Comparative study of analgesic efficacy and morphine-sparing effect of intramuscular dexketoprofen trometamol with ketoprofen or placebo after major orthopaedic surgery

M. H. Hanna,[1] K. M. Elliott[1], M. E. Stuart-Taylor,[2] D. R. Roberts,[3] D. Buggy[4] & G. J. Arthurs[5]

[1]*King's College Hospital, Pain Research Unit, London,* [2]*Southampton General Hospital, Anaesthetic Department, Southampton,* [3]*Freeman Hospital, Anaesthetic Department, Newcastle,* [4]*Leicester General Hospital, Anaesthetic Department, Leicester and* [5]*Wrexham Malor Hospital, Anaesthetic Department, Wrexham, UK*

Aims Multimodal analgesia is thought to produce balanced and effective postoperative pain control. A combined therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates could result in synergistic analgesia by acting through different mechanisms. Currently there are very few parenterally administered NSAIDs suitable for the immediate postoperative period. Therefore, this study was undertaken to assess the analgesic efficacy, relative potency, and safety of parenteral dexketoprofen trometamol following major orthopaedic surgery.

Methods One hundred and seventy-two patients elected for prosthetic surgery, were randomized to receive two intramuscular injections (12 hourly) of either dexketoprofen 50 mg, ketoprofen 100 mg or placebo in a double-blind fashion. Postoperatively, the patient's pain was stabilized, then they were connected to a patient-controlled analgesia system (PCA) of morphine for 24 h (1 mg with 5 min lockout).

Results The mean cumulative amount of morphine (CAM) used was of 39 mg in the dexketoprofen group and 45 mg in the ketoprofen group *vs* 64 mg in the placebo group. (Reduction in morphine use was approximately one-third between the active compounds compared with placebo (adjusted mean difference of −25 mg between dexketoprofen and placebo and −23 mg between ketoprofen and placebo. These differences were statistically significant: $P \leq 0.0003$; 95% CI −35, −14. Pain-intensity scores were consistently lower with the active compounds, the lowest corresponded to the dexketoprofen-treated patients. Regarding sedation, there were statistically significant differences between the two active compounds and placebo only at the 2nd and 13th hours. Wound bleeding was specifically measured with no statistically significant differences found between all the groups.

Conclusions Intramuscular administration of dexketoprofen trometamol 50 mg has good analgesic efficacy both in terms of opioid-sparing effect and control of pain after major orthopaedic surgery.

Keywords: analgesia, dexketoprofen, morphine, nonsteroidal anti-inflammatory, patient-controlled analgesia, postoperative pain

Introduction

Clearer understanding of pain mechanisms is now viewed as a complex interplay between excitatory and inhibitory systems at different levels of the central nervous system (CNS) which converge on the spinal cord [1]. One result of understanding these processes is that targeting more than one site may produce enhanced analgesia, reduced side-effects and an improved outcome. It is now well accepted that in a significant number of major surgical cases, pain is best controlled with multimodal or balanced analgesia [2].

Opioids are considered the mainstay for moderate to severe postsurgical pain management [3]. Their utilization combined with nonsteroidal anti-inflammatory drugs

Correspondence: Dr M. H. Hanna, King's College Hospital, Pain Research Unit, London, SE5 9RS UK. E-mail: magdi.hanna@kcl.ac.uk

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(NSAIDs), results in additive or synergistic analgesia by acting through different mechanisms [4]. Some clinical trials in the setting of major surgery have suggested that these effects can produce an opioid-sparing effect and enhance the quality of postoperative analgesia [5, 6]. Other beneficial effects are earlier mobilization and hospital discharge for the patient [6]. Dexketoprofen trometamol is a newly developed NSAID belonging to the aryl-propionic acid group. It is a water-soluble salt of the S(+)-enantiomer of the racemic compound ketoprofen [7]. It has been widely demonstrated in preclinical studies that the anti-inflammatory and analgesic effect of ketoprofen is due entirely to the S(+)-enantiomer (dexketoprofen), while the R(–)-enantiomer is devoid of such activity [7]. Animal models of inflammation and analgesia have shown that dexketoprofen is at least twice as potent as the parent compound ketoprofen [8]. In humans, the analgesic efficacy of dexketoprofen trometamol using an oral formulation has been demonstrated in painful conditions such as dental pain and dysmenorrhea [9, 10]. Currently, there are few available NSAIDs that can be used parenterally, which is the preferable route of administration in the immediate postoperative period [11].

