Ketoprofen for pain after hip and knee arthroplasty

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SUMMARY
In a double-blind, randomized study, we have compared the effects of i.v. ketoprofen 200 mg followed by 12.5 mg h⁻¹ over 13 h, with those of extradural morphine 4 mg in 32 patients after hip and knee arthroplasty. A visual analogue scale was used to score pain before analgesic administration (first complaint after operation), 1 h after and every 2 h subsequently. Pain reduction 1 h after the start of analgesia was mean 44% (SEM 17%) in the extradural morphine group and 54% (9%) in the ketoprofen group (ns). There were no significant differences between groups in pain scores, pain reduction and additional analgesia requirement (i.v. paracetamol). Naloxone 5 μg kg⁻¹ h⁻¹ was required for hypercapnia exceeding 6.0 kPa in three patients in the extradural morphine group (vs none in the ketoprofen group; ns). There were no differences between groups in side effects, except for urinary retention, which was more frequent in the extradural morphine group (P < 0.05). As there were few differences between i.v. ketoprofen and extradural morphine, we conclude that ketoprofen may be an efficient alternative to extradural morphine after hip and knee arthroplasty. (Br. J. Anaesth. 1994; 72: 383-387)

KEY WORDS

In recent years, non-steroidal anti-inflammatory drugs (NSAID) have become popular for relieving postoperative pain after minor [1, 2] or day-case [3, 4] orthopaedic surgery. In more painful orthopaedic procedures, NSAID have become found to reduce pain intensity, opioid requirements, or both, in comparison with placebo [5-9]. After major orthopaedic surgery, comparison with i.m. opioid administration has provided information on the analgesic efficacy of NSAID [10-13] but the intermittent use of i.m. opioids in these studies is less than ideal [14]. NSAID are usually considered as valuable adjuvant drugs in pain treatment [15] and their use as sole analgesic agents after major surgery is questionable. As NSAID do not alter ventilation [16, 17], their use has the advantage of avoiding the respiratory depression induced by opioids.

Ketoprofen is a NSAID belonging to the group of substituted 2-phenylpropionic acids. It acts by inhibition of cyclo-oxygenase, leading to a reduction in prostaglandin-mediated sensitization of the nociceptors to mechanical or chemical stimulation at the site of surgical trauma [18]. The inhibitory effect of ketoprofen on prostaglandin synthesis occurs at small concentrations of 2 μg litre⁻¹ [19]. These plasma concentrations are usually exceeded with standard therapeutic doses (10 μg ml⁻¹ for an oral dose of 100 mg) [19].

This double-blind, randomized study was designed to determine if i.v. ketoprofen has significant analgesic effects which would make it an alternative to opioids during the first hours after operation after knee and hip arthroplasty. The potency and side effects of i.v. ketoprofen were compared with those of extradural morphine, which exerts powerful analgesia both at rest [20] and with mobilization [21] after orthopaedic surgery.

PATIENTS AND METHODS
This study was approved by the Institutional Human Investigation Committee. Informed consent was obtained from 32 ASA I–II patients (aged 44–83 yr) recovering from knee (n = 16) and hip (n = 16) arthroplasty. Patients with preoperative PaCO₂ values exceeding 5.6 kPa and with increased serum creatinine concentration (>120 μmol litre⁻¹) were excluded, as were those with a history of asthma, drug allergy, sensitivity to opioids or anti-inflammatory drugs, gastrointestinal ulceration or dyspepsia. Patients requiring specific preoperative prophylaxis against deep-vein thrombosis were also excluded. No patients were receiving heparin (CNW or HNW) before operation. Treatment with short-acting NSAID before operation was continued on the evening before operation. Those taking long-acting NSAID were excluded.

After premedication with diazepam 0.2 mg kg⁻¹, an extradural catheter was inserted at L4–5 and 2 % plain lignocaine 7 ml. General anaesthesia was induced with thiopentone 5 mg kg⁻¹, fentanyl 3 μg kg⁻¹ and vecuronium 0.1 mg kg⁻¹ to facilitate tracheal intubation, and maintained with 0.5 MAC of isoflurane and nitrous oxide in oxygen (FiO₂ =...
Patients were admitted to the intensive care unit and before beginning the study, we ensured that patients had recovered fully from the extradural block by use of pinprick and the Bromage scale [22]. We considered recovery complete when no fade in tactile sensation could be discerned and when patients moved their lower limbs freely (grade 0 on the Bromage scale). The study began at the first complaint of pain (T0). At this time, all patients were fully conscious and breathing air spontaneously (FIO₂ = 0.21). The times which elapsed between induction of anaesthesia and T0 and the end of surgery and T0 were noted.

