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A COMPARATIVE STUDY OF EFFICACY AND TOLERABILITY OF DEXKETOPROFEN TROMETAMOL VERSUS DICLOFENAC SODIUM IN THE SYMPTOMATIC TREATMENT OF KNEE OSTEOARTHRITIS

Dr. Srikanth*[1], Dr. Harshad M.Shah[2], Dr. Shivamurthy M.C[3], Dr. Niveditha[3]
[1]Department of Pharmacology, Khaja Banda Nawaz institute of medical sciences, Gulbarga, 585104, India
[2]Department of Orthopedics, M.S.Ramaiah medical college, MSR nagar, MSRIT post, Bangalore, 560054, India
[3]Department of Pharmacology, M.S.Ramaiah medical college, MSR nagar, MSRIT post, Bangalore, 560054, India
*email: pharmacsrikanth@gmail.com - Tel.:+91-9880695027

Summary

Dexketoprofen in osteoarthritis

Background: Osteoarthritis is one of the most common forms of arthritis and a major cause of disability. Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in the management of osteoarthritis. An NSAID with high efficacy, good tolerability and devoid of adverse cardiovascular effects is preferred by physicians. Dexketoprofen trometamol is the tromethamine salt of dexketoprofen, the S-enantiomer responsible for the pharmacological activity of ketoprofen.

Aims: To compare the efficacy and tolerability of dexketoprofen trometamol and diclofenac sodium in osteoarthritis patients.

Materials and Methods: The study was a randomized, open label, comparative study conducted from November 2009 to April 2011. The patients were randomized in 1:1 ratio into two treatment groups. Patients either received Dexketoprofen Trometamol 25mg thrice daily or Diclofenac Sodium 50mg mg thrice daily for 8 weeks.

Statistical analysis used: Student t test (two tailed, independent), Mann Whitney U test, Chi-square/ Fisher Exact test.

Results: Of 106 patients evaluated for the study, 92 were treated (46 with dexketoprofen, 46 with diclofenac) and 85 completed (42 with dexketoprofen and 43 with diclofenac) the 8 week treatment period. Dexketoprofen improved all parameters with an efficacy comparable to diclofenac. No statistical difference was found between the two groups in terms of reduction of pain on visual analogue scale and WOMAC scale. Adverse events were mainly gastro intestinal, and were comparable between the groups.

Conclusions: Oral dexketoprofen trometamol 25mg three times daily is as effective as diclofenac 50mg three times daily for the treatment of pain in osteoarthritis of knee.

Key-words: Osteoarthritis therapy, nonsteroidal anti-inflammatory drug, dexketoprofen trometamol, diclofenac sodium

Introduction

Osteoarthritis (OA) is a most common arthritis in adults, which affects 18% women and 10% men (aged > 60 years) worldwide [1]. Osteoarthritis (OA) is recognized by degeneration of articular cartilage, synovitis, remodeling of subchondral bone and atrophy/weakness of joint muscles.

OA is a major cause of impaired mobility that has a serious detrimental impact on a patient's quality of life and their ability to perform normal daily activities [2]. Indeed, it is associated with a substantial non-fatal burden of disease, estimated to account for 2.8% of total years of living with disability [3].

The pharmacological options for treating OA pain include simple analgesics (e.g. acetaminophen/paracetamol), traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors. Although the efficacy of traditional NSAIDs for relieving OA pain is well established, they can be associated with serious gastrointestinal (GI) complications [4,5].

Since long term NSAID treatment is indicated for osteoarthritis, the ideal agent should have good efficacy and a low propensity to cause adverse effects. Diclofenac is a potent NSAID with analgesic and anti-inflammatory activity. It is the most extensively used NSAID in treatment of rheumatoid arthritis, osteoarthritis, post-traumatic and post-operative conditions.

Racemic ketoprofen is used as an analgesic and an anti-inflammatory agent, and is one of the most potent in vitro inhibitor of prostaglandin synthesis, but is also implicated as having an association with higher risk of serious gastrointestinal bleeding events than other NSAIDs [6]. Racemic ketoprofen is a 50:50 mixture of S (+) - and R (-) enantiomers.

Most or all COX inhibitory activity of ketoprofen is attributed to the S (+) enantiomer (dexketoprofen) [7]. The translation of the advantages of dexketoprofen into therapeutics is the more rapid onset of action of (S) + ketoprofen as a result of its formulation as a water soluble tromethamine salt, has been shown in several clinical trials [8-10].

Till now only two trials have tested the efficacy of dexketoprofen in osteoarthritis [11, 12] and these trials lasted only for two to three weeks. As there are few studies on comparison of dexketoprofen and diclofenac in treatment OA, the present study aims to compare the efficacy and tolerability of dexketoprofen and diclofenac in treatment of osteoarthritis.

