Use of ibuprofen in children, focusing on comparative analgesic and antipyretic efficacy and safety

Background

Currently section 2 of the 2nd WHO Model Essential Medicines List for Children (March 2009), contains the following listing for ibuprofen:

<table>
<thead>
<tr>
<th>2. ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY MEDICINES (NSAIMs), MEDICINES USED TO TREAT GOUT AND DISEASE MODIFYING AGENTS IN RHEUMATOID DISORDERS (DMARDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.1</strong> Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)</td>
</tr>
<tr>
<td>ibuprofen</td>
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<tr>
<td></td>
</tr>
<tr>
<td>paracetamol*</td>
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<tr>
<td>* Not recommended for anti-inflammatory use due to lack of proven benefit to that effect.</td>
</tr>
</tbody>
</table>

The note following the inclusion of ibuprofen in this section is explained below:

R indicates that the Subcommittee has endorsed the medicine as essential but has requested a review of the efficacy and safety to confirm this decision, or to expand use to additional age groups.

Ibuprofen is also listed in two other parts of the EML for Children, without the additional note. These are in Section 7 and Section 8.4, as shown below:

<table>
<thead>
<tr>
<th>7. ANTIMIGRAINE MEDICINES</th>
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<tbody>
<tr>
<td><strong>7.1 For treatment of acute attack</strong></td>
</tr>
<tr>
<td>ibuprofen</td>
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<tr>
<td>paracetamol</td>
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<td></td>
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</tbody>
</table>
Section 8.4:

This document presents a review of the evidence for the efficacy and safety of ibuprofen, when used for acute pain and fever in children (aged 12 years and less), for short duration (days, rather than weeks), in particular in comparison with paracetamol.

Retrieval of evidence

Evidence from systematic reviews and randomised controlled trials was sought from the MEDLINE database, accessed by means of the PubMed portal. The following searches were conducted, using the advanced search option:

- (ibuprofen AND pain OR fever AND pediatr*) AND systematic[sb]
- (ibuprofen AND pain OR fever AND pediatr*) AND (Therapy/Narrow[filter])

Systematic reviews

Three relevant systematic reviews were retrieved.

The most recent review retrieved compared the efficacy (in pain and fever) and safety of ibuprofen and paracetamol in both adults and children (Pierce and Voss 2010). This was an update of two previous reviews conducted in 2004 (Goldman, Ko et al. 2004; Perrott, Piira et al. 2004), but extended to include studies in adults. Pierce and Voss (2010) searched MEDLINE up to August 2009 and EMBASE up to January 2008, but restricted both searches to the English language only. They also sought only direct comparisons of ibuprofen and paracetamol, whether prospective or retrospective. Individual studies reporting on efficacy were only included if the method or pain or fever measurement was stated. If pain was measured on more than one scale (e.g. a visual analog and an ordinal scale), then only the continuous measure was used. Those randomized controlled trials reporting continuous measures of temperature were also included. Studies reporting on safety were only included if they reported adverse effects from direct comparisons of the two agents.

Two additional systematic reviews were included, which focused on the safety and clinical tolerability of ibuprofen compared with paracetamol, when used in paediatric pain and fever (Southey, Soares-Weiser et al. 2009) and on the occurrence of asthma-related symptoms when each agent was used in febrile children (Kanabar, Dale et al. 2007). Southey et al. (2009) searched MEDLINE (to November 2008), EMBASE (to November 2008), the Cochrane Library (to issue 3, 2007), ACP Journal Club (to November 2007) and Pascal (to November 2007), for randomised controlled trials, controlled observational studies and case series of more than 1000 participants. Kanabar et al. (2007) searched 12 databases to June 2007, but restricted the search to articles in English.
Pain in children

Pierce and Voss (2010) retrieved 18 studies in which ibuprofen was compared with paracetamol in the treatment of pain in children. The “analgesic models” used included dental/oral surgery, musculoskeletal trauma, myringotomy, sore throat, postsurgical pain, headache pain, pain upon vaccination, and discomfort in febrile children. In 11 studies, there was no significant difference in analgesic efficacy between ibuprofen and paracetamol, but in 6 studies it was reported that ibuprofen was superior. In one study ibuprofen was superior to paracetamol on the day or surgery, but not the following days. A number of these studies included “children” older than 12 years. In only 6 studies, all randomised controlled trials, was there sufficient information to calculate a standardized mean difference (SMD) in the continuous variable measured. The combined estimate of the SMD was the weighted average, where each study’s SMD was weighted by the inverse of its variance. The forest plot reported is shown below. The overall weighted estimate was 0.28 (95% CI 0.10 to 0.46), “indicating superior pain relief in the ibuprofen-treated children 2 hours after dosing”.