At T0, each patient rated pain on a visual analogue scale (VAS) graded from 0 (no pain) to 100 mm (maximum pain). Patients were then allocated randomly to receive, in a double-blind design, either an extradural injection of morphine 4 mg in isotonic saline 8 ml (extradural morphine group; n = 16) or two consecutive i.v. infusions of ketoprofen (Profénid injectable, Lab. Spécia, France) 200 mg during the first 30 min and then 12.5 mg h⁻¹ over 13 h, that is a total dose of 365 mg (ketoprofen group; n = 16). This regimen of two consecutive infusions of ketoprofen was obtained from pharmacokinetic data [23]. Doses were selected according to those usually administered by the parenteral route for postoperative analgesia [12, 24] and were nearly similar to those recommended by the Ministère de la Santé Publique in France (daily dose of 300 mg). Two consecutive i.v. infusions of saline solution of similar volume and infusion rate were administered to patients receiving extradural morphine. Conversely, in the ketoprofen group, isotonic saline 8 ml was injected through the extradural catheter. The randomization table was adjusted according to the type of surgery, that is each group included eight patients undergoing hip arthroplasty and eight undergoing knee arthroplasty. Ketoprofen or saline infusions were administered via a central venous catheter, used only for this purpose.

Pain scores were assessed at rest by VAS 1 h (T1) after the start of the analgesic drug regimen and every 2 h (T3, T5, T7, T9, T11, T13). Analgesic effects were assessed in each patient and at each time by calculating the percentage reduction in pain according to the following formula [25]: (VAS score at T0 – VAS score obtained at a specific time)/VAS score at T0. From T1, additional analgesia with paracetamol 500 mg i.v. (propacetamol HC1, Propafalgan, Lab. UPSA, France) was available on demand of use of conventional analgesic treatment. The extradural morphine group was considered to have recovered fully from the extradural block by use of pinprick and the Bromage scale [22].

Patients were observed closely for evidence of side effects, including ventilatory frequency less than 10 b.p.m., SpO₂ less than 90 % for 20 s and episodes of vomiting, pruritus, skin reaction, dizziness, epigastric discomfort and urinary retention. Urinary retention was defined by the following two criteria: lack of micturition during the first 6 h and a urinary volume greater than 300 ml after the bladder was catheterized. An arterial blood sample was obtained for blood-gas analysis (ABL 300 Acid Base Analyser, Radiometer) in all patients at T6 or when episodes of urinary retention occurred. A continuous infusion of naloxone was given in doses of 5 µg kg⁻¹ h⁻¹ for 4 h when PaCO₂ exceeded 6.0 kPa. As naloxone 5 µg kg⁻¹ h⁻¹ does not antagonize the analgesia produced by extradural morphine [26], pain assessments during naloxone infusions were not deleted from analysis. Blood loss was assessed from the volume of blood collected in the suction drains from T0 to T13. Postoperative management included a crystalloid infusion (65–80 ml h⁻¹) and replacement of blood loss with 50 % volume of red blood cells and 50 % volume of polygeline (Plasmion, Roger Bellon).

Venous blood samples were obtained for measurement of plasma ketoprofen concentrations in heparin tubes before and during infusions, at the end of the first infusion, and at T1, T3, T6, T9 and T12. Blood samples were centrifuged at 3000 rpm and plasma frozen at −30 °C before analysis. Plasma concentration of ketoprofen was measured using high pressure liquid chromatography with a limit of detection of 20 ng ml⁻¹ [27]. The intra-assay coefficients of variation were 5.3, 1.7 and 2.1 % for concentrations of 20, 50 and 100 ng ml⁻¹, respectively. The inter-assay coefficients of variation were 7.9, 1.9 and 3.7 % for concentrations of 20, 50 and 100 ng ml⁻¹, respectively.

