

Paracetamol: An evidence summary on possible harm from reducing fever

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Topic

Is the reduction of fever using paracetamol harmful?

Question

Population: All included

Intervention: Fever reduction using paracetamol

Comparison group: No treatment

Outcome: Harmful effects to the patient

Types of studies: Systematic reviews/RCTs/reviews

Rationale for question

There is a fairly entrenched assumption that all fevers should be treated with regular antipyretics. This is on the basis that fever is a negative physiological event. Fever may, however, be a useful component of combating infection.

Inclusion criteria for studies reviewed

Evidence summaries, systematic reviews, randomised controlled trials (RCTs) and review articles were included.

Search strategy

Cochrane Library, PubMed and EMBASE (June 2002).

Fever (MeSH) AND paracetamol OR acetaminophen (MeSH).

Results

There were 235 studies initially identified. There was one systematic review (SR) (Cochrane), two randomised controlled trials (RCTs) and two review articles (RA).

Systematic review

This SR was of high quality and demonstrated excellent representation of the literature and blinded evaluation of their results. They found 91 relevant publications of which 12 were eligible and included. Their studies were limited to RCTs only.

This SR evaluated two primary outcomes, one of which was relevant to this review: comparing paracetamol with placebo or no treatment for fever clearance time and febrile convulsion. They found only one trial relating to fever clearance time and there was no statistical significance between

the two groups. Only one trial mentioned febrile convulsions, however, no convulsions occurred in either group.

The SR had numerous secondary outcomes of which one was relevant to this review: symptom resolution. They found the mean time to symptom resolution or healing did not differ significantly between groups when observed over two to six days. They concluded that the data for the primary outcome was 'sparse' and therefore it was not clear whether paracetamol was effective when compared to placebo or no treatment in reducing duration of fever or reducing risk of febrile convulsions. They make this conclusion based on the lack of evidence, rather than due to paracetamol's ineffectiveness.

Review articles

RA1: This was of good quality, however, it did not outline its literature review or data analysis process. Studies used for evidence were not limited to RCTs.

It came to three main conclusions relevant to this review:

1. That the response of a fever to paracetamol in children will not indicate the severity of the illness and is a bad diagnostic indicator. They compared six studies (five prospective and one retrospective) comparing bacteremic to non-bacteremic illness. Only one study (the retrospective study) showed a significant difference in fever reduction.
2. No evidence to suggest paracetamol use is effective in suppressing febrile seizures, even when given prophylactically.
3. While general experience supports the rationale that paracetamol enhanced patient comfort there have been no carefully controlled efficacy studies to support this. Further, that there is now evidence that in some diseases it may have a negative effect:
 - i. use in chickenpox (see other review in Chickenpox chapter);
 - ii. increases viral shedding, nasal signs and symptoms and suppresses serum neutralising antibody response in adults with rhinovirus infection; and
 - iii. prolongs parasitaemia in children infected with *Plasmodium falciparum*.

RA2 was the same author as RA1 and adds no further information.

RCTs

RCT1: This RCT was of good quality. Its population was of children (aged six months to six years) but it had a low enrolment rate (225 from 654 eligible), which left it open to potential limitations in its applicability to other populations. However, its randomisation process was adequate, which should eliminate biases that would otherwise occur. It had adequate ascertainment of results and measurement techniques.

The study enrolled 225 children, 123 in the paracetamol arm and 102 in the placebo arm. Patients were enrolled only if there was no evidence of bacterial infection. Results were measured using a diary completed by the parent and via telephone questionnaire until the child was fever free for 24 hours. They found there was no statistically significant difference in fever clearance time or improvement in mood, comfort, eating or drinking between the two groups. However, children were statistically significantly more likely to be active (38% vs 11%, $p = 0.05$) and alert (33% vs 12%, $p = 0.036$) after taking paracetamol.

RCT2 has already been reviewed (effect on chicken-pox: see Chickenpox chapter).

Conclusion

In general, there appears to be a lack of good evidence in the literature to answer the question whether using paracetamol to reduce fever is harmful. Both the SR and RA1 conclude that better designed studies need to be performed. In contrast, RCT1 concludes that there was no harmful effect of paracetamol (defined as an increase in severity of symptoms), and that there was a trend towards a modest benefit in patient comfort. (It is interesting to note that despite these findings the authors of this article still conclude that 'we should treat the child and not the thermometer').

However, in specific diseases there seems to be mounting evidence that paracetamol maybe harmful. In the case of chickenpox and viral type illnesses this would be relevant to our population. The warning that paracetamol is a poor diagnostic indicator for bacterial illnesses should be noted. Further, the literature repeatedly states that paracetamol is of no use in prevention of febrile convulsions.

References

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