusion was maintained at an effect-site concentration of 1 ng ml\(^{-1}\) until extubation in the postanaesthesia care unit (PACU). In the sufentanil group, effect-site concentration was targeted at 0.25 ng ml\(^{-1}\) at the end of skin closure for all patients and maintained until extubation in the PACU.

After surgery, patients were transferred to the PACU. Then, residual neuromuscular block was reversed with atropine 15 µg kg\(^{-1}\) and neostigmine 40 µg kg\(^{-1}\).

After recovery of adequate spontaneous ventilation, the trachea was extubated. In the PACU, recording of vital signs was continued for 12 h. Oxygen was given via a facemask at 10 litres min\(^{-1}\) for 1 h and then at 3–4 litres min\(^{-1}\) until discharge.

Initially, pain was controlled only by titration of i.v. morphine administered by nurses who were blinded to the treatment group. Pain intensity was assessed by the patients using a VAS. The first analgesic medication was given when the VAS score reached 3 cm after extubation. In the two groups, the titration protocol consisted of repeated boluses of morphine 3 mg if the patient was ≤65 yr old, 2 mg if 65–75 yr and 1 mg if ≥75 yr. The titration was stopped if the Ramsay sedation score increased to 3 or the respiratory rate decreased to <12 b.p.m. Boluses were administered every 5 min until the VAS decreased to <4 cm. When the VAS score was <4 cm after titration, patients had access to a PCA device. The PCA device was set to deliver morphine 1 mg as an i.v. bolus with a lockout interval of 5 min; continuous infusion was not allowed. This PCA regimen was continued as long as needed in the PACU and the surgical ward.

Baseline heart rate and systolic arterial pressure were defined as the mean of the two lowest measurements recorded the day before anaesthesia. Values from all routine anaesthetic monitors were recorded at 10-min intervals during surgery.

Pulse oximetry, end-tidal carbon dioxide pressure, end-tidal desflurane, opioid concentration, train-of-four count and temperature were recorded every 10 min. Durations of anaesthesia and surgery, blood loss and total doses of remifentanil or sufentanil given in the operating room were also recorded.

As the anaesthetic report was sealed on arrival in the PACU, nurses were unaware of patients’ group assignments. The cumulative doses of morphine given by i.v. titration and by PCA at 4, 12 and 24 h were recorded. Pain scores were recorded using a VAS scale every 30 min during the first 4 h, every 60 min during the next 8 h and every 4 h during the last 12 h. The time between extubation and the first request for analgesic medication was recorded. Primary outcome was the consumption of morphine during the first 12 h after extubation.

Arterial blood samples for blood gas analysis were drawn at extubation and 120 and 240 min after extubation. Respiratory depression was defined in the PACU as a persistent respiratory rate <10 b.p.m., oxygen partial pressure <9.5 kPa or a carbon dioxide partial pressure >6 kPa.

Anaesthetic-related complications were recorded, including nausea, vomiting, pruritus, dysphoria, hallucinations, diplopia and shivering. Nausea and vomiting were treated with an i.v. bolus of metoclopramide 10 mg.

The degree of sedation was monitored using the six-point scale described by Ramsay and colleagues: 14 1=patient anxious, agitation; 2=patient quiet, watchful; 3=patient responsive to verbal commands; 4=patient somnolent and responsive to tactile stimulation; 5=patient asleep and responsive only to strong stimulation; 6=patient asleep without response.

In the two groups, arterial blood samples were drawn at extubation (target concentration of sufentanil, 0.25 ng ml\(^{-1}\)) and at the first morphine bolus titration for measurements of sufentanil plasma concentrations. Blood samples (5 ml) were centrifuged immediately in the PACU and separated plasma was frozen (−27°C) for storage until the time of analysis.

Plasma sufentanil concentrations were determined by chromatography and mass spectrometry (LCMS=liquid chromatography mass spectrometry mass spectrometry). The limit of detection was 0.02 ng ml\(^{-1}\), aptness 96.8% and accuracy 2.2% respectively.

**Statistical analysis**

Postoperative morphine consumption was used to calculate the statistical power. Reported postoperative morphine consumption varies widely. The average patient-controlled morphine consumption during the initial 24 h after laparotomy varies between 38 and 76 mg, with sds ranging from 7 to 45 mg.\(^1\) Our experience has indicated that morphine use over the first 24 h after major abdominal surgery is 40 (20) mg.

