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Dexketoprofen trometamol in post-operative pain management

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Summary Dexketoprofen trometamol is the dextrorotatory enantiomer of ketoprofen formulated as the tromethamine salt. Producing a single isomer formulation of ketoprofen simplifies the pharmacokinetics of the drug and allows a 50% reduction in dosage. This may reduce adverse effects by reducing metabolic and renal load. Formulation as the tromethamine salt results in faster absorption from the gut and therefore quicker onset of analgesia. This paper reviews studies of the use of dexketoprofen in acute postoperative pain, and concludes that it produces rapid and reliable onset of analgesia.

1. Introduction

The arylpropionic acids (APAs) are a group of non-steroidal anti-inflammatory drugs currently produced in the racemic form (i.e. as an equal mixture of their two enantiomers). Studies have shown that cyclooxygenase (COX) inhibition, and hence pharmacological effect, resides with the *S*(+) enantiomer [1]. As a result, many of the drugs in this class are now being released as single isomers as improvements in chiral technology [2], together with regulatory incentives [3], result in an expansion of both de novo single-isomer drugs and so-called 'chiral switches' [4]. For a comprehensive review of chiral terminology and recent developments that have allowed the commercially viable manufacture of single isomer drugs, the reader is referred to recently published articles by Sweetman [5] and Burke and Henderson [6].

In a chiral switch an existing racemate is refined into its most advantageous enantiomer. The manufacture of dexketoprofen trometamol (*S*(+) ketoprofen tromethamine salt) is an example of this. It is the dextrorotatory enantiomer of ketoprofen, a non-steroidal drug widely used as an analgesic and anti-inflammatory agent for more than 20 years [7].

This article presents new data from more than 900 patients who participated in the European clinical trials that were performed in order to obtain regulatory approval for dexketoprofen. These patients underwent a variety of orthopaedic operations and dexketoprofen was compared against placebo as well as other commonly used analgesics. The results are currently unpublished and have been made available for inclusion in this article.

2. Acute post-operative pain studies

In the first study by Vidal et al., 188 patients between the ages of 18–70 years underwent surgery to correct unilateral hallux valgus deformity and were randomised to receive placebo, dexketoprofen

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trometamol (12.5 or 25 mg) or rac-ketoprofen 50 mg tds [8]. Duration of therapy was 1 day. Patients did not receive local anaesthetic infiltration at the end of surgery. Dosing was commenced when the patients complained of moderate to severe postoperative pain, with two additional doses at 8 and 16 h.

Efficacy was assessed by a combination of criteria. Pain intensity was measured on a visual analogue scale (VAS) plus a verbal rating scale (VRS), and pain relief on a verbal scale. Analgesic efficacy was determined using a number of measures, including: sum of the pain intensity differences on the visual analogue scale (SAPID), sum of pain intensity differences on the verbal scale (SPID) and sum of the pain relief scores on the verbal scale (TOTPAR).

Secondary measures of efficacy included morphine usage (rescue medication) and an overall global evaluation of pain relief. The results are presented in Table 1.

No differences could be detected regarding the main efficacy variables but there was a significant difference in morphine usage, with patients in the placebo group requiring more morphine in the first 6 h period when compared to any of the active treatment groups. This difference persisted at 24 h but failed to reach statistical significance at this point.

Overall patient assessment was also better in the active treatment groups. No differences were seen between the two doses of dexketoprofen or between rac-ketoprofen and any dose of dexketoprofen.

The investigators concluded that NSAID administration alone was insufficient for pain relief following hallux valgus surgery. However, they were useful in reducing morphine requirements (a reduction of 35.4% in the first 6 h) and dexketoprofen trometamol 12.5 mg was as efficacious as a dose of 50 mg rac-ketoprofen in this respect.

In a study by Schreiber, 213 patients undergoing orthopaedic surgery to the knee or ankle were randomised to dexketoprofen 12.5 mg, dexketoprofen 25 mg, rac-ketoprofen 50 mg or placebo [9]. Medication was administered within the first 4 h following surgery and up to nine doses were given at 8 h intervals. Pain was measured at time zero (immediately prior to administration) and at 30 min, 1 and 2 h after each dose.

Similar efficacy characteristics were evaluated as in the previous study. Pain intensity was rated on a 4-point ordinal verbal rating scale and a visual analogue scale and subjective pain relief on a 5-point ordinal scale. The primary outcome measure was SAPID (0–66 h). Secondary outcome measures included SPID, TOTPAR and a verbal global estimate of efficacy, completed daily.