The present study was conducted to compare the analgesic efficacy and safety of intramuscular dexketoprofen trometamol 50 mg with that of intramuscular ketoprofen 100 mg and placebo, following major orthopaedic surgery (hip/knee replacement).

Methods

Study design and medications

This was a multicentre, double-blind, randomized study of three parallel treatment groups. Patients were randomized to receive two intramuscular injections of dexketoprofen trometamol 50 mg, ketoprofen 100 mg or placebo. The first injection was administered at the end of surgery, defined as the time of the first closing stitch, and the second injection 12 h later. All study medication was administered as a 2-ml solution. The active comparator used was ketoprofen, commercial formulation Oruvail®; Rhone-Poulenc Rorer, UK. In order to maintain double-blind conditions, study treatments were prepared and administered by personnel not involved in patient evaluation.

Surgery was performed under standardized general anaesthesia. The anaesthetics and other intra-operative medications used during surgery were to be short acting and, if possible, restricted to one or more of the following: propofol, fentanyl, alfentanil, atracurium, vecuronium, rocuronium, oxygen (33–35%) with nitrous oxide, isoflurane. A regional blockade was not permitted.

Following recovery from anaesthesia, patients could receive titration doses of 2–5 mg of i.v. morphine as required until their pain was stabilized, at the same time patients were connected to a patient-controlled analgesia (PCA) system with i.v. morphine.

Anti-emetics were to be administered, as appropriate, but where possible these were to be restricted to cyclizine, ondansetron or droperidol.

Because of a possible interference with the therapeutic response to the study medication, the use of the following treatments during the course of the study was not allowed, i.e. use or need of any of the following concomitant medications automaticallyled to exclusion of the patient from the study:

- other analgesics or anti-inflammatory drugs except morphine given as loading dose and via PCA
- anaesthetics except for those used as part of the premedication for anaesthesia or anaesthesia itself
- more than 300 mg acetylsalicylic acid per 24 h
- lithium salts
- systemic glucocorticoids
- methotrexate
- MAO inhibitors
- sedatives, other than short-acting
- antiepileptics
- cyclosporin.

The total amount of blood in the wound drainage was measured at set time points. Doses of morphine to be given by PCA were of 1 mg with a 5-min lockout. Routine concomitant medications were allowed as per clinical practice (i.e. antibiotics).

Efficacy assessments

The primary endpoint was the total cumulative amount of morphine (CAM) considering loading plus PCA doses during the whole study period, i.e. 24 h after the first dose of the study medication. The amount of morphine used via PCA was automatically recorded at separate time intervals.

Other parameters related to the use of morphine were considered as secondary variables: amount of morphine administered as a loading dose (CAM 1) and via PCA over two 12-h intervals: from $t = 1$ h to $t = 12$ h (CAM 2) and from $t = 12$ to $t = 24$ h (CAM 3), time from the first dose of the study medication to the loading (titration) dose, and time to first use of PCA. Additional secondary variables were the scoring of pain intensity and quality of sleep.

Pain intensity was measured using a 10-cm visual analogue scale (VAS) marked 'no pain at all' on the left extreme and 'intolerable pain' on the right, and using a verbal scale ranging from 0 to 3 (0 = none, 1 = mild, 2

= moderate, 3 = severe). Measurements were performed at different time points during study conduction, immediately prior to the loading dose of morphine immediately prior to the second dose of study medication, and at prospectively defined intervals (2, 4, 6 and 9 h after the first dose, and 1, 9 and 12 h after the second dose).

The quality of sleep was assessed by means of a 5-point ordinal scale ('excellent', 'good', 'minor discomfort', 'major discomfort' and 'hardly slept at all') at 12 h after the second dose of study medication, following the night's rest after the day of surgery.

Safety and tolerability assessments

Safety and tolerability were assessed by means of the following parameters: 1) adverse event (AEs) recording (observed by the investigator or spontaneously reported by patients), 2) sedation scoring (0 = fully awake, 1 = mildly sedated, 2 = heavily sedated, 3 = asleep), measured at the same time points as for the VAS assessment, 3) pain and/or discomfort on the injection site, 4) amount of blood loss from wound drains and 5) laboratory tests (standard haematology and biochemistry baseline and post-treatment).