![Forest plot of standardized mean difference of pain measurement for acetaminophen versus ibuprofen in children. Negative numbers denote acetaminophen treatment group had lower pain measures than the ibuprofen groups.](image)

The 6 studies included here involved a total of 694 participants. One of these (Bradley, 2007, involving 147 participants with orthodontic pain) included children aged 12-16 years and another (Salmassian, 2009, involving 60 participants with pain after orthodontic tooth movement) included children aged 12 to 18 years.

Pierce and Voss (2010) were of the opinion that their update “reiterates” the results of previous paediatric analyses, and pointed out that “no individual literature reference presented the overall conclusion that acetaminophen was superior to ibuprofen in terms of either analgesic or antipyretic efficacy in children or adults”. 

Ibuprofen in children – pain and fever
Although some trials did report data at times point beyond 2 hours, these were variable. Only the 2-hour or the post-baseline time point closest to the 2-hour mark was used in relation to the pain studies included.

**Fever in children**

Pierce and Voss (2010) retrieved 30 studies which compared the antipyretic efficacy of ibuprofen and paracetamol in children. In 15 of these, it was concluded that ibuprofen was superior, whereas in the remaining 15 no significant difference was seen. Only 7 studies were randomized controlled trials which reported data amenable to representation as a standardized mean difference. The reported forest plot for these 7 studies is below. The overall estimate was 0.26 (95% CI 0.10 to 0.41), “indicating significantly better fever control for ibuprofen at 4 hours postdose compared with acetaminophen”.

The 7 studies included involved 576 participants. Only one (Ulokol, 1999, involving 60 participants) included children aged 2 to 14 years. Only the 4-hour time point was compared for fever studies. As with the pain studies, this implied a measurement before any repeated dosing.

Pierce and Voss (2010) cited “Cohen’s rules of thumb”, according to which an SMD of 0.69 corresponds with a medium effect size. For both pain and fever, the overall SMD estimates were thus consistent with a small effect size.

**Safety of ibuprofen in children**

Pierce and Voss (2010) calculated amended odds ratios (amended by adding 0.5 to each cell of the contingency table to avoid zero denominators) for the proportion of subjects experiencing at least 1 adverse effect for each study. The numerator of the odds ratio was the odds of an adverse event in the paracetamol group, and hence odds ratios less than 1 favoured paracetamol, while values greater than 1 favoured ibuprofen. Where there was no heterogeneity, a Mantel-Haenszel estimate of the overall odds ratio was calculated, using the natural log of the amended odds ratios. As only 2 serious adverse effects were reported in the paediatric studies included, no odds ratio could be calculated.

Of 31 paediatric studies with safety data, 30 reported no difference in adverse effect, while only 1 reported that paracetamol was safer or better tolerated. Nineteen RCTs were included.
in the reported forest plot, shown below. The authors reported that the “test for heterogeneity of odds ratios was not significant, and the combined estimate of the odds ratio was 0.82 (95% CI 0.60 to 1.12), failing to show a significant difference in the proportion of pediatric subjects experiencing 1 or more AEs in the 2 treatment arms”.

However, the short-term nature of these studies, and the additional care taken to counsel trial participants and their carers needs to be taken into account. As Pierce and Voss (2010) state: “Qualitative review and quantitative analyses also found no significant difference in proportions of subjects experiencing an AE, demonstrating that ibuprofen and acetaminophen are equally safe. Known AEs of nonsteroidal anti-inflammatory drugs such as ibuprofen are upper GI bleeding and a cardiovascular risk. These effects are typically associated with long-term use. Liver toxicity is typically the main concern with acetaminophen overdose, either intentional or unintentional.” RCTs are unlikely to provide the necessary data to settle the question of the comparative safety of these two agents when in typical use.