Materials and Methods

Study design:

This was an 8-week, randomized, open labelled, comparative study. The study was initiated after the approval from institutional ethics committee. The study was conducted from Nov 2009 to April 2011. Written informed consent was obtained prior to initiation of the study. Good Clinical Practice guidelines were adhered. The patients were randomized in 1:1 ratio into two treatment groups. Patients either received Dexketoprofen Trometamol 25mg thrice daily or Diclofenac sodium 50mg thrice daily. Both the treatments were administered orally for 8weeks. Patients were allowed to take antacids to control GI symptoms. Paracetomol was used as the rescue medication. No other analgesics were allowed during the study period.

Study population:

Symptomatic patients with OA as defined by the American College of Rheumatology criteria were recruited in the study with the following inclusion and exclusion criteria.

Inclusion criteria:

1) Males and females aged between 40 to 70 years.

2) Patients fulfilling the clinical and radiological criteria of osteoarthritis of knee.

3) Minimum Western Ontario MacMaster

(WOMAC) Index score of 40, visual analogue scale (VAS) score of 4 mm at the time of screening.

4) Knee pain attributable to osteoarthritis of at least 3 months duration.

5) Patients also needed to be on NSAID or other analgesic therapy.

Exclusion criteria:

1) Patients with history of hypersensitivity to NSAIDs.

2) Pregnant and lactating women.

3) Patients with concurrent medical diseases like uncontrolled diabetes mellitus and hypertension, congestive cardiac failure, hepatic and renal impairment.

4) Patients with history of peptic ulcer, asthma and oesophageal varices.

5) Inflammatory joint diseases (rheumatoid arthritis, ankylosing spondylitis, psoriasis, gout), neuropathic, congenital or metabolic conditions affecting knee joint.

6) Patients requiring surgery for knee osteoarthritis.

7) Patients on medications such as aspirin, steroids, anticoagulants and any other concomitant medication which can interfere with the study.

Sample size calculation:

The sample size was calculated with a power of 80% to detect a difference at the 95% confidence interval. Considering a type I error (α) of 5% and type II (β) error of 20% sample size estimated was 80. Assuming that around 10% of patients will be lost to the follow up, a total of 90 patients were recruited to ensure there were 80 evaluable patients.

Assessments:

Clinical assessment was done by calculating WOMAC scores, visual analogue scores for pain and joint tenderness. Tolerability assessment was based on adverse events. Adverse events were monitored and noted at every visit.

1) Patient's pain and functional activity was assessed by WOMAC Index and a 10 mm visual analogue scale (VAS).

2) Study of joint tenderness, i.e. pain on palpation or in response to passive motion. It was graded on a 0–3 scale [(no pain on palpation =0), (patient states there is pain =1), (Pain and wincing =2), (withdraws =3)].

Adverse events were monitored at each visit. For all adverse events, the investigator recorded the intensity and relation to the test drug. Certain adverse events such as Epigastric discomfort, Dyspepsia, Abdominal pain, Diarrhoea, Flatulence, and Dizziness were specifically asked at each visit for tolerability assessment. These were anticipated adverse events, which were prospectively identified and were sought with the intention to find the difference between the two study drugs.

Method of Statistical Analysis:

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean ± SD and results on categorical measurements are presented as percentage. Significance is assessed at 5% level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups inter group analysis) on metric parameters, Mann Whitney U test has been used to find the significance between two groups for parameters on non-interval scale.

Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group. Chi-square/ Fisher Exact test has been used to find the signifi-

cance of study parameters on categorical scale between two or more groups.

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value: 0.01<P 0.05)

** Strongly significant (P value: P0.01)

Statistical software SPSS 15.0 and Stata 10.1, were used for the analysis

Results

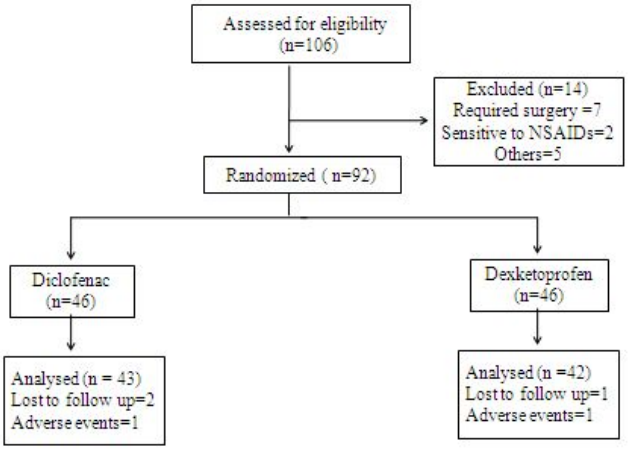

Figure 1: Flow chart of the study

see Table 1.

see Table 2.

see Table 3.

see Table 4.

see Table 5.