Statistical methods

Mean morphine usage of around 40 mg in the active treatment groups and 60 mg (s.d. ± 30 mg) in the placebo group was assumed based on the results of previous studies [12–14]. A sample size of 45 patients per group was required to detect a clinically relevant 30% difference in morphine use between active treatments and placebo with a significance level of 5% and power of 80%.

Safety was analysed for all randomized patients who received at least one dose of study drug.

Full-analysis population for efficacy comprised all patients with at least one dose of study drug and valid measurements for morphine usage at least 1 h after surgery.

Differences among groups for the primary endpoint were tested using an analysis of variance (ANOVA). Secondary endpoints were analysed using an ANOVA or Kruskall-Wallis, Chi-square, or McNemar test as appropriate.

As there were several possible treatment comparisons, the global significance level had to be limited to 5% by an adequate testing procedure for multiple testing. Therefore in a first step, the active treatment groups were to be compared with the placebo group. *P* values were to be corrected by the Bonferroni–Hochberg procedure. Only if these treatment differences were significant, in a second step, the active treatment groups were to be compared by separate *t*-tests and *P* values were to be adjusted again by using the Bonferroni–Hochberg procedure. This stepwise and adjusted-procedure limits the probability of a false rejection of at least one hypothesis to 5%.

For the statistical hypothesis testing, the type one error level (α) was set to 0.05 and 95% confidence intervals were provided.

Patients

One hundred and seventy-two (male and female) patients aged from 18 to 75 years with ASA physical status grade I-II were included at 15 active centres in the UK. All patients were undergoing elective surgery under general anaesthesia for hip or knee replacement.

Inclusion and exclusion criteria are shown in Table 1.

Patients were given written and oral information about the study, and informed consent was obtained prior to their inclusion. The trial was approved by the Ethics Committees of all participating centres and conducted in accordance with good clinical practice guidelines (CPMP/ICH/135/95) [15].

Results

One hundred and seventy-two patients were randomized and received the first dose of study treatment. The full-analysis population for efficacy comprised 168 patients (58 in the dexketoprofen group, 56 in the ketoprofen group and 54 in the placebo group). Four patients were not included because they lacked minimum valid measurement for morphine usage.

Thirty-six patients were considered as treatment-compliance withdrawals and removed from the study, for reasons such as on the patient's request or, on the investigator's decision (i.e. condition of patient), due to a lack of co-operation ($n = 22$), adverse events ($n = 4$), treatment failure ($n = 3$), therapy success ($n = 6$) or other reasons ($n = 1$). Cases were labelled as 'therapy success' if the patient refused the second dose of study medication because of being pain-free at 12 h. (It was deemed unethical to give patients who were pain-free at 12 h a second injection).

For statistical analysis purposes, the last cumulative dose prior to withdrawal was carried forward to replace the missing cumulative amounts of morphine usage at $t = 24$ h.

Details on patient disposition are displayed in Figure 1. Demographic baseline data are enclosed in Table 2. No statistically significant differences were found between the three treatment groups regarding these variables. No notable differences were seen with regard to pre- or concomitant medication, including anticoagulants.

Table 1 Inclusion/exclusion criteria.

Inclusion criteria

Male or female patients over 18 years & up to 75 years of age
Inability to remain at the hospital for the duration of the study
Hip or knee
Grade I-II physical status as defined by the American Society of replacement surgery under general anaesthesia (24 h)
Anaesthesiologists [24]Grade I-II physical status as defined by the American Society of Morphine not the drug of choice for patient-controlled analgesia
Written informed consentAnaesthesiologists [24]

Exclusion criteria

Inability to remain at the hospital for the duration of the study
Hip or knee replacement surgery under general anaesthesia (24 h)
Morphine not the drug of choice for patient-controlled analgesia
Contraindication for treatment with ketoprofen or other nonsteroidal
Written informed consentsteroidal anti-inflammatory drugs
Systemic infection or infection at the site of operation before surgery is is performed
Complication during or after surgical procedure
Patients with planned concomitant medication during the study with any of of the following: lithium, more than 300 mg acetyl salicylic acid per day, other nonsteroidal anti-inflammatory drugs, systemic glucocorticoids, methotrexate, cyclosporin, sedatives (other than short acting premedications), MAO inhibitors, inhibitors, antiepileptics
Allergy to ketoprofen or other nonsteroidal anti-inflammatory drugs
History of peptic ulcer, gastrointestinal bleeding or severe gastropathy gastropathy
Moderate or severe renal, hepatic or respiratory impairment in the opinion opinion of the investigator
Recent history of asthma, bronchospasm, angioedema or coagulation disorder
Diabetes mellitus, heart failure or hypertension not well controlled
Drug addiction or alcoholism
Epilepsy, psychosis or other psychiatric disorders
Current participation or participation within the previous 3 months in other clinical trials with unlicensed medicines or in other clinical trial with unlicensed medicines in the previous 3 months.
Pregnancy or lactation, including ectopic pregnancy
Inadequate contraception (females)