Southey et al. (2009) included data from 24 RCTs comparing the efficacy and tolerability and safety of ibuprofen or paracetamol with placebo, and 12 observational studies (controlled observational studies and case series with more than 1000 participants). Dichotomous data were analysed by calculating the relative risk (RR) for each trial using the Mantel–Haenszel method, while continuous data were analysed by calculating the weighted mean difference (WMD) between groups. The reported forest plots are shown below.
The authors summarized the results as follows: ‘Meta-analysis of systemic reactions demonstrated that tolerability and safety of ibuprofen was similar to placebo, as was
Ibuprofen in children – pain and fever  March 2011

paracetamol: ibuprofen versus placebo relative risk (RR) 1.39 (95% CI: 0.92, 2.10); paracetamol versus placebo RR 1.57 (95% CI 0.74, 3.33). A total of 2937 systemic AEs occurred in 21 305 patients taking ibuprofen compared with 1466 systemic AEs in 11 164 patients taking paracetamol: RR 1.03 (95% CI 0.98, 1.10). There was no significant difference between the two groups. Narrative analysis of AE data identified conflicting evidence regarding hepatic injury with paracetamol and group A streptococcal infections with ibuprofen or paracetamol treatment”. They concluded that “ibuprofen, paracetamol and placebo have similar tolerability and safety profiles, especially in terms of GI symptoms, asthma and renal adverse effects”.

The issue of asthma-related symptoms was specifically reviewed by Kanabar et al. (2007), who included data from 3 sources, two of which were from the large Boston University Fever Study. The authors concluded that the “evidence reviewed in this article suggests a low risk for asthma-related morbidity associated with ibuprofen use in children and a possible protective and therapeutic effect compared with acetaminophen. The findings also suggest that acetaminophen use in children is associated with an increased risk for wheezing”.

Additional RCTs
Only 1 recent randomized controlled trial was found which would not have been included in the systematic review by Pierce and Voss (2010). In this double-blind RCT, ibuprofen was compared with a combination of paracetamol and codeine in 336 children with arm fractures (Drendel, Gorelick et al. 2009). The authors concluded that “[i]buprofen was at least as effective as acetaminophen with codeine for outpatient analgesia for children with arm fractures. There was no significant difference in analgesic failure or pain scores, but children receiving ibuprofen had better functional outcomes. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen”. However, in both arms, as many as 30% needed a rescue medication. Nonetheless, this study does not contradict the findings reviewed by Pierce and Voss (2010).

Costs of ibuprofen and paracetamol

If there are few differences between ibuprofen and paracetamol in terms of efficacy and safety, when used for the acute treatment of pain or fever in children, then the relative costs of these agents need to be considered.

Costs were obtained from the MSH International Drug Price Indicator Guide (2009), accessible at http://erc.msh.org/. Supplier piece data from 8 sources of paracetamol 120mg/5ml suspension were shown, ranging from the ubiquitous 100ml to a 5000ml bulk packaging. The median price was US$0.0039 per ml, ranging from US$0.0010 to US$0.0101. Most children would be given a 100ml bottle, which could be sold at a median cost of US$0.39. Buyer prices from 8 health systems were reported, with the median price of US$0.0043 per ml (ranging from US$0.0026 to US$0.0070). The median procurement price for a 100ml size would thus be US$0.43. Data from a narrow range of suppliers (3) for ibuprofen 100mg/5ml suspension were reported. The median supplier price was US$0.0043 per ml, ranging from US$0.0024 to US$0.0162. The median buyer price, based on data from 6 health systems, was US$0.0087 per ml, ranging from US$0.0033 to US$0.0154. A 100ml bottle of suspension could thus be procured for a median price of US$0.87.

While neither is expensive as a single purchase, the median buyer price for paracetamol remains lower than that for ibuprofen.
Recommendation

It is recommended that the “R” note is respect of ibuprofen in section 2 be removed, and that the 200mg/5ml suspension be added as an option under this section.

Once the WHO Guidelines for the for pharmacological treatment of persisting pain in children with medical illnesses are finalised, consideration can be given to the removal of the asterisk and note in section 8.4.

Whether ibuprofen suspension should be added in section 7 (migraine) is beyond the scope of this review, but it is noted that a qualitative systematic review did identify some studies in which ibuprofen was tested as part of migraine regimens (Bailey and McManus 2008).

References


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