Discussion

Osteoarthritis is a chronic degenerative disorder characterized by cartilage loss. It is highly prevalent and major cause of disability in the elderly. Osteoarthritis is an appropriate model for assessing the efficacy of new analgesics at repeated doses [13]. The decision to use NSAIDs in patients with osteoarthritis requires a delicate balance between the effective pain relief and potential adverse reactions and complications.

Recently, the new cyclo-oxygenase-2 (COX-2) selective inhibitors have been increasingly used. Their efficacy is comparable to conventional NSAIDs. Although COX-2 inhibitors seem to have lower risk of GI toxicity, rofecoxib has been found to be associated with an increased risk of cardiovascular event, resulting in its withdrawal from the market on September 30, 2004[14, 15]. It is not clear whether this is a class effect for all COX-2 inhibitors.

Dexketoprofen trometamol is a water-soluble salt of ketoprofen, an NSAID used therapeutically since 1973. Whereas racemic ketoprofen is one of the most potent known in vitro inhibitors of prostaglandin synthesis, this effect is exclusively due to the S(+) enantiomer (dexketoprofen), R(–) ketoprofen (levoketoprofen) being devoid of such activity.

Racemic ketoprofen has potent analgesic properties that have been demonstrated in a large number of studies, including the treatment of arthritic diseases [16]. When using a ratio measuring the dissociation between the analgesic and anti-inflammatory effects in animal models, ketoprofen shows a potency ratio that clearly favours its analgesic over its anti-inflammatory effects; this result correlates with its potency shown in clinical models of analgesia.

Pharmacokinetic studies in healthy volunteers have shown a favourable pharmacokinetic profile of dexketoprofen compared with the acid form of dexketoprofen and racemic ketoprofen, especially in terms of a shorter time in reaching maximum plasma concentrations, which is likely to translate into a more rapid onset of action [17].

In the present study dexketoprofen improved all outcome parameters. Dexketoprofen reduced both WOMAC score and VAS more than that of diclofenac though it did not have statistically significance (P>0.05). Joint tenderness also was reduced more

with dexketoprofen, but it did not have statistically significance (P>0.05).

This finding suggests that in the treatment of knee osteoarthritis, the therapeutic benefits of dexketoprofen are at least equal to those obtained with diclofenac. It is conceivable that dexketoprofen may even be somewhat superior to diclofenac in longer term treatment, as it has shown significantly greater analgesic effect in comparison with diclofenac regarding the percentage decrease of pain severity.

Regarding tolerability, the nature and frequency of adverse events seen in this study are consistent with those usually seen with other NSAIDs. Most adverse events of both the study medications were of mild or moderate intensity, the most common being gastrointestinal disorders such as abdominal pain and dyspepsia.

Dexketoprofen was associated with less number of adverse events when compared with diclofenac, but it did not have statistical significance (P>0.05).

Two trials tested dexketoprofen 25 mg three times a day against ketoprofen 150 mg daily and diclofenac 150 mg daily in patients with established arthritis [11, 12]. Over a period of two or three weeks of treatment there were no differences between dexketoprofen and diclofenac at these doses, though dexketoprofen 75 mg daily was superior to ketoprofen 150 mg daily.

A recent systematic review concluded that, dexketoprofen was at least equivalent in efficacy to the comparator drugs with known analgesic efficacy [18]. Regarding adverse events, this systematic review concluded that adverse event withdrawal was not different between dexketoprofen and comparator analgesics, the different conditions and comparators studies precluded any formal analysis.

Although dexketoprofen has been evaluated in various conditions such as postsurgical pain, dental pain, acute low back pain etc, due to some unknown reasons till now only few trials have evaluated the efficacy and safety of dexketoprofen in osteoarthritis.

Dexketoprofen has been evaluated in international studies and is indicated for the relief of pain and inflammation associated with postsurgical pain, dental pain, acute low back pain etc; however its efficacy in Indian patients has not been evaluated. This study not only evaluates its efficacy in patients with osteoarthritis but also compares it with diclofenac, which is one of the widely used drug for chronic pain.

Limitations of the Study

Limitation of the present study is the study design, it was an open labelled study, and quality of life was not assessed in the present study, which is important in chronic diseases such as osteoarthritis.More randomized, double blind studies with large sample size are needed to establish the efficacy and tolerability of dexketoprofen.

