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.
### Study Characteristics and Outcomes for Pain Relief, Febrile Temperature Reduction, and Safety

<table>
<thead>
<tr>
<th>Source</th>
<th>Model</th>
<th>Mean Age, y</th>
<th>% Girls</th>
<th>Dosage, mg/kg</th>
<th>No. of Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acetaminophen</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acetaminophen</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGaw et al, 1987</td>
<td>Pain (dental)</td>
<td>14</td>
<td>62</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Moore et al, 1985</td>
<td>Pain (dental)</td>
<td>8</td>
<td>30</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Schachtel and Thoden, 1993</td>
<td>Pain (sore throat)</td>
<td>9</td>
<td>51</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauffman et al, 1992</td>
<td>Fever (temp)</td>
<td>6</td>
<td>73</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Wilson et al, 1991</td>
<td>Fever (trb)</td>
<td>3</td>
<td>NA</td>
<td>12.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Wong et al, 2001</td>
<td>Fever (trb)</td>
<td>3</td>
<td>46</td>
<td>12%</td>
<td>5% or 10%</td>
</tr>
<tr>
<td>Walson et al, 1999</td>
<td>Fever (temp)</td>
<td>6</td>
<td>53</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Autret et al, 1994</td>
<td>Fever (trb)</td>
<td>2</td>
<td>42</td>
<td>10%</td>
<td>7.5%</td>
</tr>
<tr>
<td>McIntyre and Hull, 1996</td>
<td>Fever (trb)</td>
<td>2</td>
<td>41</td>
<td>12.5%</td>
<td>5%</td>
</tr>
<tr>
<td>Starha et al, 1994</td>
<td>Fever (temp)</td>
<td>5</td>
<td>NA</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Van Esch et al, 1995</td>
<td>Fever (temp)</td>
<td>2</td>
<td>27</td>
<td>10%</td>
<td>5%</td>
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<tr>
<td>Vauzelle-Kervoedan et al, 1997</td>
<td>Fever (temp)</td>
<td>4</td>
<td>49</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Walson et al, 1992</td>
<td>Fever (trb)</td>
<td>6</td>
<td>52</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>10 mg/kg ibuprofen only</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Safety only‡‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertin et al, 1991</td>
<td>Otitis media</td>
<td>8</td>
<td>44</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Bertin et al, 1994</td>
<td>Sore throat</td>
<td>3</td>
<td>56</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Hämmäläinen et al, 1997</td>
<td>Migraine</td>
<td>11</td>
<td>50</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Sidler et al, 1990</td>
<td>Fever</td>
<td>NA</td>
<td>NA</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; temp, fever outcome measure was between-drug difference in temperature at given time point; trb, fever outcome was between-drug difference in temperature reduction from baseline.

*After attrition, at 4 hours (6 hours for Walson et al).††Studies that examined safety that were not already included in the pain for fever analysis.

#The exact dosage was 5 mg/kg if the initial temperature was less than 39.2°C; or 10 mg/kg otherwise.

‡‡The number of patients included in the minor harm analysis. For the major harm analysis, there were 899 participants in the acetaminophen arm and 914 in the ibuprofen arm.

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## INCLUSION AND EXCLUSION CRITERIA

We included studies with participants younger than 18 years receiving either drug for treatment of fever or moderate to severe pain, randomly allocated to treatment arms in a blinded design. Otherwise relevant studies were excluded if any prior or concurrent medication was a potential confound (eg, lidocaine, codeine, and others), if the data were already included in another study, or if insufficient data were provided to calculate a value for the relevant outcome measures. The latter criterion resulted in the exclusion of 3 studies from the pain analysis17-19 and 1 from the fever analysis20 (but did not prohibit their inclusion in the safety analysis), and in the exclusion of 1 study from the safety analysis.21

For multidose studies, we included only the data for the first dose in the pain and fever analyses. No study included more than 1 acetaminophen treatment arm, but 4 studies used 2 ibuprofen treatment arms at different dosages.9,13,20,22 To preserve independence of effect sizes,22 we included only the ibuprofen treatment arm at the higher dosage, which was less than or equal to the corresponding acetaminophen dosage.

