Safety profile of topical diclofenac: a meta-analysis of blinded, randomized, controlled trials in musculoskeletal conditions

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CRD summary
The review concluded that topical diclofenac appeared to be generally well tolerated for cutaneous use in acute and chronic musculoskeletal conditions. The differences across the studies, small sample sizes and uncertain methodological quality of included trials limits the reliability of the pooled results so the authors’ conclusions should be interpreted with a degree of caution.

Authors' objectives
To evaluate the risk of adverse events with topical diclofenac for the treatment of acute and chronic musculoskeletal conditions.

Searching
MEDLINE was searched to March 2010. Search terms were reported. The reference lists of relevant articles were searched.

Study selection
Blinded randomised controlled trials (RCTs) of topical diclofenac in patients with osteoarthritis, rheumatic disease and musculoskeletal soft tissue injuries were eligible for inclusion. Unblinded trials were excluded. Trials in patients with mouth or eye diseases, actinic keratoses, post-surgical pain or healthy patients were excluded. Direct comparisons of diclofenac formulations were also excluded.

The included trials studied topical diclofenac versus active and non-active comparators in patients with a mean age of 56.6 years. The most common diclofenac formulation was gel. Around half of the trial patients had a diagnosis of osteoarthritis. The proportion of male patients was 48%.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state if they assessed quality.

Data extraction
Data were extracted (using a standard form) on all adverse events, local adverse events, withdrawals due to all adverse events, withdrawals due to local adverse events and physician and/or patient rated tolerance. Data were used to calculate relative risks (RRs), with 95% confidence intervals (CIs). Trial authors were contacted for missing data, where necessary.

One reviewer extracted data, which was checked for accuracy by a second reviewer.

Methods of synthesis
Fixed-effect meta-analysis was used to calculate pooled relative risks, with 95% confidence intervals. Analyses were stratified by active versus non-active comparator. Statistical heterogeneity was assessed using I² and X². If statistical heterogeneity was detected then a random-effects model was used. Subgroup analysis was undertaken for the type of diclofenac formulation and the indication. Meta-regression was used to determine the association between adverse events and several factors. Publication bias was assessed using funnel plots and Egger’s test.

Results of the review
A total of 37 blinded RCTs (7,661 patients) were included in the review. The study sample size ranged from 10 to 1,575 patients. The mean length of follow-up was three weeks.
Diclofenac versus non-active comparator: Compared with non-active comparator, topical diclofenac was associated with a statistically significantly greater rate of: all adverse events (RR 1.11, 95% CI 1.02 to 1.20; 20 RCTs); withdrawals due to all adverse events (RR 1.65, 95% CI 1.10 to 2.48; 19 RCTs); local adverse events (RR 1.40, 95% CI 1.15 to 1.70; 19 RCTs); and withdrawals due to local adverse events (RR 2.37, 95% CI 1.22 to 4.63; 18 RCTs). There was a marginally statistically significant difference in physician rated tolerance favouring topical diclofenac (RR 1.04, 95% CI 1.00 to 1.09; four RCTs) but there was no significant difference in patient rated tolerance.

Diclofenac gel versus active comparator: Compared with active topical comparator, topical diclofenac gel was associated with a statistically significantly lower rate of all adverse events (RR 0.53, 95% CI 0.32 to 0.89; 11 RCTs), but there was no difference in terms of withdrawals due to all adverse events, local adverse events, withdrawals due to local adverse events, physician rated or patient rated tolerance. Compared with active oral comparator, topical diclofenac was associated with statistically significantly more local adverse events (RR 8.38, 95% CI 5.08 to 13.85; 3 RCTs) and withdrawals due to local adverse events (RR 31.0, 95% CI 4.25 to 225.80; 2 RCTs), but there was no statistically significant difference in all adverse events or withdrawals due to all adverse events.

There was no evidence of statistical heterogeneity in the analyses, apart from withdrawals due to all adverse events in the diclofenac versus active oral comparator (I²=74%). Subgroup analysis indicated a difference in the rates of adverse events depending on the formulation of diclofenac (highest with solution) but meta-regression did not support this finding. Meta-regression indicated that older age was a predictor of local adverse events with topical diclofenac, and studies with longer follow-up were also associated with local adverse events. There was no evidence of publication bias.

Authors’ conclusions
Topical diclofenac appeared to be generally well tolerated for cutaneous use in acute and chronic musculoskeletal conditions.

CRD commentary
Inclusion criteria for the review were clearly defined, but the search was limited as only one relevant data source was searched. Publication bias was not detected. Attempts were made to reduce reviewer error and bias during data extraction, but the authors did not state if such measures were taken for study selection.

Quality assessment did not appear to have been undertaken, but all of the included trials were blinded RCTs. The studies varied considerably in terms of patient characteristics, diclofenac formulation and comparator, which the authors acknowledged. Several studies had small sample sizes. Trials were combined using standard statistical methods and statistical heterogeneity was assessed. The differences across the studies, small sample sizes and uncertain methodological quality of included trials limits the reliability of the pooled results; hence the authors’ conclusions should be interpreted with a degree of caution.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that diclofenac formulations differ in respect to adverse event risk and should be analysed separately. Future studies should use standardised methods of recording adverse events. A systematic review of long-term safety studies would be a useful complement to the current review.

Funding
Authors were employees or received consultancy payments from Novartis, and the manuscript was prepared by a medical writer sponsored by Novartis.

Bibliographic details

PubMedID
21231861
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.