The safety profile of nonprescription ibuprofen in multiple-dose use: a meta-analysis

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Authors' objectives
To compare the incidence of adverse experiences during the multiple-dose use of non-prescription ibuprofen to a placebo.

Searching
MEDLINE, EMBASE, BIOSIS Previews, International Pharmaceutical Abstracts, SciSearch, TOXLINE and Chemical Abstract Search were searched (years and search terms not stated). Bibliographies of recent review articles were search. Independent studies conducted by Whitehall-Robins Healthcare over a period of 5 years were included (not stated how these studies were identified).

Study selection
Study designs of evaluations included in the review
Randomised, double-blind placebo controlled parallel group clinical trials (RCTs).

Specific interventions included in the review
Multiple doses of a marketed formulation of racemic ibuprofen, within over the counter (OTC) limits - up to 1200mg/day for a maximum of 10 days, for conditions appropriate for a non-prescription analgesic/antipyretic. Six studies used 1200mg/day and 2 used 800mg/day.

Participants included in the review
Participants were aged 12-97 with a mean age of 47, 43% male and 86% Caucasian, 9% black, 1% Asian and 4% Hispanic.

Outcomes assessed in the review
Spontaneously reported adverse effects in the treatment groups. Adverse effects were mapped to the most clinically appropriate COSTART (Coding Symbol Thesaurus for Adverse Reaction Terms) term and then classified according to the COSTART dictionary-assigned body system.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
Adverse effects were coded according to COSTART terms (see Other Publication of Related Interest). No further details provided.

Methods of synthesis
How were the studies combined?
A meta-analysis was conducted by pooling individual study data from all included studies, separately for only the single-day studies and for the multi-day studies, and separately by each COSTART body system. The fixed-effect method was used to pool studies. Odds-ratios were calculated and pooled as adjusted Mantel-Haenszel odds ratios with their 95% confidence intervals.
How were differences between studies investigated?
Breslow-Day p-values were calculated to test for heterogeneity of the odds-ratios among studies.

Results of the review
Eight clinical trials, all sponsored by Whitehall-Robins Healthcare. Three studies were in osteoarthritis pain, two in delayed-onset muscle soreness, one in sore throat pain, one in dental pain, and one on maximum-use safety and tolerance of ibuprofen. Study duration ranged from 1 to 10 days: 4 lasted one day, and 4 had multiple day duration. The total number of subjects in these trials was 1094 in the ibuprofen groups and 1093 in the placebo groups.

In each individual study the number of reported adverse effect frequency among subjects receiving ibuprofen was less than or equal to the placebo. The Breslow-Day p-value for the presence of heterogeneity was 0.736 suggesting that there was little heterogeneity in the odds ratios between studies. The pooled odds ratio for any adverse effect in the ibuprofen compared to the placebo group was 0.79 (95% CI: 0.65, 0.96, p=0.018) suggesting that there were fewer adverse effects in the ibuprofen compared to the placebo groups. This was largely due to the greater incidence of headaches in the placebo groups (15.9% in the placebo group compared to 9.9% of ibuprofen groups, p<0.001). Excluding headaches the placebo and control groups had comparable proportions of subjects who experienced adverse effects. The pooled odds ratios were similar for the single day (0.73, 95% CI: 0.37, 1.44) and multi-day studies (0.79, 95% CI: 0.64, 0.98) were similar. A sub-group analysis was performed to investigate whether any specific adverse effects were greater in the ibuprofen than the placebo groups. The only specific adverse effects that were significantly or marginally significantly greater in the ibuprofen treatment groups were urinary tract infection (4/1094 subjects in the ibuprofen groups compared to 0 in the placebo group, p=0.045) and dizziness (OR=2.04, p=0.052). There were no significant differences for any specific digestive system adverse effects between the ibuprofen and placebo groups.

Authors’ conclusions
Nonprescription ibuprofen has an excellent side effect profile in multiple-dose use.

CRD commentary
A reasonable review of the area. It appears that a thorough literature search was conducted. However, the authors do not state the years the databases were searched, or what search terms were used. Studies conducted by Whitehall-Robins Healthcare were identified but it is not stated how these were identified and why other such studies were not searched for. This is of particular importance as only studies conducted by this organisation were included in the review. The authors do not state whether there were any restrictions on language of publication. Inclusion and exclusion criteria are clearly stated and the reason that some of the identified studies did not meet inclusion criteria are discussed. No information is provided on how studies were assessed for relevance or how and what data was extracted from the included studies. No validity assessment was undertaken. An appropriate statistical analysis was carried out. The authors conclusions are supported by the data presented. However, the fact that all the studies were sponsored by the same organisation suggests that these results may be susceptible to bias and thus should be interpreted with caution.

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

Bibliographic details

PubMedID
10234601

Other publications of related interest
1. U.S. Food and Drug Administration. COSTART: Coding Symbol Thesaurus for Adverse Reaction Terms. 3rd ed.
Rockville (MD): Center for Drugs and Biologics, Division of Drug and Biological Products Experience; 1989.

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