There was a consistent trend towards better quality analgesia, faster in onset, with the higher dose (25 mg) of dexketoprofen. This did not reach

Table 1 Main efficacy results

Variable	Placebo ($n = 43$)	DKP (12.5 mg, $n = 45$)	DKP (25 mg, $n = 41$)	Ketoprofen (50 mg, $n = 43$)	Test, *P*-value ($^*P < 0.05$)
Mean SPID at 6 h	−3.9	1.3	4.0	−2.0	Kruksal–Wallis (0.1286); ANOVA (0.0932)
Mean SAPID at 6 h	−347.3	−126.1	−77.8	−280.8	ANOVA (0.0692)
Mean TOTPAR at 6 h	2.5	7.4	7.4	2.7	Kruksal–Wallis (0.1210); ANOVA (0.1666)
Percentage of patients who required rescue medication at 2 h	93	86	88	95	
Percentage of patients who required rescue medication at 6 h	100	91	93	98	
Mean morphine usage at 6 h (mg)	12.7	9.2*	8.2*	9.9*	Kruksal–Wallis (0.0124)
Mean morphine usage at 24 h (mg)	23.0	17.1	17.0	17.1	Kruksal–Wallis (0.0736)

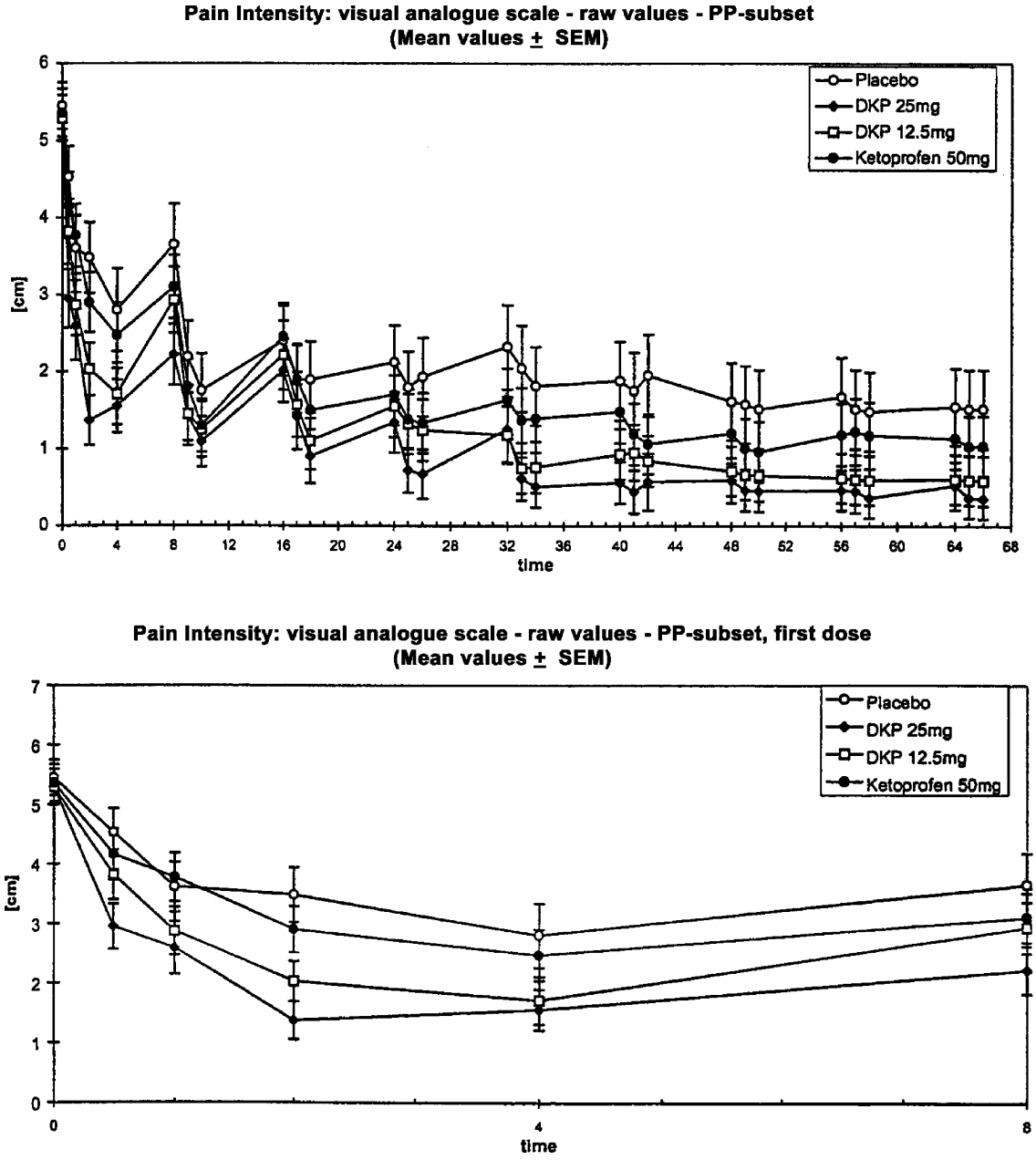

Fig. 1 Pain scale intensity: visual analogue—raw values (PP-subset).

statistical significance for the primary outcome measure however (SAPID 0–66 h).

