ORIGINAL ARTICLE

Randomised controlled trial of the onset of analgesic efficacy of dexketoprofen and diclofenac in lower limb injury

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Objective: To assess the time of onset and difference in analgesic efficacy of oral dexketoprofen compared with oral diclofenac in patients with acute lower limb injury.
Design: A prospective, double blind, randomised controlled trial.
Interventions: Patients who fitted the study criteria were given either 25 mg oral dexketoprofen trometamol or 50 mg sodium diclofenac immediately after triage; baseline and 15 minute pain scores were then recorded for one hour.
Results: 122 patients were studied (diclofenac = 57 and dexketoprofen = 65). There were no significant differences in age, sex, type of injury, or baseline pain scores between the two groups. The differences in group mean pain scores between diclofenac and dexketoprofen at 15, 30, 45, and 60 minutes were; 0.53 (95% confidence intervals −0.03 to 1.09), 0.70 (0.16 to 1.24), 0.89 (0.32 to 1.47), and 0.83 (0.21 to 1.45). Odds ratios for a decrease in pain score of at least 1 from baseline (on the 11 point scale) when given dexketoprofen rather than diclofenac at 15, 30, 45, and 60 minutes were; 2.66 (1.19 to 5.98), 3.52 (1.60 to 7.73), 4.48 (1.72 to 11.65), and 5.54 (1.90 to 16.15). Corresponding odds ratios for a decrease in pain score of ⩾2 were; 6.88 (1.48 to 32.0), 3.79 (1.59 to 9.01), 5.19 (2.29 to 11.78), and 5.87 (2.68 to 12.88).
Conclusions: Dexketoprofen trometamol is an effective and rapidly acting analgesic for the treatment of acute musculoskeletal injuries.

Dexketoprofen trometamol is the water soluble salt of the S-isomer of the racemic non-steroidal anti-inflammatory (NSAID) drug ketoprofen.[1] S-isomers rotate polarised light to the right, while R isomers rotate it to the left. Dexketoprofen acts by inhibition of cyclooxygenase, thus diminishing prostaglandin synthesis. It has been shown that the stereo-isomer of ketoprofen is about 3000 times more potent than the R-isomer at doing this.[2 3] Additionally in vitro studies have shown greater COX-1 inhibition with this S-isomer of ketoprofen, compared with other racemic NSAIDs.[4] The trometamol salt form of dexketoprofen was formulated to improve the pharmacokinetics of the orally administered drug. The maximum concentration is greater and the time to it less, with the trometamol salt compared with the free acid form of dexketoprofen.[5 6]

This study was designed to assess whether this new form of NSAID using enantiomer selectivity would perform more effectively in the ED setting than a standard NSAID. The criteria for effectiveness were time of onset of effect and size of effect. Diclofenac was chosen as the comparator as it is the most widely used NSAID in England.[7]

METHODS

This study was set in an inner city teaching hospital emergency department (annual census >100 000 new patients) between October 2000 and March 2001. Eligibility for inclusion included; age 18–65, injury to knee, ankle, or foot within the past 48 hours, no NSAID ingestion since injury, and no contraindications to NSAIDs.

All patients with an acute lower limb injury as above were assessed by the triage nurse and a pain score was elicited using an 11 point discrete numeric/verbal rating scale (0 to 10 inclusive).[8] If the patient had a score of 3 or higher they were offered enrolment in the study. Patients who the triage nurse felt required narcotic analgesia were excluded from the study. Once informed consent had been obtained the patient was randomised to either 25 mg of oral dexketoprofen trometamol or 50 mg sodium diclofenac. Randomisation was achieved by opening sequentially numbered sealed opaque envelopes that contained the name of the study drug (A or B) to dispense, generated from a computerised random number table. The two study drugs were kept in individual single dose boxes and labelled as either drug A or drug B. The patients, nursing staff, and doctors were all blinded to treatment allocation.

Patients were provided with four copies of the same 11 point pain ladder, which was explained to them at their initial triage. They were asked to score their pain at 15 minute intervals until one hour had elapsed. Data were collected on the nature and mechanism of the injury, examination findings, investigations performed, treatment, and outcomes

A power calculation was performed that showed that 204 patients would give a 90% power to detect a difference in pain scores of 1 on the 11 point scale, if treated as a continuous variable, given an $\alpha = 0.05$ and pooled standard deviation of 2.2. Planned interim data analysis showed that our standard deviation was only 1.54 and thus, with the 122 patient thus far recruited, we had 95% power to detect a difference of at least 1 point on the scale, if such a difference existed. As a difference of this magnitude had not been detected, the study was terminated. The study received the approval of the local hospital ethics committee.

