Efficacy and Safety of Acetaminophen vs Ibuprofen for Treating Children’s Pain or Fever

A Meta-analysis

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Objective: To summarize studies testing the efficacy and safety of single-dose acetaminophen and ibuprofen for treating children’s pain or fever.

Data Sources: Reports were gathered by searching computerized databases (from their inception through May 2002) and registries, relevant journals, and bibliographies of key articles.

Study Selection: Seventeen blinded, randomized controlled trials with children (<18 years) receiving either drug to treat fever or moderate to severe pain.

Data Extraction: Under a fixed-effects model, outcome measures for an initial single dose of ibuprofen vs acetaminophen were the risk ratio for achieving more than 50% of maximum pain relief, effect size for febrile temperature reduction, and risk ratio for minor and major harm.

Data Synthesis: Ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) showed comparable efficacy (3 pain relief trials; 186 children). The risk ratio point-estimates was 1.14 (95% confidence interval [CI], 0.82-1.58) at 2 hours after receiving the dose, and 1.11 (95% CI, 0.89-1.38) at 4 hours. Ibuprofen (5-10 mg/kg) reduced temperature more than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours after treatment (respective weighted-effect sizes: 0.19 [95% CI, 0.05-0.33], 0.31 [95% CI, 0.19-0.44], and 0.33 [95% CI, 0.19-0.47]) (9 fever trials; 1078 children). For ibuprofen 10 mg/kg (acetaminophen, 10-15 mg/kg), corresponding effect sizes were 0.34 (95% CI, 0.12-0.56), 0.81 (95% CI, 0.56-1.03), and 0.66 (95% CI, 0.44-0.87). There was no evidence the drugs differed from each other (or placebo) in incidence of minor or major harm (17 safety trials; 1820 children).

Conclusions: In children, single doses of ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5-10 mg/kg) was a more effective antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours post-treatment.
The independent coders (D.A.P. and T.P.) were blinded to identifying information about the author, institutional affiliation, financial support, source, and year of publication until the meta-analyses were completed. Outcome variables were independently coded with a median agreement across coded variables of 100% (median, \( \kappa = 0.99 \); minimum, \( \kappa = 0.75 \)). Disagreements were resolved by discussion.
The outcome measure for pain relief was the risk ratio for achieving at least 50% of maximum pain relief with ibuprofen vs acetaminophen treatment. To determine the risk ratio, we estimated from area under the curve statistics for pain relief vs time the proportion of participants showing at least 50% of maximum pain relief for each treatment arm. This was done following guidelines and regression equations provided by McQuay and Moore. The risk ratio was computed by dividing the proportion of patients experiencing major harm in the ibuprofen treatment arm by the corresponding proportion in the acetaminophen treatment arm.

We defined major harm as the withdrawal of a patient from the study owing to an adverse event (eg, abdominal pain, vomiting, or hypothermia). The risk ratio for major harm was computed by dividing the proportion of patients experiencing major harm in the ibuprofen treatment arm by the corresponding proportion in the acetaminophen treatment arm. We also computed risk ratios for minor and major harm for each drug compared with placebo.

### DATA ANALYSIS

We analyzed data under a fixed-effects inverse-variance model. To determine whether outcomes were consistent across studies, we calculated a homogeneity statistic, Q, which has an approximate χ² distribution with k − 1 df, where k is the number of outcomes. For example, k = 3 for the pain analysis, because each of the 3 studies contributed 1 outcome. Where we rejected the null hypothesis of homogeneity (using a criterion of P < .05), we used the method of Hedges to examine whether effect sizes varied according to particular study characteristics such as dosage.

### RESULTS

Of 127 studies of potential relevance, 17 met the inclusion criteria, providing 3 data sets for the pain relief analysis, 9,13,14,22,28-33 10 data sets for the fever reduction analysis, 9,13,14,22,28-33 and 17 data sets for the safety analysis. 9,13,14,17-20,22,26-33 Studies were typically single-dose, randomized, double-blinded trials of 10 mg/kg of each drug, published between 1985 and 2002, with approximately 40 participants in each condition (Table). All dosages for