Conclusion

From the results of this study it can be concluded that dexketoprofen 25mg three times daily has an efficacy profile equivalent to that of diclofenac 50mg three times daily for oral symptomatic treatment of knee osteoarthritis, and a better tolerability profile than diclofenac. It is a well-tolerated alternative to diclofenac.

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Variables	Diclofenac	Dexketoprofen	P value
Number of patients	43	42	-
Male : Female	18:25	15:25	0.561
Age in years	56.02±5.71	54.67±4.65	0.234
Weight (kg)	64.28±5.38	64.10±5.72	0.879
Duration of OA in months	9.12±2.07	9.12±2.58	0.996
OA knee (one: Both)	32:11	30:12	0.756
SBP (mm Hg)	126.14±5.48	127.04±5.64	0.454
DBP (mm Hg)	80.19±3.17	79.52±3.33	0.350

Table 1: Demographic data in the treatment groups
OA=osteoarthritis SBP=systolic blood pressure DBP=diastolic blood pressure
Baseline demographics are similar in two groups with no statistically significant difference

WOMAC score	Diclofenac n=43	Dexketoprofen n=42	P value
Baseline	49.12±2.85	50.12±3.09	0.124
2nd week	43.63±2.63	43.17±3.26	0.474
4th week	38.51±3.01	38.14±3.35	0. 595
8th week	32.40±2.81	32.31±2.97	0.891
Difference from baseline			
2nd week	5.48±0.74	6.95±0.96	-
4th week	10.61±1.42	11.98±1.93	-
8th week	16.72±1.58	17.81±2.13	-
P value from baseline			
2nd week	<0.001**	<0.001**	-
4th week	<0.001**	<0.001**	-
8th week	<0.001**	<0.001**	-

Table 2: Comparison of WOMAC score in two groups of patients
**both the treatments reduced the Womac score which was highly significant.

No statistically significant difference between the two groups (P>0.05).

VAS	Diclofenac (n=43)	Dexketoprofen (n=42)	P value
Baseline	7.09±0.75	6.93±0.81	0.334
2nd week	6.12±0.85	5.81±0.77	0.086+
4th week	5.14±0.80	5.07±0.75	0.687
8th week	4.30±0.67	4.21±0.57	0.516
Difference from baseline			
1st month	0.97±0.74	1.12±0.88	-
4th week	1.95±0.87	1.86±0.89	-
8th week	2.79±0.94	2.71±0.89	-
P value from baseline			
2nd week	<0.001**	<0.001**	-
4th week	<0.001**	<0.001**	-
8th week	<0.001**	<0.001**	-

Table 3: Comparison of pain on visual analogue scale at rest in two groups of patients
+ Suggestive significance (P value: 0.05<P<0.10)
**both the treatments reduced the visual analogue scale (VAS) at rest which was highly significant.
No statistically significant difference between the two groups (P>0.05)

Joint tenderness	No pain	Pain	Pain and Wincing	Withdrawal
Diclofenac(n=43)				
Baseline	7(16.3%)	22(51.2%)	9(20.9%)	5(11.6%)
2nd week	15(34.9%)	19(44.2%)	6(14%)	3(7%)
4th week	20(46.5%)	15(34.9%)	5(11.6%)	3(7%)
8th week	25(58.1%)	12(27.9%)	4(9.3%)	2(4.7%)
% change	+41.8%	-23.3%	-11.6%	-6.9%
Dexketoprofen(n=42)				
Baseline	8(18.6%)	19(44.2%)	10(23.3%)	5(11.6%)
2nd week	16(37.2%)	14(32.6%)	10(23.3%)	2(4.7%)
4th week	20(46.5%)	12(27.9%)	8(18.6%)	2(4.7%)
8th week	25(58.1%)	10(23.3%)	5(11.6%)	2(4.7%)
% change	+39.6%	-20.9%	-11.7%	-6.9%
P value between the groups				
Baseline = 0.966	2nd week = 0.903	4th week = 0.924	8th week = 0.988	

Table 4: Comparison of Joint tenderness on 0-3 point scale in two groups of patients
No statistically significant difference between the two groups (P>0.05).

Adverse events	Diclofenac (n=43)	Dexketoprofen (n=42)	P value
Epigastric discomfort	16(37.2%)	12(28.6%)	0.397
Dyspepsia	10(23.3%)	9(21.4%)	0.840
Abdominal pain	7(16.3%)	6(14.3%)	0.799
Nausea	9(20.9%)	10(23.8%)	0.750
Diarrhoea	6(14%)	7(16.7%)	0.728
Flatulence	6(14%)	6(14.3%)	0.965
Dizziness	1(2.3%)	0(0%)	1.000

Table 5: Comparison of adverse events in two groups of patients
No statistically significant difference between the two groups (P>0.05).