Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever

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CRD summary
This review concluded that ibuprofen, paracetamol and placebo for paediatric pain and fever had comparable profiles for gastrointestinal symptoms, asthma and renal adverse effects. This was generally a well-conducted review and the authors’ conclusions are likely to be reliable, although (as the authors acknowledged) some caution may be merited based on comparisons with placebo from a few small studies.

Authors’ objectives
To compare the tolerability and safety of ibuprofen and paracetamol when used as anti-pyretic and analgesic agents in children up to 18 years of age.

Searching
MEDLINE, EMBASE, The Cochrane Library, ACP Journal Club and Pascal were searched for publications in English, French, Dutch, German or Portuguese. Search dates ranged from 1950 to November 2008. The search strategy for one database was available as an online supplement; other databases were available on request from the authors.

Study selection
Randomised controlled trials (RCTs), controlled observational studies (assessing rare adverse events) and large case series (>1,000 participants) that compared efficacy, safety and tolerability of ibuprofen and/or paracetamol with placebo in children up to 18 years of age with pain and/or fever were eligible for inclusion. Outcome measures included: adverse events that required discontinuation of medication; systemic reactions related to ibuprofen or paracetamol; fatal or life-threatening adverse events or those that required hospitalisation; and serious adverse events that did not require hospitalisation.

Included studies were undertaken in North America, Europe and Asia (half of them in either USA or France). Most of the included RCTs compared ibuprofen with paracetamol. A third of the studies were funded by pharmaceutical companies.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved through consensus and checked by a third reviewer.

Assessment of study quality
Two reviewers independently assessed study validity using checklists for RCTs and other study designs from CRD report 4. No specific details of criteria used were reported but use of allocation concealment, sequence generation, blinding and intention to treat analysis were reported. Disagreements were resolved through consensus.

Data extraction
Data for dichotomous outcomes were extracted to calculate relative risks (RR) or odds ratios (OR) with 95% confidence intervals (CIs). Means and standard deviations were extracted for continuous outcomes to calculate the weighted mean difference (WMD) and 95% CI.

Two reviewers independently performed data extraction; disagreements were resolved by consensus.

Methods of synthesis
Pooled relative risks, odds ratios and weighted mean differences, and their 95% CI, were calculated using a fixed-effect model. Heterogeneity was assessed using the I² test. A narrative synthesis was reported where it was not suitable to pool data.

Results of the review
A total of 24 RCTs (119,176 participants) were included in the review. Allocation generation sequence was unclear in seven studies. Allocation concealment was unclear in 12 studies. Information on blinding was included in 15 studies. Intention-to-treat analysis was undertaken in 17 studies. A further 12 studies (non-RCTs) met the inclusion criteria for adverse event data: seven case control studies (1,221 participants); two cohort studies (213,828 participants); and three case series (6,410 participants).

For ibuprofen, paracetamol and placebo serious adverse events were rare and all groups had comparable tolerability and safety profiles with no significant difference in systemic reactions between the groups. Relative risk for experiencing an adverse event with ibuprofen versus placebo was 1.39 (95% CI 0.92 to 2.10; four studies). Relative risk for experiencing an adverse event with paracetamol versus placebo was 1.57 (95% CI 0.74 to 3.33; four studies). Relative risk for experiencing an adverse event with ibuprofen compared with paracetamol was 1.03 (95% CI 0.98 to 1.10; 18 studies). There was no significant heterogeneity for these comparisons.

The narrative synthesis of results from non-RCTs revealed conflicting evidence regarding hepatic injury for paracetamol (two studies) and necrotising fasciitis during primary varicella infection for ibuprofen and paracetamol treatment (four studies).

**Authors’ conclusions**
Ibuprofen, paracetamol and placebo had similar tolerability and safety profiles in terms of gastrointestinal symptoms, asthma and renal adverse effects. These data may not have reflected over-the-counter use, but the results were still relevant in the context of any safety concerns related to general ibuprofen or paracetamol treatment in children.

**CRD commentary**
The review question and inclusion criteria were clear. Little information was provided about participants in the included studies, which made it difficult to assess how generalisable the results of the review were. A number of relevant databases were searched for studies in English, French, Dutch, German or Portuguese; therefore, language bias could not be ruled out. It was unclear whether efforts were made to locate unpublished studies; some studies may have been missed. All stages of the review process were undertaken in duplicate, which reduced potential for error and bias.

Seemingly appropriate criteria were used to assess the quality of included studies, but measures and criteria used were not reported in detail for each study. Appropriate methods were used for the meta-analyses. Heterogeneity was assessed. The findings of the meta-analyses that compared ibuprofen and paracetamol were driven by one large study; small numbers of studies were compared to placebo for either of the treatment regimens. A narrative synthesis was appropriate to use where it was inappropriate to pool studies.

This was generally a well-conducted review and the authors’ conclusions are likely to be reliable, although (as acknowledged by the authors) some caution may be merited based on comparisons with placebo from a few small studies.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that future RCTs should be rigorously designed to assess safety and tolerability of ibuprofen and paracetamol for management of paediatric pain and fever; long-term studies were required to monitor adverse events from these treatment regimens.

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