### TRIALS

<table>
<thead>
<tr>
<th>Safety Assessment Interval, h</th>
<th>Maximum No. of Doses</th>
<th>Safety Risk Ratio (95% CI)†</th>
<th>Time, h ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Minor Harm</td>
<td>Major Harm</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>1</td>
<td>1.05 (0.77 to 1.22)</td>
<td>1.05 (0.92 to 1.30)</td>
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<td>1</td>
<td>0.80 (0.52 to 1.27)</td>
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</tr>
<tr>
<td>6</td>
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<td>2.93 (0.32 to 69.96)</td>
<td>2.93 (0.32 to 69.96)</td>
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<td>NA</td>
<td>NA</td>
<td>1.14 (0.62 to 1.50)</td>
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<tr>
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<td>1</td>
<td>1.00 (0.99 to 4.51)</td>
<td>1.00 (0.99 to 4.51)</td>
</tr>
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<td>12</td>
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<td>1.00 (0.99 to 4.92)</td>
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<td>342</td>
<td>1</td>
<td>4.13 (0.47 to 36.61)</td>
<td>0.97 (0.14 to 6.81)</td>
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<td>8</td>
<td>1</td>
<td>1.03 (0.37 to 2.86)</td>
<td>7.97</td>
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<td>12</td>
<td>1.78 (0.62 to 5.07)</td>
<td>1.50 (0.28 to 8.73)</td>
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<td>0.60 (0.03 to 1.20)</td>
<td>0.85 (0.33 to 2.23)</td>
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<td>0.73 (0.02 to 35.64)</td>
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<td>12</td>
<td>0.79 (0.31 to 2.05)</td>
<td>1.06 (0.02 to 51.84)</td>
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<tr>
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<td>NA</td>
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<tr>
<td>48</td>
<td>6</td>
<td>1.69 (0.42 to 6.82)</td>
<td>0.02 (0.02 to 50.41)</td>
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<tr>
<td>48</td>
<td>6</td>
<td>1.71 (0.43 to 6.91)</td>
<td>1.03 (0.02 to 51.11)</td>
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<tr>
<td>NA</td>
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</tbody>
</table>

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each drug fell within the recommended range for clinical practice.

**PAIN**

A risk ratio of 1 indicates the drugs were equally effective for achieving 50% of maximum pain relief. Risk ratios greater than 1 indicate that ibuprofen was superior to acetaminophen treatment.

The point-estimate of the weighted mean was 1.14 (95% confidence interval [CI], 0.82-1.58) after 2 hours, and 1.11 (95% CI, 0.89-1.38) after 4 hours (Table). Although the point-estimates were in favor of ibuprofen treatment, the 95% confidence intervals also contained risk ratios in favor of acetaminophen treatment. There was no evidence that the risk ratio varied in magnitude across the individual studies (P>.30 for the Q-test of heterogeneity at 2 and 4 hours).

**FEVER**

An effect size of 0 indicates that the drugs were equally effective for reducing febrile temperature. Effect sizes greater than 0 indicate that ibuprofen was superior to acetaminophen treatment.

All point-estimates of the mean weighted-effect sizes for comparisons between ibuprofen and acetaminophen were positive (ie, favoring ibuprofen), with values of 0.19 (95% CI, 0.05-0.33) at 2 hours, 0.31 (95% CI, 0.19-0.44) at 4 hours, and 0.33 (95% CI, 0.19-0.47) at 6 hours (Table). The 95% CIs for each of these point-estimates were fairly narrow and did not contain 0. Since this analysis included 3 studies with low (5-mg/kg) dosages of ibuprofen (cf acetaminophen, 10-12.5 mg/kg), we performed a more focused analysis that included only those studies comparing 10 mg/kg of ibuprofen to 10 mg/kg or more of acetaminophen. The point-estimates in favor of ibuprofen were approximately twice as large in these analyses (Table), bounded by fairly narrow 95% CIs.

**SAFETY**

The median duration of adverse effects assessment was 48 hours after commencing treatment, but there was considerable variability across studies, ranging from 4 hours to 14 days. There was also considerable variability in the method of assessment of adverse effects: 1 study relied on spontaneous participant reports; 3 studies each used participant diaries or direct questioning by the investigator; and the assessment method was not reported in the remaining 10 studies.

For the minor and major harm analyses, a risk ratio of 1 indicates that the drugs did not differ in safety. Risk ratios greater than 1 indicate that ibuprofen was less safe than acetaminophen, and values less than 1 indicate the converse.

The point-estimate for the risk ratio was 0.96 (0.68-1.36) for minor harm and 1.00 (0.55-1.82) for major harm (Table). As the 95% CIs contained values on either side of 1.00, these data provide no clear evidence that the drugs differed from each other in safety. There was also no evidence that the risk ratio varied in magnitude across the individual studies (P values for the Q-test of heterogeneity were >.70 for each comparison).

Nine studies9,13,17-19,22,26,27 reported minor and major harm data for a placebo arm. As a supplementary analysis, we used these data to compute risk ratios for minor and major harm compared with placebo. For minor harm, the risk ratio for acetaminophen vs placebo was 0.79 (95% CI, 0.42-1.48); the risk ratio for ibuprofen vs placebo was 1.17 (95% CI, 0.68-2.03). For major harm, the risk ratio for acetaminophen vs placebo was 0.90 (95% CI, 0.25-3.29); the risk ratio for ibuprofen vs placebo was 1.51 (95% CI, 0.45-5.05). Although for both minor and major harm the risk ratio point-estimates were close to 1 for both drug-placebo comparisons, the width of the 95% CIs suggests that these data are inconclusive as to safety, especially for major harm. In summary, these data do not provide any evidence to suggest that treatment with ibuprofen and acetaminophen are less safe than each other or placebo.
retic than acetaminophen in terms of maximum temperature reduction and the length of antipyretic action.