An estimate sample size indicated that 15 patients per group would give a β risk of 80% at an α level of 0.05 for
detecting a difference in morphine consumption of at least 30%. The study size was thus set prospectively to 30 patients. Results are expressed as mean (SD), range and/or 95% confidence interval (CI).

Age, weight, height, time intervals, average desflurane concentration, temperature at end of study, $P_{aO_2}$, $P_{aCO_2}$, i.v. morphine doses given by titration and PCA morphine consumption were compared between the two groups using the Mann–Whitney U-test. VAS pain scores over 12 h were analysed by analysis of variance for repeated measurements. If an interaction between two variables (postextubation time and group assignment) was found, data at different times were compared between the two groups using the Mann–Whitney U-test.

The proportion of patients not requiring supplementary postoperative morphine was evaluated with survival curves and compared with the Kaplan–Meier log-rank test. The relative frequencies of genders, ASA statuses and side-effects were compared with Fisher’s exact test or the $\chi^2$-test. A $P$ value less than 0.05 defined the statistical significance level.

For each blood sample, the percentage performance error (PE) of the predicted sufentanil plasma concentration was calculated as follows:

$$PE=\frac{\text{measured value} - \text{predicted value}}{\text{predicted value}} \times 100.$$ $PE$ is an indicator of the bias of the concentration achieved, and the absolute value of PE (|PE|) is a measure of precision (inaccuracy). The percentage median prediction error (MDPE) or median performance error reflects the bias of the TCI model. The percentage median absolute prediction error (MDAPE) or median absolute performance error indicates the inaccuracy of the TCI model.

### Results

Thirty patients were studied. Patient characteristics, the type of surgical procedure and the durations of anaesthesia and surgery were similar in the two groups (Table 1). No patient required blood transfusion.

Figure 1 summarizes sufentanil and remifentanil concentrations (mean and SD) during surgery. Times: A=10 min after tracheal intubation; B=10 min after incision; C=dissection; D=end of colectomy; E=beginning of closure; F=end of closure. The scale ratio is 10. (b) Intraoperative end-tidal desflurane concentration (mean and SD) during surgery. Times: A=10 min after tracheal intubation; B=10 min after incision; C=dissection; D=end of colectomy; E=beginning of closure; F=end of closure. There were no statistically significant differences between the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Sufentanil (n=15)</th>
<th>Remifentanil (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70 (52–83)</td>
<td>64 (47–85)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68 (15)</td>
<td>76 (12)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 (8)</td>
<td>168 (8)</td>
</tr>
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<td>Sex ratio (M, F)</td>
<td>9, 6</td>
<td>10, 5</td>
</tr>
<tr>
<td>ASA I, II, III</td>
<td>3, 9, 3</td>
<td>3, 11, 1</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
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<td>Right colectomy</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Left colectomy</td>
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<td>9</td>
</tr>
<tr>
<td>Abdominoperineal amputation</td>
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<td>1</td>
</tr>
<tr>
<td>Total colectomy</td>
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<td>2</td>
</tr>
<tr>
<td>Pathology</td>
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<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Sigmoiditis</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>278 (105)</td>
<td>293 (95)</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>223 (106)</td>
<td>236 (93)</td>
</tr>
</tbody>
</table>

Fig 1 (A) Intraoperative sufentanil and remifentanil concentrations (mean and SD) during surgery. Times: A=10 min after tracheal intubation; B=10 min after incision; C=dissection; D=end of colectomy; E=beginning of closure; F=end of closure. The scale ratio is 10. (B) Intraoperative end-tidal desflurane concentration (mean and SD) during surgery. Times: A=10 min after tracheal intubation; B=10 min after incision; C=dissection; D=end of colectomy; E=beginning of closure; F=end of closure.
during the first 2 h after tracheal extubation in the remifentanil group, and were similar in the two groups during the next 10 h. The mean VAS scores were never >4 cm in the sufentanil group during the first 12 h after surgery.

All patients in the remifentanil group and all patients but one in the sufentanil group required titration in the PACU before PCA initiation (Fig. 3).

