A REVIEW ARTICLE

Effectiveness of Oral vs Rectal Acetaminophen

A Meta-analysis

Lee Hilary Goldstein, MD; Maya Berlin, BPharmSce; Matitiahu Berkovitch, MD; Eran Kozer, MD

Objective: To determine, on the basis of published studies, the efficacy of rectal vs oral acetaminophen as treatment of fever and pain.

Data Sources: MEDLINE, PubMed, and the Cochrane database as well as major pharmacologic textbooks and the references of all included studies were searched for studies comparing oral and rectal administration of acetaminophen.

Study Selection: Randomized and quasi-randomized controlled studies comparing rectal and oral administration of acetaminophen were included. Reviews, letters, and studies that compared combined treatments or additional drugs were excluded.

Main Exposure: Oral vs rectal acetaminophen.

Main Outcome Measures: Standardized measures of temperature and pain reduction.

Results: For temperature reduction, 4 studies met the inclusion criteria. The decline in temperature 1 hour after administration of acetaminophen was no different between rectal and oral administration (weighted mean difference [WMD], −0.14°C; 95% confidence interval [CI], −0.36°C to 0.08°C; P for heterogeneity = .49). There was no difference in the decline of temperature 3 hours after administration (WMD, −0.10°C; 95% CI, −0.41°C to 0.21°C; P = .84), the maximum decline in temperature (WMD, −0.10°C; 95% CI, −0.24°C to 0.04°C; P > .99), or the average time to temperature reduction of 1°C (WMD, −0.06°C; 95% CI, −1.34°C to 1.23°C; P < .001). We did not perform a meta-analysis comparing rectal and oral acetaminophen for pain reduction because only 1 study fulfilled the inclusion criteria.

Conclusions: Rectal and oral acetaminophen are comparable with respect to temperature reduction. The American Academy of Pediatrics recommendation to refrain from rectal acetaminophen in children should possibly be revised.


Acetaminophen is one of the most common drugs administered to children, mostly as an antipyretic and analgesic agent, and is currently available for oral and rectal administration as different preparations. The rectal suppositories are often essential for treating febrile children with emesis or other circumstances in which oral treatment is contraindicated. Previous studies on the antipyretic efficacy of rectal acetaminophen have shown conflicting results.1-3 Pharmacokinetic studies of rectal administration of acetaminophen showed up to 9-fold variation of the peak drug levels, often not achieving therapeutic levels.3,5-5 Moreover, the time to peak levels was substantially longer than with oral administration,4 and the appropriate drug interval was longer, 6 to 8 hours compared with 4 to 6 hours for oral administration.5 The variations in pharmacokinetic measures could be a result of variability of venous drainage from the rectum. Drugs administered distally bypass the liver, whereas drugs administered in the proximal part of the rectum are drained into the portal system and are subject to the hepatic first-pass effect.6 The American Academy of Pediatrics (AAP) has therefore discouraged the use of rectal suppositories of acetaminophen owing to concerns of toxic effects and unpredictable pharmacokinetics and pharmacodynamics due to poor and erratic absorption.6

Two recent studies suggested that single doses of oral and rectal acetaminophen have a similar effect on temperature decline in children.8,9 In light of this, we set

Author Affiliations: Medicine C, Haemek Medical Center, Afula, Israel (Dr Goldstein); and Clinical Pharmacology and Toxicology Unit (Ms Berlin and Dr Berkovitch) and Pediatrics Emergency Ward (Dr Kozer), Assaf Harofeh Medical Center, Zerrifin, Israel.
out to find clinical evidence to support or oppose the AAP recommendation. We systematically reviewed the literature and conducted a meta-analysis of all the studies that compared efficacy of oral vs rectal acetaminophen as treatment of pain or fever.

**METHODS**

**DATA SOURCES AND STUDY SELECTION**

A search of the literature was conducted during October 2007 for studies comparing oral and rectal administration of acetaminophen. The following databases were searched electronically by a pharmacist (M. Berlin): MEDLINE (1966 to October 2007), PubMed (1950 to October 2007), the Cochrane database of systematic reviews (2007), and major pharmacologic textbooks.10,11 Keywords were acetaminophen, drug administration routes, dosage forms, body temperature changes, analgesics, pain, and pain measurement. Textbook references, as well as the references of the bibliographies of all the included studies and reviews that were identified by this search strategy, were searched manually.

**INCLUSION CRITERIA**

The inclusion criteria in this study were randomized and quasi-randomized controlled studies comparing rectal and oral administration of acetaminophen, published in any language, with an English abstract. Studies were included only if the principal objective was acetaminophen treatment and only if they specified the temperature reduction or had a scale of monitoring pain reduction and specified the time of temperature and pain measurements. Studies enrolling human patients of all ages were included.

