Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone

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CRD summary
The author concluded there was little evidence of benefit or harm from paracetamol and ibuprofen combined compared to using each alone; there was no evidence of increased toxicity. Due to the relatively small size and number of studies, imperfections in the conduct of the review, uncertain study quality and limited comparability of the studies, reliability of the conclusions is unclear.

Authors' objectives
To evaluate the evidence on paracetamol and ibuprofen combined to treat fever.

Searching
MEDLINE and EMBASE were searched up to May 2011. Guidelines from National Institute for Health and Clinical Excellence (NICE) on the treatment of fever in children under five years old and from the American Academy of Pediatrics were searched for additional references. Only studies in English were included. Search terms were reported.

Study selection
Studies were eligible if they compared the effect of any dose of a combination of paracetamol and ibuprofen (together or separately) with either drug alone in children with fever. Randomised controlled trials (RCTs) that reported measures of temperature, comfort, side effects or toxicities were eligible.

Participant age ranged from six months to 14 years. Most patients had a temperature of at least 38°C, which was measured by a variety of routes. Dosages, timings and combinations varied between studies. Paracetamol doses ranged from 10 to 15mg/kg and ibuprofen ranged from five to 10mg/kg. No dosage adjustments were performed for the combination treatments. Dosing intervals were similar: paracetamol was given every four to six hours, and ibuprofen every six to eight hours. Treatments in the intervention group were either combined or alternated.

The author did not state how many reviewers selected the studies for inclusion.

Assessment of study quality
Quality of was assessed using the Consolidated Standards of Reporting Trials (CONSORT) statement checklist which included: eligibility criteria and setting, details of intervention; primary and secondary outcomes clearly defined, sample size, randomisation, statistical method, blinding, loss to follow-up, baseline characteristics, results and generalisability.

Each item was rated as excellent, sufficient, moderate or insufficient. A score ranging from 0 to 22 was given to each study. Higher scores indicated higher reporting quality.

The author did not state how many reviewers performed the quality assessment.

Data extraction
Data on temperature (the primary outcome), comfort and side effects were extracted. Data on side effects were reported qualitatively.

Data were extracted by a single reviewer on two separate occasions.

Methods of synthesis
A narrative synthesis was used, structured by outcome and time-point.

Results of the review
Seven studies were included in the review (more than 906 children). Reporting quality scores ranged from 17 to 22 out of 22. Follow-up ranged from two hours to ten days.
Effect on temperature

There were no significant benefits at time periods below four hours; thereafter studies showed statistically significant declines in temperature \((p \leq 0.05)\) which favoured combined treatment compared to individual therapy. Two trials showed temperature declines of 0.6°C four hours after combined treatment was received, between 0.8°C and 1.1°C at five hours and between 0.1°C and 1.2°C at six hours. Alternating therapy showed comparable benefits according to one trial, with reductions of 0.6°C at four hours, 1.2°C at five hours and 1.6°C at six hours.

More children were afebrile in the combined group compared to ibuprofen at seven and eight hours, but no significant difference was found at six hours follow-up, according to one study. Longer term outcomes were also reported.

Effect on discomfort and side effects

No evidence of difference in side effects between intervention and control groups was found. There was conflicting but limited evidence on the effect of treatment on comfort; one of two studies reported a significant difference between intervention and control, which favoured paracetamol alone on the first day and combined treatment on subsequent days.

Authors’ conclusions

There was little evidence of benefit or harm from combined paracetamol and ibuprofen compared to using each drug alone.

CRD commentary

The review question and inclusion criteria were clear. A limited number of sources were searched. Studies not written in English were excluded. The author acknowledged that some studies may have been missed for this reason. The potential impact of this limitation on the review findings was unclear. The author did not state how many reviewers selected the studies and extracted the data. Only one reviewer performed the quality assessment, but this was on two separate occasions.

Studies were generally scored as being high quality, but there were no details on which criteria were problematic. The choice of a narrative synthesis appeared appropriate, given the differences between the studies (notably in outcomes and follow-up duration). The author did not state what statistical methods were used to calculate effect sizes within the included studies, or whether he attempted to extract or calculate confidence intervals, which made the interpretation of the results difficult.

Studies were generally small so some may have been underpowered (as noted by the author). Follow-up duration was short, which limited the reliability of the results (notably side effects and toxicities).

The conclusions generally reflected the evidence. Due to the relatively small size and number of studies, imperfections in the conduct of the review, lack of clarity around the validity and limited comparability of the studies, the reliability of the conclusions is unclear.

Implications of the review for practice and research

Practice: There was insufficient evidence to recommend the combined use of paracetamol and ibuprofen. Intervention should focus instead on education of professionals and parents to promote a better understanding of fever, notably that it was a symptom. Resources such as the NICE "traffic light" system should be used to properly address the underlying condition.

Research: Further research on the benefits of combined therapy may not have been needed.

Funding

Not stated.

Bibliographic details

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Record Status
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.