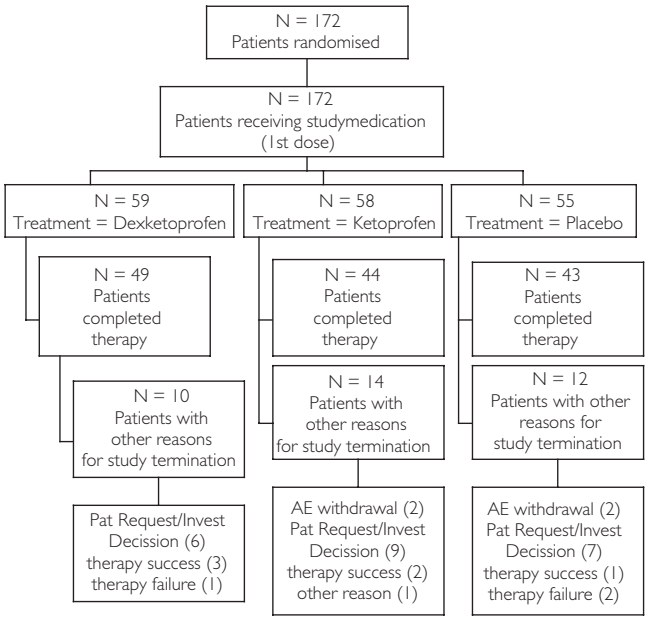

Figure 1 Patient disposition.

Table 2 Demographic data.

Patient details	*DKP.TRIS* n = *59*	*Ketoprofen* n = *58*	*Placebo* n = *55*	*Total* n = *172*
Sex [n (%)]				
Male	31 (52.5)	26 (44.8)	30 (54.5)	87 (50.6)
Female	28 (47.5)	32 (55.2)	25 (45.5)	85 (49.4)
Age (years)				
Mean	64.7	62.1	58.7	61.9
s.d.	7.5	11.0	11.1	10.2
Height (cm)				
Mean	165.9	168.6	167.8	167.4
s.d.	9.8	9.4	10.2	9.8
Body weight (kg)				
Mean	77.0	85.0	82.1	81.3
s.d.	14.9	18.0	17.2	16.9

Efficacy

The results for the primary endpoint are displayed in Figure 2. The mean CAM used during the whole study period was 39.1 mg in the dexketoprofen group, 41.3 mg in the ketoprofen group and 64.8 mg in the placebo group. These data show that the requirements for morphine were reduced by approximately one-third in both dexketoprofen trometamol and ketoprofen groups compared with the placebo group. These differences were statistically significant for both active treatments. As shown in Tables 3 and 4, the reduction in morphine used of approximately one-third was also seen between each active treatment group and placebo during each interval studied.

The mean time to loading dose of morphine after the first injection of study medication was 36 and 38 min in the dexketoprofen and ketoprofen groups, respectively, compared with 29 min in the placebo group. Only the difference between the ketoprofen and placebo groups was statistically significant ($P < 0.05$; 95% CI 4.40, 15.25). The mean time between loading dose and first use of PCA was 44 min in the placebo group compared with 78 min in the dexketoprofen group and 96 min in the ketoprofen group, with no statistically significant differences found between groups. The timecourse of pain

intensity after recovery from anaesthesia as measured by the VAS and verbal scale is shown in Figure 3 (VAS) and Figure 4 (verbal scale). The three pain-intensity *vs* time curves of means showed largely parallel courses. At all measurement times mean pain intensity in the placebo group was greater than in the two active treatment groups. Prior to administration of the morphine loading dose, VAS means were approximately 6 cm in the active treatment groups, decreased to approximately 3 cm at $t = 4$ h and remained at that level, or below, during the entire course of the study whereas the placebo group was mostly over this level for the 24 h period. For statistical analysis purposes pain-intensity summary scores were determined for three periods of time: P1 ($t = 1$ h–$t = 6$ h), P2 ($t = 9$ h–$t = 12$ h) and P3 ($t = 13$ h–$t = 24$ h).