**EXCLUSION CRITERIA**

We excluded reviews, letters, and uncontrolled or nonrandomized studies. Studies that compared combined treatments or had additional drugs were excluded.

The literature search was performed by one of the reviewers (M. Berlin). Titles, abstracts, and, if necessary, full texts and bibliographies of the search results were reviewed by this reviewer. On the basis of this preliminary review, 2 reviewers (a clinical pharmacologist [L.H.G.] and a pharmacist [M. Berlin]) chose studies for detailed review. These 2 reviewers applied selection criteria and decided independently on the studies to be included in the final analysis. A third reviewer (E.K., a pediatrician-toxicologist) resolved any disagreements as to the inclusion or exclusion of a study. The reviewers were not blinded to the source of publications or the authors.

**DATA EXTRACTION AND SYNTHESIS**

The 2 reviewers extracted data by using structured data collection tables. All data entries were double-checked manually, and all discrepancies were resolved by discussion. Each study reported different end points, so we analyzed end points that had been reported in at least 2 of the studies.

We used the Cochrane Review Manager software (RevMan 4.2) to calculate the weighted mean difference (WMD) and 95% confidence interval (CI), assuming a random-effects model.12 Four analyses were conducted. The first 2 analyses compared the temperature decline at 1 and 3 hours, respectively. The third analysis compared the maximum decline in temperature and the fourth compared the time to a temperature reduction of 1°C.

**RESULTS**

**RECTAL VS ORAL ACETAMINOPHEN FOR FEVER REDUCTION**

The search generated 35 titles, of which 14 were selected for complete review. Four of these studies8,9,13,14 met the inclusion criteria (Table) and 10 were excluded. The reasons for exclusion were as follows: no detailed method of randomization,15-18 no specified temperature reduction,15,19-23 not randomized,19-24 uncontrolled,19-23 not rectal vs oral,17,18,21,22 and letter to the editor.16 In 3 of the included studies the subjects were children, and 1 study was of adults. There was a good degree of agreement between the 2 reviewers, and only 1 disagreement had to be resolved by the third reviewer, concerning inclusion of a study published as a letter to the editor. The study was not included.16

We analyzed 4 different aspects of acetaminophen efficacy in temperature reduction. The decline in temperature 1 hour after administration of acetaminophen was no different in rectal vs oral administration (WMD, −0.14°C; 95% CI, −0.36°C to 0.08°C) (Figure 1). Similarly, there was no difference in the decline in temperature 3 hours after administration (WMD, −0.10°C; 95%
phen (WMD, −0.06°C; 95% CI, −1.34°C to 1.23°C) was no difference between oral and rectal acetaminophen (WMD, −0.10°C; 95% CI, −0.24°C to 0.04°C) (Figure 1). The last aspect we analyzed was the average time to temperature reduction of 1°C with rectal vs oral acetaminophen. The results were heterogeneic (P < .001), but there was no difference between oral and rectal acetaminophen (WMD, −0.06°C; 95% CI, −1.34°C to 1.23°C) (Figure 4).

**Table 1.** Oral vs rectal acetaminophen: decline in temperature at 1 hour. CI indicates confidence interval; WMD, weighted mean difference.

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Rectal, Mean (SD)</th>
<th>No.</th>
<th>Oral, Mean (SD)</th>
<th>Prefers rectal</th>
<th>Prefers oral</th>
<th>Weight, %</th>
<th>WMD (Random) (95% CI), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maron and Ickes</td>
<td>20</td>
<td>0.20 (0.76)</td>
<td>20</td>
<td>0.23 (0.48)</td>
<td>20</td>
<td>20</td>
<td>31.30</td>
<td>−0.03 (−0.42 to 0.36)</td>
</tr>
<tr>
<td>Vernon et al</td>
<td>12</td>
<td>0.70 (1.10)</td>
<td>10</td>
<td>0.80 (0.40)</td>
<td>10</td>
<td>10</td>
<td>10.82</td>
<td>−0.10 (−0.77 to 0.57)</td>
</tr>
<tr>
<td>Vernon et al younger</td>
<td>7</td>
<td>0.50 (0.50)</td>
<td>8</td>
<td>1.00 (0.50)</td>
<td>8</td>
<td>8</td>
<td>18.88</td>
<td>−0.50 (−1.01 to 0.01)</td>
</tr>
<tr>
<td>Vernon et al older</td>
<td>24</td>
<td>0.80 (0.68)</td>
<td>23</td>
<td>0.87 (0.55)</td>
<td>23</td>
<td>23</td>
<td>39.00</td>
<td>−0.07 (−0.42 to 0.26)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>63</td>
<td>61</td>
<td></td>
<td></td>
<td>100.00</td>
<td></td>
<td>100.00</td>
<td>−0.14 (−0.26 to 0.08)</td>
</tr>
</tbody>
</table>

**Figure 1.** Oral vs rectal acetaminophen: decline in temperature at 1 hour. CI indicates confidence interval; WMD, weighted mean difference.