Data were analysed using SYSTAT software. The data collected were discrete ordinal data on an 11 point scale (0 to 10 inclusive). This has been analysed using the non-parametric Kruskal-Wallis test for analysis of variance. Tabulated results were analysed with χ^2 tests. Repeated measures analysis of variance (which assumes that the data are continuous) was used to study between group differences over time for subjects who completed the whole protocol (n = 83).

Table 1 Demographic variables

Variable	Total study population	Diclofenac group	Dexketoprofen group	p Value
Mean age (y)	30.3	31.0	29.7	0.50
Sex distribution (%)				
Male	61.1	64.9	57.4	0.37
Female	38.1	33.3	42.7	
Location of injury (where recorded, n = 116)				
Knee	14	7	7	
Ankle	80	37	43	0.96
Foot	21	10	11	
Radiological result (where performed, n = 88)				
No fracture	73	32	41	
Minor avulsion fracture	4	2	2	0.47
All other fractures	11	7	4	

Odds ratios (OR)[8] were calculated for clinically relevant end points. Thus the odds ratios presented represent the ratio of the probability that dexketoprofen will have decreased the pain score by that amount (1 or ⩾2), compared with the probability that diclofenac will, at that point in time. The end points (minimum clinically significant differences) were extrapolated[9] from work using the continuous VAS score,[10 11] which showed a single point reduction on the pain score would be a reliable estimate of efficacy.

RESULTS

This trial has been reported using the revised CONSORT statement guidelines.[12] There were 143 patients randomised and 19 patients had either missing data sheets or the study drug boxes were found to be empty after randomisation, leaving 122 patients for analysis (65 received dexketoprofen and 57 diclofenac). There were no significant differences in baseline demographics, mechanism or timing of injury between the two groups. Furthermore, the body areas injured and the clinical findings were also similar (summarised in table 1). Only eight patients required or requested further analgesia, five in the diclofenac group and three in the dexketoprofen group (p = 0.32). There were no reported drug related adverse effects seen.

Mean pain scores were equivalent at baseline. However, over the ensuing 60 minutes the mean pain score in the dexketoprofen group fell more rapidly than the diclofenac group (table 2). This is shown in figure 1 over the five recording intervals. Odds ratios were calculated for the clinically relevant timings of a decrease in ⩾1 point from baseline on the discrete 11 point pain scale and of ⩾2 points. These showed that dexketoprofen was much more likely at any point in time to provide an absolute improvement in the patients pain score relative to diclofenac. Though the confidence intervals were wide the odds were always greater than 1 for dexketoprofen providing a whole interval decrease in pain score. The difference was more marked where a 2 point reduction was observed.

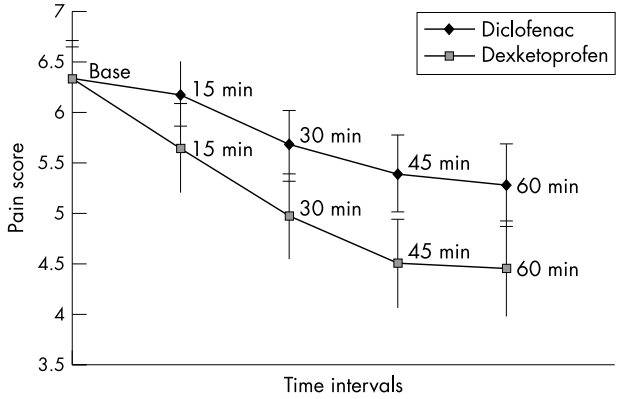

Figure 1 Total group mean pain scores by drug allocation (with 95% CI for group means).

The Kruskal-Wallis test of analysis of variance at each time point showed a significant difference in overall mean pain score from 15 minutes. Repeated measures analysis of variance showed an overall significant effect of the study drug over 60 minutes (p = 0.001).