## DATA EXTRACTION AND OUTCOME DEFINITIONS

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, κ=0.99; minimum, κ=0.75).24 Disagreements were resolved by discussion.
Assessment

<table>
<thead>
<tr>
<th>Safety Assessment Interval, h</th>
<th>Safety Risk Ratio (95% CI)†</th>
<th>Time, h ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum Harm</td>
<td>Major Harm</td>
</tr>
<tr>
<td>4</td>
<td>1.05 (0.77 to 1.42)</td>
<td>1.05 (0.77 to 1.42)</td>
</tr>
<tr>
<td>6</td>
<td>2.93 (0.12 to 69.64)</td>
<td>2.85 (0.12 to 67.97)</td>
</tr>
<tr>
<td>24</td>
<td>1.00 (0.02 to 45.13)</td>
<td>1.00 (0.02 to 45.13)</td>
</tr>
<tr>
<td>72</td>
<td>1.78 (0.62 to 5.07)</td>
<td>1.50 (0.26 to 8.73)</td>
</tr>
<tr>
<td>48</td>
<td>1.69 (0.42 to 6.82)</td>
<td>1.01 (0.02 to 50.41)</td>
</tr>
<tr>
<td>52</td>
<td>1.71 (0.43 to 6.91)</td>
<td>1.03 (0.02 to 51.11)</td>
</tr>
<tr>
<td>72</td>
<td>0.89 (0.36 to 2.19)</td>
<td>1.00 (0.02 to 49.84)</td>
</tr>
<tr>
<td>24</td>
<td>0.42 (0.04 to 4.31)</td>
<td>0.27 (0.01 to 6.27)</td>
</tr>
<tr>
<td>52</td>
<td>0.96 (0.68 to 1.36)</td>
<td>1.00 (0.55 to 1.82)</td>
</tr>
</tbody>
</table>

### RESULTS

#### TRIALS

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, 8,9,13,14,17,20,22,26-33 and 17 data sets for the safety analysis, 8,9,13,14,17,20,22,26-33

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

#### Pain

The main outcome measure for safety was the risk ratio for minor and major harm for ibuprofen vs acetaminophen treatment. We defined minor 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 $\chi^2$ distribution with $k-1$ df, where $k$ is the number of outcomes. For example, $k$ was 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 Hedges33 to examine whether effect sizes varied according to particular study characteristics such as dosage.

### TRIALS

The main outcome measure for safety was the risk ratio for minor and major harm for ibuprofen vs acetaminophen treatment. We defined minor harm as the occurrence of an adverse event not leading to withdrawal from the study (eg, nausea, sweating, or cutaneous rash). The risk ratio for minor harm was computed by dividing the number of minor harm events per patient for the ibuprofen treatment arm by the corresponding figure for 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.

### SAFETY

Safety

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.23 The risk ratio was computed by dividing the proportion for the ibuprofen treatment arm by that for the acetaminophen treatment arm.

### FEVER

Half of the fever studies reported efficacy in terms of the mean between-drug difference in temperature at 2, 4, and 6 hours after treatment, whereas the remainder described it in terms of the mean between-drug difference in temperature reduction from baseline at these time points (Table). By converting these outcomes into standardized effect sizes, using the method of Hedges33 to correct for small sample bias, we were able to include all 10 studies in a single analysis. In each study, differences across treatment arms in baseline temperature were negligible.
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 studies 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, 0.43-5.05). 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.

**COMMENT**

**PAIN**

In the context of postextraction dental pain and sore throat pain in children, 3 small but otherwise good quality trials did not provide any evidence that ibuprofen (+10 mg/kg) and acetaminophen (7-15 mg/kg) differ in their relative efficacy. Point-estimates at 2 and 4 hours after treatment were in a direction slightly favoring ibuprofen, but 95% CIs were wide enough to also include values that favored acetaminophen.

**FEVER**

In the context of single doses of ibuprofen, 5 to 10 mg/kg, vs acetaminophen, 10 to 15 mg/kg, ibuprofen was the superior antipyretic. This relative superiority was more pronounced at 4 and 6 hours after treatment (cf 2 hours), with effect sizes in the order of 0.30 (cf 0.20). A more intuitive way to gauge the practical value of effect sizes is to consider them in binomial effect size display format, in which the effect size is a measure of the percentage of people likely to have shown improvement from a given treatment. Following this metric, at 4 and 6 hours after treatment approximately 15% more children were likely to have a febrile temperature reduction with ibuprofen than with acetaminophen.

Restricting the analysis to 10 mg/kg of ibuprofen vs 10 to 15 mg/kg of acetaminophen roughly doubled the effect sizes in favor of ibuprofen. Four hours after treatment, the effect size was 0.81, which is large and corresponds to a 38% increase in the number of children likely to have a febrile temperature reduction with ibuprofen compared with acetaminophen. Ninety-five percent confidence intervals surrounding point-estimates for mean weighted-effect sizes were relatively narrow in these analyses and did not contain values less than or equal to 0 that would have favored acetaminophen. These findings are consistent with a recent meta-analysis of a smaller sample of trials that were not all randomized or blinded that concluded that ibuprofen was a more efficacious antipy-
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 84,192 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) insofar as 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