CI, −0.41°C to 0.21°C (Figure 2). The maximum decline in temperature was reported in 2 of the 4 included studies and again indicated no difference between oral and rectal administration of acetaminophen (WMD, −0.10°C; 95% CI, −0.24°C to 0.04°C) (Figure 3). The last aspect we analyzed was the average time to temperature reduction of 1°C with rectal vs oral acetaminophen. The results were heterogeneic (P < .001), but there was no difference between oral and rectal acetaminophen (WMD, −0.06°C; 95% CI, −1.34°C to 1.23°C) (Figure 4).

**Table 2.** Oral vs rectal acetaminophen: decline in temperature at 3 hours. CI indicates confidence interval; WMD, weighted mean difference.

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Rectal, Mean (SD)</th>
<th>No.</th>
<th>Oral, Mean (SD)</th>
<th>Prefers rectal</th>
<th>Prefers oral</th>
<th>Weight, %</th>
<th>WMD (Random) (95% CI), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scolnik et al</td>
<td>24</td>
<td>1.60 (1.00)</td>
<td>23</td>
<td>1.70 (0.70)</td>
<td>23</td>
<td>23</td>
<td>8.31</td>
<td>−0.10 (−0.59 to 0.39)</td>
</tr>
<tr>
<td>Nabulsi et al</td>
<td>18</td>
<td>1.60 (0.18)</td>
<td>16</td>
<td>1.70 (0.25)</td>
<td>16</td>
<td>16</td>
<td>91.69</td>
<td>−0.10 (−0.25 to 0.05)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42</td>
<td>39</td>
<td></td>
<td></td>
<td>100.00</td>
<td></td>
<td>100.00</td>
<td>−0.10 (−0.24 to 0.04)</td>
</tr>
</tbody>
</table>

**Figure 2.** Oral vs rectal acetaminophen: decline in temperature at 3 hours. CI indicates confidence interval; WMD, weighted mean difference.

**Figure 3.** Oral vs rectal acetaminophen: maximum decline in temperature. CI indicates confidence interval; WMD, weighted mean difference.

**Figure 4.** Oral vs rectal acetaminophen: time to temperature reduction by 1°C. CI indicates confidence interval; WMD, weighted mean difference.

**Table 3.** Oral vs rectal acetaminophen: maximum decline in temperature. CI indicates confidence interval; WMD, weighted mean difference.

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Rectal, Mean (SD)</th>
<th>No.</th>
<th>Oral, Mean (SD)</th>
<th>Prefers rectal</th>
<th>Prefers oral</th>
<th>Weight, %</th>
<th>WMD (Random) (95% CI), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vernon et al younger</td>
<td>12</td>
<td>1.25 (0.80)</td>
<td>10</td>
<td>1.08 (0.80)</td>
<td>10</td>
<td>10</td>
<td>32.34</td>
<td>0.17 (−0.56 to 0.84)</td>
</tr>
<tr>
<td>Vernon et al older</td>
<td>7</td>
<td>1.75 (0.70)</td>
<td>8</td>
<td>0.92 (0.50)</td>
<td>8</td>
<td>8</td>
<td>32.73</td>
<td>0.83 (0.21 to 1.45)</td>
</tr>
<tr>
<td>Nabulsi et al</td>
<td>18</td>
<td>2.40 (0.33)</td>
<td>16</td>
<td>3.50 (0.45)</td>
<td>16</td>
<td>16</td>
<td>34.93</td>
<td>−1.10 (−1.37 to −0.83)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>34</td>
<td></td>
<td></td>
<td>100.00</td>
<td></td>
<td>100.00</td>
<td>−0.06 (−1.34 to 1.23)</td>
</tr>
</tbody>
</table>

**Figure 4.** Oral vs rectal acetaminophen: time to temperature reduction by 1°C. CI indicates confidence interval; WMD, weighted mean difference.

**Table 4.** Oral vs rectal acetaminophen: time to temperature reduction by 1°C. CI indicates confidence interval; WMD, weighted mean difference.

RECTAL VS ORAL ACETAMINOPHEN FOR ANALGESIA

The search generated 53 titles, of which 10 were selected for complete review. Only 1 study met the inclusion criteria, with no disagreement between reviewers. One hundred children undergoing tonsillectomies with or without adenoidectomy were included. Fifty of the children received oral acetaminophen elixir, 40 mg/kg, 40 minutes preoperatively, and the other 50 were administered a 40-mg/kg acetaminophen suppository.