The time between extubation and the first analgesic request in the PACU was significantly longer in the sufentanil group (55 (64) vs 11 (7) min; \( P < 0.001 \)) (Table 2).

Survival curve analysis of the first morphine administration shows that patients in the remifentanil group required morphine significantly earlier than those in the sufentanil group (\( P < 0.05 \)) (Fig. 3).

The cumulative dose of morphine given by nurses in the PACU for titration was significantly greater in the remifentanil group (20.9 (9.9) mg) than in the sufentanil group (11.4 (5.2) mg) (\( P < 0.01 \)) (Table 2).

PCA morphine consumption was significantly greater at 12 and 24 h in the remifentanil group than in the sufentanil group (12 h, 32 (19) and 19 (11) mg (95% CI −24.4, −1)); 24 h, 56 (29) and 37 (20) mg (95% CI −37.7, −0.9) respectively; \( P < 0.05 \) (Table 2).

The cumulative morphine dose used during titration and PCA was significantly greater in the remifentanil group than in the sufentanil group at 4 h (31 (13) vs 19 (7) mg (95% CI −19.9, −4.2)), 12 h (52 (24) vs 29 (12) mg (95% CI −37.7, −5.3)) and 24 h (77 (34) vs 48 (21) mg (95% CI −52.6, −4.6)) (\( P < 0.05 \)) (Fig. 4).

Mean sufentanil plasma concentration was 0.089 (0.038) ng ml\(^{-1}\) at extubation and 0.058 (0.042) ng ml\(^{-1}\) at first morphine bolus titration. Gepts’s pharmacokinetic model overestimated sufentanil concentration in all patients at extubation (predicted sufentanil concentration, 0.25 ng ml\(^{-1}\)). The MDPE and the MDAPE were −68 and 68% respectively. Furthermore, plasma concentrations were always lower when measured at the start of titration compared with the extubation time.

There was no difference in mean respiratory rate and \( \text{SpO}_2 \) at any time between the two groups. One patient in the remifentanil group experienced a respiratory rate <10 b.p.m. without desaturation under 95% and recovered rapidly.

### Table 2

<table>
<thead>
<tr>
<th>Anaesthetic characteristics, extubation time, postoperative morphine use and side-effects. Data are mean (SD) or number of patients. *These data are not compared because of the different potencies of the two compounds. ^Statistically significant difference between the two groups (( P &lt; 0.05 ))</th>
<th>Sufentanil (( n=15 ))</th>
<th>Remifentanil (( n=15 ))</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-weighted mean opioid dose^* (μg kg(^{-1}) min(^{-1}))</td>
<td>0.008 (0.003)</td>
<td>0.148 (0.053)</td>
<td></td>
</tr>
<tr>
<td>End-tidal desflurane at end of surgery (%)</td>
<td>2.8 (1.4)</td>
<td>3.0 (1.1)</td>
<td>−1.2, 0.7</td>
</tr>
<tr>
<td>Estimate peroperative blood loss (ml)</td>
<td>225 (312)</td>
<td>266 (372)</td>
<td>−299, 215</td>
</tr>
<tr>
<td>Central temperature in PACU (°C)</td>
<td>36.4 (0.5)</td>
<td>36.6 (0.6)</td>
<td>−0.5, 0.3</td>
</tr>
<tr>
<td>Extubation time (min)</td>
<td>13 (6)</td>
<td>14 (6)</td>
<td>−6.3, 3.3</td>
</tr>
<tr>
<td>Time to first morphine titration (min)</td>
<td>55 (64)</td>
<td>11 (7)^*</td>
<td>10.1, 78.01</td>
</tr>
<tr>
<td>Morphine given by i.v. titration in PACU (mg)</td>
<td>11.4 (5.2)</td>
<td>20.9 (9.9)^*</td>
<td>−15.7, −3.5</td>
</tr>
<tr>
<td>Cumulative 24-h postoperative PCA morphine consumption (mg)</td>
<td>37 (20)</td>
<td>56 (29)^*</td>
<td>−37.7, −0.9</td>
</tr>
<tr>
<td>Postoperative nausea, vomiting (no. of patients)</td>
<td>7, 1</td>
<td>6, 1</td>
<td></td>
</tr>
<tr>
<td>Ramsay score 30 min after extubation</td>
<td>2.4 (1.1)</td>
<td>1.7 (0.8)</td>
<td>−0.06, 1.4</td>
</tr>
<tr>
<td>Ramsay score 6 h after extubation</td>
<td>2.5 (0.7)</td>
<td>2.53 (0.8)</td>
<td>−0.7, 0.5</td>
</tr>
<tr>
<td>Ramsay score 12 h after extubation</td>
<td>2.8 (1.1)</td>
<td>2.7 (0.9)</td>
<td>−0.7, 0.8</td>
</tr>
</tbody>
</table>