SAFETY

There was no evidence that the drugs differ from each other or placebo in safety. Rather, these data were inconclusive on this point. Point-estimates for minor and major harm for the risk ratios for ibuprofen vs acetaminophen were close to the neutral value of 1, but 95% CIs were wide enough to contain values indicating one drug’s being safer than the other. Given that adverse events from either drug or placebo were rare in the current sample, a large-scale randomized trial (or its equivalent as several smaller studies) would be required to detect any small but real differences in safety. The only large-scale randomized trial addressing this issue used risk of hospitalization as the measure of safety and, thus, did not meet our safety meta-analysis inclusion criteria. It was found across 84192 febrile children taking acetaminophen (12 mg/kg) vs ibuprofen (5 to 10 mg/kg) in a single dose or short-term repeated doses, that safety did not differ according to drug. Interpreting these results along with our own, we conclude that there does not appear to be any evidence that ibuprofen and acetaminophen differ from each other in terms of major harm events, but more research is required to draw firmly the same conclusion for minor harm events.

LIMITATIONS AND IMPLICATIONS FOR RESEARCH

We included only published reports in our meta-analysis because our literature search did not locate any unpublished studies. It is possible that this led to a publication bias (at the study level, in favor of either drug) so that studies with null findings were less likely to have been published. As acknowledged in the “Methods” section, we also excluded a few studies because we could not extract relevant outcomes from the reported data. For the single fever study we excluded on this basis and for one of the 3 pain studies, ibuprofen was found to be superior to acetaminophen on the particular outcome measure used. The second pain study reported a trend for ibuprofen to be superior to acetaminophen. The third study did not directly compare the 2 drugs but reported that pain relief was greater than that for placebo for the ibuprofen treatment arm but not the acetaminophen treatment arm. The basic direction of effect in these excluded data was thus consistent with our results.

Reporting the main outcome measures in more detail in the original studies would have enabled more fine-grained analyses, especially for the safety data, where sometimes only the number of adverse events was reported rather than the number of patients experiencing particular adverse events. In terms of sheer number of studies, more data have been gathered addressing the antipyretic properties of the drugs, as opposed to their analgesic properties. We suggest that it would be useful for future studies to investigate the kinds of pain for which these drugs are typically indicated, such as headache, cold and flu pain, muscular aches, and menstrual cramps. Participants should be sampled from the broader global community of children for whom these drugs are acquired on an over-the-counter basis, in contrast to the prior research focus on accessible clinical samples from North America and Europe that may not be adequately representative. Researchers have not studied children younger than 2 years; especially infants younger than 6 months.

Further issues that may be interesting for future research include the potentially differing time courses in efficacy of the 2 drugs (especially in light of evidence suggesting nonlinear pharmacodynamic profiles) and the net therapeutic benefit of regular repeated doses for either pain or fever, given that the prevalence of persistent or frequently recurring pain in older children and adolescents is estimated to be 15% to 20%.

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

Ibuprofen and acetaminophen are the most widely available over-the-counter drugs on the market for relief of pain and fever. We conducted the present research because we saw no consensus in the health care literature as to their relative efficacy and safety in the pediatric population.

On the basis of evidence published up to May 2002, we draw the following general conclusions: (1) ibuprofen, 4 to 10 mg/kg, is as effective a pediatric analgesic as acetaminophen, 7 to 15 mg/kg; (2) ibuprofen, 5 to 10 mg/kg, especially a 10-mg/kg dosage, is a more efficacious pediatric antipyretic than acetaminophen, 10 to 15 mg/kg; and (3) there is no indication that the drugs differ in safety from each other or from placebo. More research is required, especially on the categories of pain for which the drugs are typically marketed as pediatric medications, using heterogeneous community samples, and for multidose regimens lasting more than a few hours.

Until such evidence is accrued, and all other things being equal, the logical implication for practice of the present meta-analyses is that when pediatric antipyresis is appropriate, 5 to 10 mg/kg of ibuprofen should be generally preferred over 10 to 15 mg/kg of acetaminophen for short-term use. For pediatric analgesia, these data do not support a clear preference for one drug over the other; both were more effective than placebo and equally safe at the studied dosages.

Accepted for publication January 22, 2004.

This study was supported in part by Boots Healthcare Australia Pty Ltd, North Ryde, New South Wales, Australia.

Dr Champion was a member of the Children’s Paracetamol Focus Group of GlaxoSmithKline in 2001.

We acknowledge Anna Cole, BAppSc (Hearing and Speech), and Amanda Purcell, MCom, for assistance in obtaining and preparing literature.

Neither Boots Healthcare Australia Pty Ltd nor GlaxoSmithKline played any decision-making role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

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Ibuprofen and acetaminophen are the most widely available over-the-counter drugs for relief of pain and fever, yet their safety and efficacy is uncertain. Literature reviews typically have concluded that the drugs were equally effective but that acetaminophen should be preferred because its safety seemed more assured.

We performed a systematic meta-analytic review of randomized controlled trials assessing the efficacy and/or safety of single-doses of ibuprofen and acetaminophen for short-term treatment of children’s pain or fever. Contrary to the conclusions of prior literature reviews, the results did not indicate any difference between the drugs in analgesic efficacy, nor in safety, but did indicate ibuprofen to be the superior antipyretic.

REFERENCES