©2008 American Medical Association. All rights reserved.
after induction of anesthesia. The children in the oral group had a higher mean acetaminophen concentration and a lower median pain score than those who were given suppositories. The analgesia was satisfactory when the acetaminophen levels were above 0.07 mmol/L. The authors concluded that these concentrations could have been reached with the rectal route, but the duration of surgery and predicted plasma concentrations at emergence from anesthesia should be taken into consideration.

Despite an extensive search of the literature, we found few studies that compared oral and rectal administration of acetaminophen. In all the aspects we analyzed, including fever reduction 1 and 3 hours after administration, maximal temperature decline, and time to 1°C decline in temperature, we found no difference between oral and rectal administration. The heterogeneity in the studies included in the analysis of the time to 1°C decline in temperature could possibly be explained by the fact that the studies were small, included different age groups, and differed in design. The results of the fever reduction meta-analysis indicate that there is no pharmacodynamic consequence of the possible differences in pharmacokinetic measures such as peak blood levels that have been shown in previous studies.\textsuperscript{2,4,5} We cannot say the same for the analgesic effect of acetaminophen; we were unable to perform a meta-analysis because only 1 study fulfilled the inclusion criteria.

Interpretation of analgesic and antipyretic responses to acetaminophen are confusing because the response is not directly related to the blood concentration but rather to the concentration in an effect compartment, in which concentrations equate approximately to those observed in the cerebrospinal fluid and not in the blood.\textsuperscript{26} This might be a possible explanation for the fact that there was no difference in pharmacodynamic measures, as evident from this meta-analysis, between oral and rectal administration, despite the fact that many pharmacokinetic studies did find differences. The variations in pharmacokinetic measures could result from variability of venous drainage from the rectum. Drugs administered distally bypass the liver, whereas drugs administered in the proximal part of the rectum are drained into the portal system and are subject to the hepatic first-pass effect.\textsuperscript{6} Another possible explanation for the variation in pharmacokinetic studies of rectal acetaminophen is the differences in the bioavailability of the various rectal acetaminophen formulations.\textsuperscript{2,21}

These differences in pharmacokinetic measures led the AAP to advise against routine use of rectal acetaminophen, putting pediatricians in the awkward position of not being able to treat all their febrile patients efficiently. Some febrile children are unable to take the oral form because of emesis, obtundation due to febrile convulsions, and so forth, and the rectal form is the only means of treating them. Our meta-analysis shows that, for treatment of fever, there is no clinical difference between oral and rectal forms of acetaminophen; moreover, a previous study demonstrated no difference in parental satisfaction between rectal and oral administration of acetaminophen,\textsuperscript{8} suggesting again that rectal acetaminophen administration is a reasonable alternative to oral administration.

This study has a few limitations. The search strategy did not include other databases, such as EMBASE; however, it is unlikely that this affected the results of our meta-analysis.\textsuperscript{27} There was a difference in the dosage forms of acetaminophen. The oral forms were tablets or elixir for the younger children, and the rectal form was either suppositories or enema and as such may differ slightly with regard to absorption. Another limitation is the fact that 3 of the studies were pediatric studies and only 1 was in adult patients. All the studies included were of single doses of acetaminophen, and, as such, toxic effects due to accumulation of acetaminophen, which was one of concerns of the AAP, after multiple rectal doses could not be assessed.

In conclusion, according to the results of this meta-analysis, there seem to be no pharmacodynamic differences between oral and rectal acetaminophen for fever reduction. Further studies evaluating possible pharmacodynamic differences in toxic effects between oral and rectal acetaminophen are required.

Accepted for Publication: May 7, 2008.
Correspondence: Lee Hilary Goldstein, MD, Medicine C, Haemek Medical Center, Afula, Israel 18101 (Goldstein_le@clalit.org.il).

Author Contributions: Study concept and design: Goldstein, Berlin, Berkovitch, and Kozer. Acquisition of data: Goldstein and Berlin. Analysis and interpretation of data: Goldstein, Berlin, and Kozer. Drafting of the manuscript: Goldstein, Berlin, and Berkovitch. Critical revision of the manuscript for important intellectual content: Berlin, Berkovitch, and Kozer. Statistical analysis: Kozer. Study supervision: Berkovitch.

Financial Disclosure: None reported.

REFERENCES

At age 15, novelist Upton Sinclair began writing a series of dime novels in order to pay for his education at the City College of New York.

—From the foreword to Oil! by Upton Sinclair, 1927.