Statistically significant differences between dexketoprofen and placebo were found for all the three periods, whereas for ketoprofen *vs* placebo differences were significant only for the first period (see Table 5).

The time courses of mean pain-intensity scores assessed by means of a verbal rating scale (see Figure 4 and Table 6) were similar to those assessed by means of VAS.

Among the 147 patients evaluated for quality of sleep, 21/47 (44.7%) in the placebo group hardly slept, com-

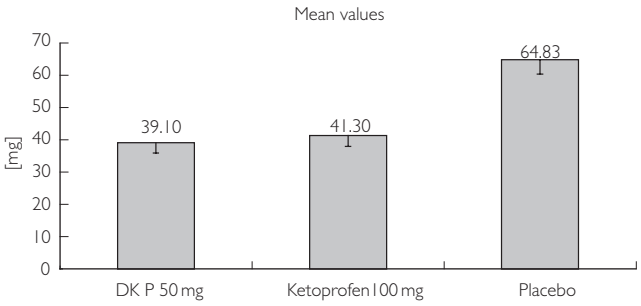

Figure 2 Cumulative amount of morphine usage (primary efficacy endpoint). Cumulative morphine usage (CAM) until 12 hours after the 2nd administration of study medication – t-tests, confidence intervals. [1]p-values adjusted according to the Bonferroni-Hochberg; [2]raw p-values (not adjusted for multiplicity of testing).

Table 3 Cumulative morphine usage (CAM) [mean (s.d.)] per interval.

	DKP.TRIS n = *58*	*Ketoprofen* n = *56*	*Placebo* n = *54*
CAM 1 (mg)	7.5 (7.0)	7.4 (5.3)	11.8 (9.2)
CAM 2 (mg)	19.1 (14.9)	19.8 (13.9)	27.6 (15.1)
CAM 3 (mg)	11.4 (10.0)	13.9 (11.9)	25.2 (16.9)

DKP, dexketoprofen.

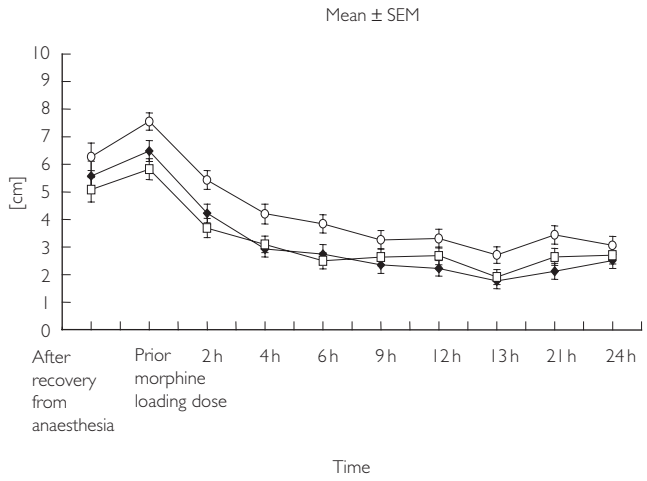

Figure 3 Pain intensity as measured by the visual analogue scale: time course of means. ◆, Dexketoprofen 50 mg; □, ketoprofen; ○, placebo.

Table 4 Cumulative morphine usage (CAM) until 12 h after the second administration of study medication.

	Lower 95% confidence limit	*Adjusted mean difference*	*Upper 95% confidence limit*	t-*tests*P *values*
FA data set				
DKP ↔ KET	−11.3	−1.6	8.1	0.7448[1] (0.7448)[2]
DKP ↔ PLC	−34.8	−25.0	−15.2	≤ 0.0003[1] (0.0001)[2]
KET ↔ PLC	−33.2	−23.4	−13.6	≤ 0.0003[1] (.0001)[2]
PP data set				
DKP ↔ KET	−11.8	0.5	12.9	0.9332[1] (0.9332)[2]
DKP ↔ PLC	−35.4	−22.8	−10.2	0.0015[1] (0.0005)[2]
KET ↔ PLC	−36.1	−23.3	−10.5	0.0015[1] (0.0005)[2]

[1]*P* values adjusted according to Bonferroni–Hochberg. [2]Raw *P* values (not adjusted for multiplicity of testing, based on tables in Section 16.1.9) [3]DKP, dexketoprofen; KET, ketoprofen.

