Reviewer’s report

**Title:** Equal antipyretic efficacy of oral and rectal acetaminophen: a randomized controlled trial [ISRCTN 11886401]

**Version:** 2  Date: 23 March 2005

**Reviewer:** karel allegaert

**Reviewer’s report:**

Nabulsi and colleagues are to be congratulated for their effort to perform a clinical study on a ‘common’ symptom and ‘common’ treatment by comparing the efficacy (antipyretic effect) of paracetamol with the specific emphasis on the relevance of the route and dose. The authors hereby stress the fact that their study used a double blind, double dummy design.

When the aim of the study is considered, this is in line with earlier reports already available in literature and cited in the manuscript, although we found one additional reference (Keinanen S, Eur J Clin Pharmacol 1977).

**Major concerns:**

There are potential biases based on the subject selection criteria (antipyretics stopped > 8 h is rather short, especially for ibuprofen or other non-selective COX inhibitors, antibiotics administered). Although this very likely reflects ‘real clinical life’, it might have confounded the pharmacodynamic effect. This should at least be mentioned in the discussion part of the paper.

It was anticipated that the pharmacodynamic effect might also be variable based on the variability in paracetamol dose administered and route of administration, being the main outcome variable of the study. It is already well known that paracetamol resorption after rectal administration shows much more variability compared to the enteral route (Anderson), that a higher enteral loading dose results in a faster and more pronounced antipyretic effect (Treluyer et al, Pediatrics 2001).

An additional source of variability in pharmacodynamics in the present study very likely is the fact that the authors succeeded to administer the intended 15 mg/kg for the children allocated to the enteral arm of the study, but not in both rectal arms of the study (14.1, range 10.7–18.5) and (31.7, range, 12.5 – 43.4), resulting in an quasi continuum of rectally administered doses instead of two groups. This much higher interindividual dose variation also reflects ‘real clinical life’ but very likely also contributed to the pharmacodynamic variability observed.

It might therefore at least be appropriated to reanalyse the data in both rectal arms to check whether there is a correlation between both ‘continuous’ variables (dose to time to maximum antipyresis).

**Suggestions/minor:**

Why not try an AUC approach to analyse your data ?
Time until temperature < 38.5° might also be a clinical relevant outcome variable
Please recheck your references, authorship in ref 4 is wrong.
The study procedure: it might be better to rephrase the alinea on the administration of investigational drugs (baseline pg 6- top pg 7), it reads as if the investigator know with child receives with drug.
Conclusions: the conclusions part of the paper should be limited to the conclusions, and therefore, it is appropriated to move the sentences on in- versus outpatients and on safety issues to the discussion part of the paper. In addition, it seems correct to state that your observations are in line with the earlier studies.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

The review was in part based on
Prescott LF: Paracetamol, a critical bibliographic review.
Yaffe, Aranda. Neonatal and Pediatric Pharmacology

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
'I declare that I have no competing interests'