Results are expressed as mean (SEM). Patient data, times elapsed between the onset of analgesia and T0, bleeding and blood-gas data at T6 were compared using Student’s t tests. The Mann–Whitney test was used for intergroup comparison of analgesic effects. The number of patients who received 0, 1, 2 or 3 paracetamol injections, the number of paracetamol injections, and the number of patients with ventilatory frequency less than 10 b.p.m., vomiting, pruritus, skin reaction, dizziness, epigastric discomfort and urinary retention were compared using chi-square tests. Changes in plasma concentrations of ketoprofen were compared by one-way analysis of variance for repeated measurements, followed by Schéffe’s test when the F test was significant. Statistical significance was assumed for P < 0.05.
TABLE I. Patient data (mean (SEM or range) or number). There were no significant differences between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Morphine group (n = 16)</th>
<th>Ketoprofen group (n = 16)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>65 (42-78)</td>
<td>68 (44-83)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 (3)</td>
<td>64 (4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161 (3)</td>
<td>159 (2)</td>
</tr>
<tr>
<td>Gender ratio (M/F)</td>
<td>6/10</td>
<td>4/12</td>
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<td>Patients on previous NSAID</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Time between induction and T0 (min)</td>
<td>259 (33)</td>
<td>267 (35)</td>
</tr>
<tr>
<td>Time between end of surgery and T0 (min)</td>
<td>143 (16)</td>
<td>121 (15)</td>
</tr>
</tbody>
</table>

The greatest value of the standardized normal deviate was obtained at T7. Pain reduction was similar in both groups (fig. 1). The percentage reduction in pain at T1 was 44 (17) in the extradural morphine group and 54 (9) in the ketoprofen group (ns). The percentage of patients who experienced satisfactory analgesia, that is who did not require supplementary paracetamol, was 69% in both groups. There were no significant differences in the number of patients who received 0, 1, 2 or 3 paracetamol injections (fig. 2). During the first 13 h after starting the analgesic regimens, patients in the extradural morphine group received a dose of 188 (77) mg of paracetamol, compared with 250 (120) mg in the ketoprofen group (ns).

Three cases of hypercapnia were noted in the oldest patients in the extradural morphine group (vs none in the ketoprofen group; ns). In each case, hypercapnia was diagnosed because one or several episodes of \( \text{SpO}_2 \) less than 90% prompted us to measure arterial blood-gas tensions (table II). Naloxone was prescribed in each case. Two patients had increased pain scores during naloxone infusion. No patient required artificial ventilation. At T6, no differences were present between the two groups in arterial blood-gas tensions: \( P_{\text{O}_2} \) 11.3 (0.7) kPa, \( P_{\text{CO}_2} \) 5.1 (0.1) kPa and pH 7.44 (0.07) in the ketoprofen group; and \( P_{\text{O}_2} \) 12.4 (1.3) kPa, \( P_{\text{CO}_2} \) 5.3 (0.3) kPa and pH 7.42 (0.20) in the extradural morphine group (ns).

The number of patients with vomiting, pruritus, skin reaction, dizziness, epigastric discomfort or urinary retention are shown in figure 3. Except for urinary retention, there were no significant differences between the groups. There were no differences in blood loss (cumulative volume 902 (120) ml in the extradural morphine group and 1044 (99) ml in the ketoprofen group). No increases in serum creatinine concentration were observed after

<table>
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<th>Patient No. 1</th>
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<th>Patient No. 3</th>
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<tr>
<td>Group</td>
<td>Morphine</td>
<td>Morphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>78</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Time between morphine injection and respiratory depression (min)</td>
<td>420</td>
<td>180</td>
<td>540</td>
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<td>Mental status</td>
<td>Disturbed</td>
<td>Sedated</td>
<td>Sedated</td>
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<tr>
<td>( P_{\text{CO}_2} ) (kPa) Before naloxone</td>
<td>6.6</td>
<td>6.4</td>
<td>6.4</td>
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<tr>
<td>( P_{\text{CO}_2} ) During naloxone</td>
<td>5.7</td>
<td>5.4</td>
<td>4.8</td>
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<tr>
<td>VAS (mm)</td>
<td>0</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>No. paracetamol doses during naloxone</td>
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<td>0</td>
<td>1</td>
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</table>

FIG. 1. Pain scores on a 100-mm visual analogue scale and pain reduction (VAS score at T0 - VAS score obtained at a specific time)/VAS score at T0, in the ketoprofen (●) and extradural morphine (○) groups. There are no significant differences between groups.