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**Fig 2** VAS pain scores (0–10 cm) in the two groups during the first 12 h after tracheal extubation. Values are mean and sd. Asterisks indicate statistically significant differences between the two groups (\( P < 0.05 \)).

**Fig 3** Cumulative survival curves for patients who did not request additional morphine injection after extubation. One patient in the sufentanil group did not require morphine by titration. The two groups differed significantly (\( P < 0.05 \), log-rank test).
without any specific treatment. $P_{a\text{CO}_2}$ was significantly higher in remifentanil group at 2 h (6.2 (0.7) vs 5.6 (0.8) kPa (95% CI −1.2, −0.02)) and 4 h (6.1 (1.0) vs 5.4 (0.8) kPa (95% CI −1.4, 0)) after extubation ($P<0.05$).

As patients in the two groups received postoperative oxygen, $P_{a\text{O}_2}$ was constantly >10 kPa at 0, 2 and 4 h (sufentanil group, 21 (10), 15 (4) and 15 (3) kPa respectively; remifentanil group, 20 (9), 14 (5) and 14 (3) kPa).

The sedation score did not differ between the two groups during the 12 h after extubation (Table 2). Nausea and vomiting were the most prevalent adverse events. There was no significant difference between the two groups (Table 2).

**Discussion**

This prospective, randomized study confirmed our hypothesis that peroperative sufentanil TCI is more effective than remifentanil TCI followed by morphine in the management of postoperative pain after major abdominal surgery. Consequently, the first administration of morphine occurred earlier in the remifentanil group patients. The total titration morphine dose and cumulative PCA morphine use over the first 24 h were greater in the remifentanil group. Despite the increased dose of morphine in the remifentanil group, the pain score was higher in this group during the first 2 h after extubation.

This study was not designed in a double-blind fashion for several reasons. First, when using Stanpump software it was not possible to hide the computer screen. Secondly, as the pharmacokinetic and pharmacodynamic profiles of remifentanil and sufentanil are so different, the infusion rate of these agents during the procedure indicates the agent used. Thirdly, safety was enhanced when the physician in charge of the patient knew which agent was infused. Finally, as the medical staff involved in postoperative pain evaluation were blinded, our results were not affected by the lack of preoperative blinding.

Pain appears rapidly at the end of remifentanil administration, particularly after painful surgery, because remifentanil is a short-acting opioid. Its context-sensitive half-time is constant whatever the duration of infusion (4–6 min). In contrast, the context-sensitive half-time of sufentanil increases with the duration of constant-rate infusion. From 20 min after 100 min of constant-rate infusion, it increases to 60 min after 600 min of infusion. This pharmacokinetic characteristic explains the residual analgesia that exists after using sufentanil.

Thus, an effective analgesic protocol needs to be established before stopping remifentanil infusion to control postoperative pain. A number of studies have investigated this issue. Different options have been proposed: regional analgesia, maintenance of continuous remifentanil infusion in the PACU at a rate as low as 0.1 $\mu$g $kg^{-1}$ min$^{-1}$ or a peroperative bolus of morphine 0.15 $mg$ $kg^{-1}$ given 30 min before the end of surgery, to provide adequate pain relief with minimal risk of respiratory depression. Increasing the morphine bolus dose to 0.20 or 0.25 $mg$ $kg^{-1}$ improved the quality of analgesia but also increased respiratory depression. However, whatever the dose of morphine used, 50% of patients suffered from postoperative pain with a VAS score >3 cm. Our results obtained in the remifentanil group are in agreement with the results of these previous studies.