Forty-three patients did not remain in the study for the defined period (due to receiving 'escape medication', etc.), so an additional analysis was performed on SAPID for the first 8 h. This did demonstrate a statistically significant difference between DKP in both the 12.5 and 25 mg dosages when compared with placebo.

Visual analogue scores of pain intensity for the 3-day study period are presented in Fig. 1.

The weighted sum of pain intensity differences (SAPID, SPID) are presented in Figs. 2 and 3.

There was a statistically significant difference in the overall TOTPAR scores at the 5% level between placebo and both doses of DKP, but not ketoprofen. There was also a significant difference between DKP 25 mg and ketoprofen 50 mg.

In the global evaluation of efficacy, pain relief was rated excellent or good by 91.9% of patients in the DKP 25 mg group, 90.0% in the DKP 12.5 mg group, 73.8% in the ketoprofen 50 mg group and 64.0% in the placebo group. Rescue medication was greater in the placebo group than the active treatment groups. At the beginning of the second study day, 65.2% of patients in the placebo group had

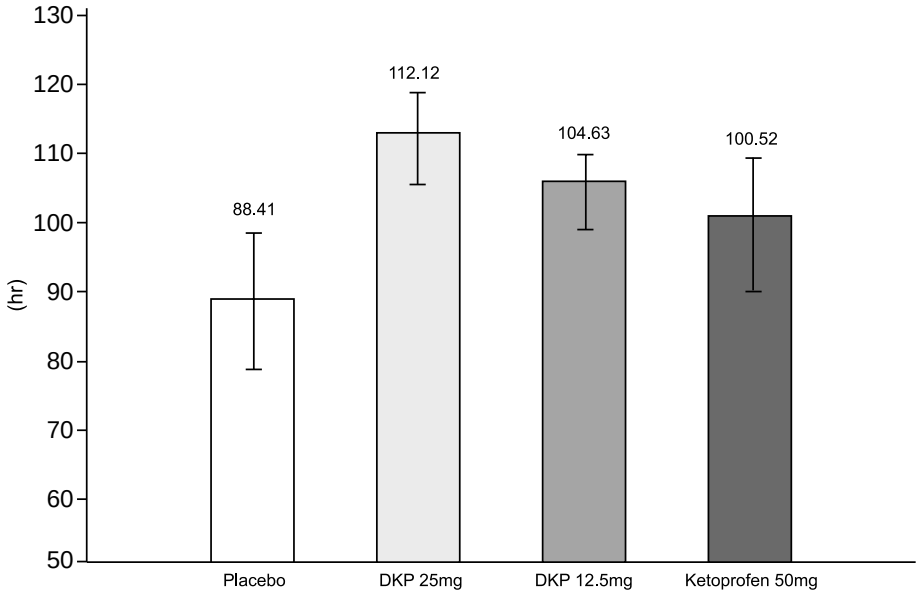

Fig. 2 SPID (0–66 h) (weighted sum of pain intensity ratings)—PP-subset.

received rescue medication, compared with 25.0, 31.1 and 35.4% in the DKP 25 mg group, DKP 12.5 group and ketoprofen 50 mg group, respectively.

Another study by Schreiber compared the efficacy and tolerability of dexketoprofen and tramadol [10]. The objective of the study was to demonstrate that oral DKP 25 mg was at least as effective as tramadol 50 mg in the first three post-operative days. One hundred and three patients undergoing orthopaedic surgery on an out-patient basis were recruited and treatment commenced at the first report of mild-moderate pain. Rescue medication was with paracetamol 500 mg.

Pain intensity was assessed with a visual analogue scale (primary outcome measure). Secondary outcomes included time to onset of analgesia and an overall subjective assessment.

During the 72 h treatment period, pain intensity decreased continuously, predominantly within the first 24 h. Time to onset of analgesia was similar with both drugs. Within the first 60 min, pain decreased by 60.85% from baseline in the DKP group and by 51.54% in the tramadol group. Analgesic activity was then maintained for the subsequent 72 h from surgery for both treatments. A lower number of patients in the DKP group took rescue medication (20 versus 29) but this was not significant.