DISCUSSION

In our study we used a composite pain score equivalent to the standard VAS as a pragmatic tool.[13] The pain ladder combines a verbal rating scale, a visual analogue scale, and a functional assessment, and each component can be used alone or in combination with another, to assess a patient's pain. We feel that this is more valid than the standard VAS as nursing staff in UK emergency departments are using this discrete scale at triage and making decisions based upon it,[14] they are not

Table 2 Mean pain scores over time

Drug	Baseline	15 minutes	30 minutes	45 minutes	60 minutes
Diclofenac (n = 57)	6.33 (6.01 to 6.66)	6.18 (5.85 to 6.50)	5.68 (5.34 to 6.03)	5.40 (5.02 to 5.78)	5.29 (4.88 to 5.70)
Dexketoprofen (n = 65)	6.35 (5.99 to 6.72)	5.65 5.20 to 6.09)	4.98 (4.57 to 5.40)	4.51 (4.07 to 4.95)	4.46 (3.98 to 4.93)
Difference in mean pain scores	−0.02 (−0.51 to 0.47)	0.53 (−0.03 to 1.09)	0.70 (0.16 to 1.24)	0.89 (0.32 to 1.47)	0.83 (0.21 to 1.45)
Kruskal-Wallis one way analysis of variance (n = 122)	p = 0.58 (test statistic = 1957.5)	p = 0.026 (test statistic = 2275)	p = 0.009 (test statistic = 2353)	p = 0.002 (test statistic = 1842)	p = 0.008 (test statistic = 1363)

Figures in parentheses are 95% confidence intervals unless stated otherwise.

Table 3 Cumulative proportions of patients with a reduction in pain score over time and odds ratios for difference between study drugs

	By 15 minutes	By 30 minutes	By 45 minutes	By 60 minutes
Pain score reduction of ⩾1				
Diclofenac	0.21	0.51	0.65	0.68
Dexketoprofen	0.42	0.78	0.89	0.92
p Value (χ^2)	0.015 (5.86)	0.001 (10.24)	0.001 (10.42)	<0.0001 (11.33)
Odds ratio for improvement with dexketoprofen compared with diclofenac	2.66 (1.19 to 5.98)	3.52 (1.60 to 7.73)	4.48 (1.72 to 11.65)	5.54 (1.90 to 16.15)
Pain score reduction of ⩾2				
Diclofenac	0.04	0.16	0.19	0.26
Dexketoprofen	0.20	0.41	0.55	0.77
p Value (χ^2)	0.005 (7.66)	0.001 (9.68)	<0.001 (16.7)	<0.001 (21.7)
Odds ratio for improvement with dexketoprofen compared with diclofenac	6.88 (1.48 to 32.0)	3.79 (1.59 to 9.01)	5.19 (2.29 to 11.78)	5.87 (2.68 to 12.88)

Figures in parentheses are 95% confidence intervals unless stated.

measuring along 10 cm lines for every patient. The results however, are comparable to other analgesia studies in emergency departments that have used the VAS alone,[15] as well as other studies using dexketoprofen in a similar dose.[16–20]

Our study showed that there was an earlier onset of analgesic efficacy with dexketoprofen compared with diclofenac, which may be attributable to more rapid absorption due to the trometamol base. Study participants given dexketoprofen were significantly more likely to have a reduction in pain score of ⩾1 or ⩾2 points on the scale at any intervals studied, up to one hour from oral ingestion, though this was a post hoc analysis. This was in contrast with the finding that there was no overall mean pain score reduction of >1, or clinically significant reduction (equivalent to >1.3 cm on VAS)[10 21] between the two drugs (prespecified analysis). Thus, summary measures comparing group means may provide less useful results than patient specific end points. Though, while the mean maximal difference at 45 minutes was only 0.89, the difference from baseline was 1.89 for dexketoprofen and only 1.04 for diclofenac at one hour, diclofenac failing to achieve a clinically relevant decrease in pain score.

Several potential problems may limit the generalisability of this study. These include; unmeasured effect on pain scores after 60 minutes, low number of fractures, minimal use of analgesic adjuvants (for example, ice), no placebo control, single dose only, no longer term follow up for side effects.

We have shown that compared with a commonly prescribed analgesic for limb injury an alternative formulation of a standard NSAID compound can produce more effective results. It would be interesting to test this finding in other settings and perhaps in patients with more significant injuries. Whether the decreases in pain score remain after the initial drug distribution phase is over and also in serial dosing have not been tested. Thus we have shown that dexketoprofen is a reasonable choice of analgesic in acute musculoskeletal injury.

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