Table 5 Differences in pain intensity as measured by the visual analogue scale (*P* value, (95% CI difference between means)).

	t*1*	t*2*	t*3*
DKP 50 mg *vs* placebo	0.0007 (−7.41, −2.01)	0.0131 (−3.75, −0.45)	0.0102 (−5.19, −0.71)
Ketoprofen 100 mg *vs* placebo	0.0001 (−8.47, −3.14)	–	–

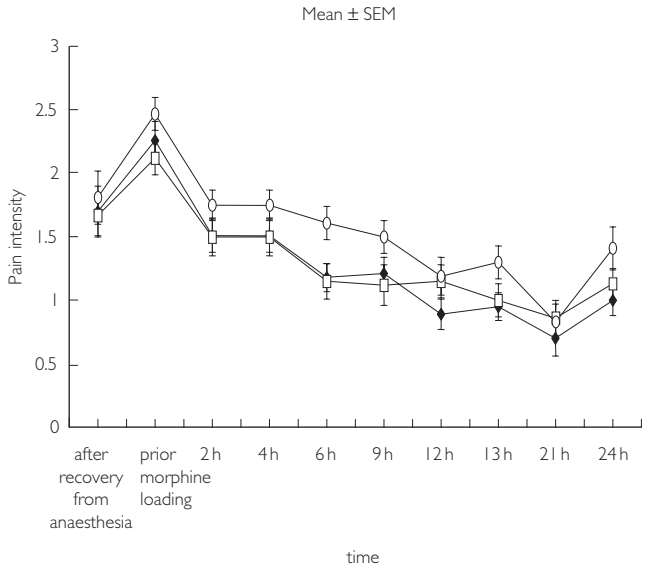

Figure 4 Time course of pain intensity (verbal scale). ◆, Dexketoprofen 50 mg; □, ketoprofen; ○, placebo. o, none; l, mild; 2, moderate; 3, severe.

pared with 9/51 (17.8%) in the dexketoprofen and 8/49 (16.3%) in the ketoprofen group. The comparative analysis showed that the quality of sleep was significantly improved in both active treatment groups compared with placebo ($P = 0.0001$ and $P = 0.0002$, respectively).

Safety and tolerability

A total of 338 adverse events (AEs) were reported in 139 (81%) of the 172 patients treated. Approximately one-third of AEs was considered to be related to treatment, whereby no distinction was made between study medication and morphine in the causality assessment. There were no significant differences between groups in the overall incidence of AE and treatment-related AE. The most frequently affected system was the gastrointestinal, being postoperative nausea and vomiting (PONV). It was the commonest adverse reaction reported and accounted overall for 48 (32%) of treatment-related AEs. The incidence of PONV for both active treatment groups was lower than for the placebo group, indirectly reflecting the opiod-sparing effect of the combined analgesia (21% for dexketoprofen and 34% for ketoprofen *vs* 47% for placebo).

Table 6 Differences in pain intensity as measured by the verbal scale (*P* values).

	t*1*	t*2*	t*3*
DKP 50 mg *vs* placebo	0.0005	0.0009	0.0155
Ketoprofen 100 mg *vs* placebo	0.0001	–	0.0329

DKP, dexketoprofen.

A very low incidence of gastrointestinal bleeding was noted ($n = 3$; two patients in the dexketoprofen group, one patient in the ketoprofen group). No cases of abnormal renal function or acute renal failure were detected. Injection site reactions (pain at rest or on movement, erythema and swelling) were also relatively common (up to 16%), with no significant differences found between groups. A total of four serious AEs were reported, one in the ketoprofen and three in the placebo group; only the serious AE in the ketoprofen group (postoperative haemorrhage) was considered possibly related to study medication.

Mean scores for sedation (maximum score: 3 = asleep) were between 0 and 1.5 at all times during the study, There were statistically significant differences between the two active compounds and placebo at the 2nd and 13th hour, both dexketoprofen and ketoprofen resulting in more sedation than placebo at these two time points (Figure 5). There were no significant differences among groups in the incidence of injection site reactions (pain at rest or on movement, erythema and swelling), when this was recorded as a specific and independent variable.

The mean wound bleeding in drainage ranged from 388 to 523 ml between groups after the first dose of study medication and from 535 to 586 ml after the second dose. Although it was not part of the power of the study, there were no statistically significant differences between the groups.