In a study of in-patient orthopaedic surgery at the hip or the knee (but not isolated arthroscopy), dexketoprofen 25 mg was given six-hourly and again compared with tramadol 50 mg six-hourly for 2 days [11]. One hundred and sixty-eight patients were recruited and the following variables were analysed: pain intensity differences (using both VRS and VAS), SAPID, SPID, TOTPAR and onset time to analgesia. SAPID (0–6 h) with dexketoprofen 25 mg was significantly superior to tramadol but there were no other significant differences found.

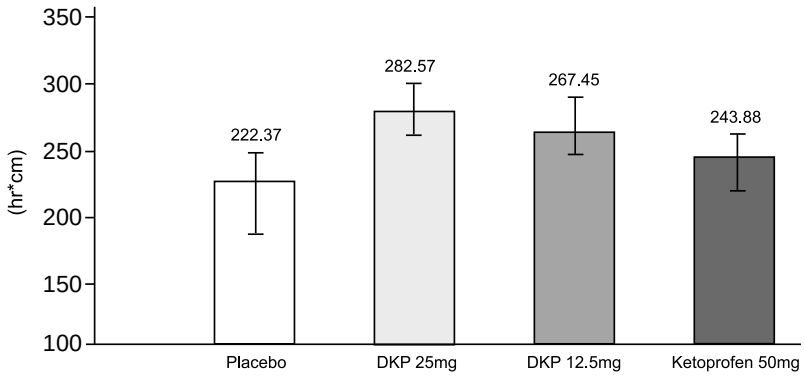

Fig. 3 SPID (0–66 h) (weighted sum of VAS-scales)—PP-subset.

The morphine sparing effects of dexketoprofen 25 mg were compared with Dafalgan codeine (paracetamol 500 mg, codeine 22.5 mg) in a study by Latarjet of 177 patients undergoing total hip replacement under general anaesthesia [12]. Drugs were administered on an eight-hourly basis, commencing within the first 4 h post-operatively. The primary measure of efficacy was a comparison of the quantity of self-administered morphine in the first 24 h period.

The quantity of self-administered morphine was virtually identical between the groups (16.63 ± 15.50 mg for DKP 25 mg and 16.63 ± 16.66 mg for the paracetamol codeine preparation). This low dose of morphine (approximately 0.69 mg/h) in the two groups produced effective analgesia, with a mean pain score at 28 h of 2.50 cm in the DKP group and 2.71 cm in the paracetomol codeine group. The patient's overall assessment of efficacy was regarded as good in 75.14% of patients in the DKP group and 78.02% in the paracetomol codeine group.

3. Discussion

The results presented above support previous work in the literature that reveal dexketoprofen to be an effective analgesic for the treatment of mild to moderate pain, with a clinical profile similar to other commonly available oral analgesics. It produces a marked reduction in postoperative opioid requirements when used as part of a balanced analgesic regime, thereby diminishing the potential for opioid-induced side-effects. Other authors have confirmed these findings, and additionally demonstrated attenuation of the pro-inflammatory mediator IL-6 postoperatively [13]. Formulating the drug as a single isomer has many potential advantages, including the possibility of increasing the therapeutic index and simplifying the pharmacokinetic profile. Use of the active enantiomer in isolation allows a 50% dosage reduction. This may reduce adverse effects by lowering the metabolic and renal load, as previous work has established a relationship between NSAID-associated gastric irritation and dose [14].

Pharmacokinetic studies in human volunteers show that preparation as the tromethamine salt results in a faster absorption rate as a result of greatly increased solubility [15]. In the first part of a two-phase study, Barbanoj et al. randomised volunteers to receive a single oral capsule of either *S*(+) ketoprofen free acid 25 mg, *S*(+) ketoprofen trometamol 37 mg (corresponding to 25 mg of the acid) or rac-ketoprofen 50 mg. *S*(+) ketoprofen trometamol showed the most rapid absorption rate and achieved a significantly higher C_{max} than dexketoprofen acid at 0.50 h (3.70 ± 0.72 μg/ml versus 2.02 ± 0.69 μg/ml). Of note, t_{max} values for *S*(+) ketoprofen trometamol (0.25–0.75 h) were much less variable than those for either *S*(+) ketoprofen free acid (0.5–3 h) or rac-ketoprofen (0.25–3 h), suggesting that onset of analgesia should be both more rapid and reliable compared to other formulations.

The development of dexketoprofen trometamol is a refinement to the parent compound, ketoprofen; an analgesic with a long history as an effective analgesic and anti-inflammatory agent. It continues the trend encouraged by the regulatory authorities to produce drugs as single enantiomers wherever possible, and additionally has been produced in a preparation that provides rapid and reliable onset of analgesia. As such, it has a useful role to play in the provision of acute pain relief.

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