The large postoperative morphine consumption during the first 24 h after remifentanil administration could be due to acute opioid tolerance. Acute tolerance occurs rapidly when using a short-acting opioid such as remifentanil, and is enhanced when the total dose administered during the surgical procedure is increased. In our study, patients required a remifentanil concentration >10 times the
sufentanil concentration; the potency ratio between the two opioids is close to 10.

This remifentanil overconsumption was not associated with a decrease in end-tidal desflurane concentration. The most likely explanation for the greater morphine requirement in the remifentanil group is the development of acute opioid tolerance. However, in our study the remifentanil infusion rate (0.15 μg kg⁻¹ min⁻¹) was lower than that in the study of Guignard and colleagues (0.30 μg kg⁻¹ min⁻¹). However, it has been documented that acute opioid tolerance may be present even after a low remifentanil infusion rate (0.1 μg kg⁻¹ min⁻¹) when the infusion duration is longer than 90 min.²¹ ²²

After using sufentanil during major surgery, transition analgesia seems easier to achieve. To date, intraoperative non-opioid analgesics (propacetamol, non-steroidal anti-inflammatory drugs, tramadol or nefopam, local infiltration) are usually proposed because several studies have demonstrated their effectiveness.²³ ²⁴

Using sufentanil TCI, the target plasma concentration required to reduce pain relief without respiratory depression is not well defined. Previous studies have already determined the sufentanil plasma concentration needed for postoperative analgesia. Using sufentanil PCA after major gynaecological surgery, Lehmann and colleagues²⁵ demonstrated that the effective plasma concentration to achieve satisfactory pain relief was 0.086 ng ml⁻¹. After renal transplantation, analgesia was achieved with a sufentanil plasma concentration ranging from 0.1 to 0.15 ng ml⁻¹.²⁶ Three studies have determined the plasma concentration at which respiratory depression is prevented (from 0.21 to 0.25 ng ml⁻¹), but the authors did not study its effect on postoperative pain.²⁷–²⁹ Thus, we chose 0.25 ng ml⁻¹ as the target concentration at the time of extubation. In our study, the mean measured plasma concentration at this time was approximately 0.09 ng ml⁻¹. Our data confirm that this target concentration allowed safe extubation and adequate initial pain relief.

Recovery of anaesthesia may be delayed for several reasons: residual effect of the anaesthetic agent; residual paralysis; hypothermia; or opioid-induced respiratory depression. Our study protocol was designed to avoid three of these factors.

Desflurane was used to maintain anaesthesia because several studies have shown that patients receiving desflurane showed more rapid emergence and could be extubated earlier than when isoflurane or propofol was given in lengthy procedures.³⁰ ³¹ All patients in both groups had a central temperature >35.5°C on arrival in the PACU. Residual neuromuscular block was reversed in all patients in the PACU with neostigmine and atropine. As the residual effect of sufentanil is prolonged compared with that of remifentanil, we could expect that recovery in patients receiving sufentanil occurs later than in patients receiving remifentanil. However, our data showed that extubation time was comparable between the two groups. This could be explained by the use of TCI to infuse opioid.

Different sufentanil pharmacokinetic models are available with Stanpump software. We chose Gepts’s model instead of Hudson or Bovill’s for several reasons: the study of Gepts included the largest number of patients, sufentanil concentrations were determined until 48 h, optimizing the determination of the pharmacokinetic variables, and precision and bias were 20.7 and ±10% respectively in a concentration range from 0.2 to 1 ng ml⁻¹.³² Hudson determined plasma sufentanil concentrations only for 24 h, and thus the steady-state distribution volume was overestimated compared with the results of Gepts. Furthermore, the performance of Hudson’s model (precision=130%, bias=+116%) was worse than that of Gepts’s model.³³ Bovill determined plasma sufentanil concentrations only over 8 h and the steady-state distribution volume as the elimination half-life was underestimated. No study has validated this model clinically.

However, we were unable to confirm the predictability of the Gepts model. At a fixed target effect-site concentration, the kinetic analysis showed precision and bias equal to 68 and –68% respectively. Thus, the model overestimated sufentanil concentrations for all patients.

In summary, our findings suggest that sufentanil infused in TCI mode (target concentration at extubation: 0.25 ng ml⁻¹) is more effective than the association remifentanil–morphine (0.15 mg kg⁻¹) during the postoperative care after major abdominal surgery without compromising recovery.

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