Discussion

NSAIDs have been shown to provide effective postoperative analgesia in orthopaedic surgery [13, 16]. The mechanism of action is thought to be by suppressing prostaglandin synthesis [17]. Recent evidence has proposed a separate central mechanism for the early analgesic effects [18–20]. This study was designed to assess the

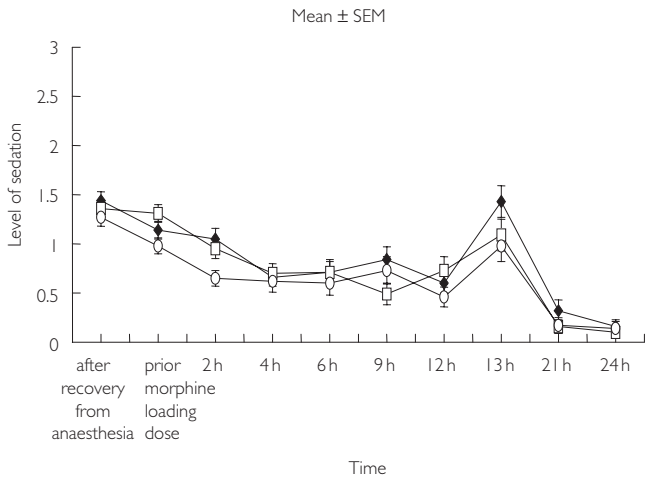

Figure 5 Time course of the level of sedation assessed by the investigator. ◆, Dexketoprofen 50 mg; □, ketoprofen; ○, placebo. O, Fully awake; l, mildly sedated; 2, heavily sedated; 3, asleep.

analgesic efficacy, influence on morphine usage and safety of dexketoprofen trometamol 50 mg, given as two intramuscular doses 12 h apart, after orthopaedic surgery, with reference to a standard parenteral NSAID, ketoprofen, and placebo. The main efficacy variable was the cumulative amount of morphine used during the study, which is considered a useful variable to measure pain in this type of study.

The results showed a statistically significant morphine-sparing effect of approximately one-third for both active treatments compared with placebo. This extent of decrease in morphine requirements has been considered clinically relevant in previous publications [12–14]. Results also showed a longer time interval until administration of the loading dose and PCA and lower pain-intensity scores, as well as significant improvement in the quality of sleep in the active treatment groups compared with placebo. All these data considered as a whole indicate an improved overall quality of analgesia with no increase in the incidence of side-effects compared with placebo. In this study patients were well matched, as treatment groups were comparable for demographic and baseline features. The mean age of the studied population was around 60 years, as would be expected for the intended indication.

It is worthy of note that the incidence of PONV for both active treatment groups was lower than for the placebo group, indirectly reflecting the opioid-sparing effect of the combined analgesia.

Dexketoprofen is the S(+)-enantiomer of the racemic compound ketoprofen. In preclinical studies, dexketoprofen has been shown to be a more potent analgesic than the parent compound; this has been confirmed in the acute pain model in man. Dexketoprofen has been shown to be very active in the central nervous system, probably at the spinal cord level in nociception and in depressing a wind-up phenomenon [21], which would make it a particularly appropriate drug in this model.

With regard to sedation (a well-recognized side-effect in the use of opioids), it was fascinating to note that there were significant differences between the active compounds and placebo at the 2nd and 13th postoperative hour. This could be explained either by improved quality of analgesia in the active compound groups leading to relaxation and sleep, the difficulty by the different observers in assessing sedation (central effect) or a possible pharmacokinetic interaction [22, 23].

A potential risk of bleeding when using NSAIDs during the peri-operative period cannot be excluded because they inhibit platelet aggregation and thus prolong the bleeding time via inhibition of prostaglandin synthesis. However, data from studies on the clinical significance of NSAIDs on bleeding are inconclusive [4]. Blood loss was specifically assessed in this study by recording the total amount of blood in the wound drainage. It is also worth noting that the amount of wound bleeding was comparable between groups. These data give no evidence for any increased risk to the patient in concomitant administration of antithrombotics and dexketoprofen trometamol, compared with ketoprofen or placebo.

In conclusion, this study showed that intramuscular administration of dexketoprofen trometamol 50 mg has good analgesic efficacy both in terms of opioid-sparing effect and control of pain after major orthopaedic surgery.

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