FIG. 2. Number of patients who received 0, 1, 2 or 3 injections of paracetamol in the ketoprofen (●) and extradural morphine (○) groups. There are no statistically significant differences between groups.
operation; in the extradural morphine group it varied from 72 (4) \(\mu\)mol litre\(^{-1}\) before operation to 75 (6) \(\mu\)mol litre\(^{-1}\) 12 h after surgery, and then the ketoprofen group from 80 (5) to 74 (5) \(\mu\)mol litre\(^{-1}\).

Plasma concentrations of ketoprofen were 24.6 (1.9) \(\mu\)g ml\(^{-1}\) at the end of the first infusion (200 mg during 30 min) and decreased significantly to 12.5 (1.5) \(\mu\)g ml\(^{-1}\) at T1 and 4.8 (0.7) \(\mu\)g ml\(^{-1}\) at T3. Plasma concentrations of ketoprofen then stabilized from 4.8 (0.7) \(\mu\)g ml\(^{-1}\) at T3, 3.0 (0.5) \(\mu\)g ml\(^{-1}\) at T6 to 2.2 (0.1) \(\mu\)g ml\(^{-1}\) at T12.

### DISCUSSION

We have compared the effects of ketoprofen 200 mg i.v. followed by a continuous infusion of 12.5 mg h\(^{-1}\) on postoperative pain relief with extradural morphine 4 mg, which we considered as the reference standard for analgesia after surgery on the lower extremities [26, 28]. As onset of action is more than 45 min with extradural morphine [28] and as ketoprofen acts rapidly, producing analgesia 10 min after an i.v. 100-mg bolus dose [29], we did not record pain scores until the first hour (T1).

We have found that both i.v. infusion of ketoprofen and extradural morphine produced reduction in pain of approximately 50% at 1 h and before additional analgesia with paracetamol was available. In both groups, pain reduction exceeded 80% in the later course of the study in the presence of low-dose paracetamol.

Mean scores were relatively low before our study commenced. This finding may be attributed partly to the conditions under which pain scores were obtained, that is at rest and not during stimulation. It may be attributed also to the duration of pain in our population. Patients undergoing hip and knee arthroplasty are usually patients with chronic arthritis, taking NSAID, who have lived for some time with a variable degree of daily pain; they often believe that no effective solutions are available to relieve the pain. We defined the effects of ketoprofen alone in our postoperative patients by ensuring that recovery from the effects of drugs used during operation was complete before the start of the study, and by administering i.v. ketoprofen or extradural morphine as soon as analgesia was requested. However, this end-point varied markedly according to each patient's threshold for pain. The method did not preclude the possibility that intraoperative analgesia may have persisted beyond this subjective end-point. The lack of statistical differences does not imply that there were no real differences in pain relief between our two groups; this may reflect the small number of patients in the study.

At the end of the 200-mg infusion, the plasma concentration of ketoprofen was 24.6 \(\mu\)g ml\(^{-1}\), which may be considered safe [30]. At steady state, plasma concentrations were approximately 4 \(\mu\)g ml\(^{-1}\). According to Hurault de Ligny and colleagues [23], these concentrations result in 70% reduction in the pain of acute renal colic. As the effects of ketoprofen are dependent on plasma concentrations [31], greater analgesia may have been obtained in our study if larger doses of ketoprofen had been given. However, the risk of undesirable side effects would also have increased. Recent warnings about ketorolac and renal function and bleeding [32] apply equally to ketoprofen.

In this study, the use of extradural morphine resulted in a large proportion of patients requiring bladder catheterization, with its potential risk of sepsis. It also exposed patients to the risk of respiratory depression, requiring administration of naloxone in three patients, but this treatment may induce or facilitate the occurrence of breakthrough pain. If the absence of request for paracetamol during the 13-h study is considered as the index of analgesia, 69% of our patients experienced good pain relief in both the i.v. ketoprofen and also the extradural morphine groups. These results suggest therefore that in most patients ketoprofen was an effective alternative to opioids after knee and hip arthroplasty and decreased the risk of postoperative respiratory depression. However, our study did not fully evaluate the potential side effects of ketoprofen, as sophisticated assessments of renal physiology or serial endoscopy would have been unreasonable in these patients undergoing hip or knee replacement.

### REFERENCES


I.V. KETOPROFEN VS EXTRADURAL MORPHINE


