Combined and alternating acetaminophen and ibuprofen therapy for febrile children

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For the current issue of the *Journal*, we asked Drs Niraj Mistry and Alan Hudak to comment on and put into context the Cochrane Review on combining and alternating acetaminophen and ibuprofen for treating fever in children (1).

Background

Health care professionals frequently recommend fever treatment regimens for children that either combine acetaminophen and ibuprofen or alternate them. However, there is uncertainty about whether these regimens are better than the use of single agents, and about the adverse-effect profile of combination regimens.

Methods

Search strategy: In September 2013, the Cochrane Infectious Diseases Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS and International Pharmaceutical Abstracts (2009-2011) were searched.

Selection criteria: Randomized controlled trials comparing alternating or combined acetaminophen and ibuprofen regimens with monotherapy in children with fever were included.

Data analysis: One review author and two assistants independently screened the searches and applied inclusion criteria. Two authors assessed risk of bias and graded the evidence independently. Separate analyses were conducted for different comparison groups (combined therapy versus monotherapy, alternating therapy versus monotherapy and combined therapy versus alternating therapy).

Results

Six studies, enrolling 915 participants, were included.

Compared with giving a single antipyretic alone, giving combined acetaminophen and ibuprofen to febrile children resulted in a lower mean temperature at 1 h after treatment (mean difference [MD] −0.27°C [95% CI −0.45 to −0.08]; two trials, 163 participants, moderate-quality evidence). If no additional antipyretics are given, combined treatment likely also results in a lower mean temperature at 4 h (MD −0.70°C [95% CI −1.05 to −0.35]; two trials, 196 participants, moderate-quality evidence), and in fewer children remaining or becoming febrile for at least 4 h after treatment (RR 0.08 [95% CI 0.02 to 0.42]; two trials, 196 participants, moderate-quality evidence). Only one trial assessed a measure of child discomfort (fever-associated symptoms at 24 h and 48 h), but did not find a significant difference in this measure between the treatment regimens (one trial, 156 participants, evidence quality not graded).

In practice, caregivers are often advised to initially give a single agent (acetaminophen or ibuprofen), and then give a further dose of the alternative if the child's fever fails to resolve or recurs. Giving alternating treatment in this way may result in a lower mean temperature 1 h after the second dose (MD −0.60°C [95% CI −0.94 to −0.26]; two trials, 78 participants, low-quality evidence) and may also result in fewer children remaining or becoming febrile for up to 3 h after it is given (RR 0.25 [95% CI 0.11 to 0.55]; two trials, 109 participants, low-quality evidence). One trial assessed child discomfort (mean pain scores at 24 h, 48 h and 72 h) and found that mean scores were lower with alternating therapy, despite fewer doses of antipyretic being given overall (one trial, 480 participants, low-quality evidence).

Only one small trial compared alternating therapy with combined therapy. No statistically significant differences were observed in mean temperature or the number of febrile children at 1 h, 4 h or 6 h (one trial, 40 participants, very low-quality evidence).

There were no serious adverse events in the trials that were directly attributed to the medications used.

Conclusions

There is some evidence that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy alone. However, the evidence for improvements in measures of child discomfort remains inconclusive. There is insufficient evidence to determine whether combined or alternating therapy may be more beneficial. Future research needs to measure child discomfort using standardized tools, and assess the safety of combined and alternating antipyretic therapy.

The full text of the Cochrane Review is available in The Cochrane Library (1).

EXPERT COMMENTARY

Fever is a normal physiological response, typically to infectious agents. An integral part of the human host defense, fever impedes the proliferation of viruses and bacteria, and assists in the body's acute-phase reaction (2,3). However, fever is often accompanied by symptoms of the underlying illness and discomfort, resulting in caregiver distress.

Multiple guidelines advocate that the primary aim of fever treatment is to relieve child discomfort (4-6). The primary outcome of the review (1) was to assess the effectiveness of combined and alternating antipyretics in reducing measures of child discomfort. However, 'discomfort' is poorly defined and difficult to assess. There is a lack of evidence describing the correlation between degree of fever and patient discomfort. Only one trial included in the review measured child discomfort and found no differences between combined and alternating antipyretics compared with monotherapy. All of the included studies (n=6) examined temperature as a second primary outcome and found a possible small benefit of combined and alternating antipyretic therapy in reducing temperature. However, the clinical significance of a 0.27°C to 0.7°C reduction is debatable.

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Accepted for publication October 22, 2014

There were no serious adverse events reported in the review, although all of the included studies involved small sample sizes with limited follow-up periods, resulting in poor statistical power to make any recommendations regarding safety. Acetaminophen and ibuprofen are effective, well tolerated and safe when used as single agents (7). However, administrative data (8) and case reports (9) suggest that concomitant use may be associated with increased risk for acute kidney injury and/or hepatotoxicity. Furthermore, acetaminophen and ibuprofen have different administration dosages and intervals, increasing the potential for parental confusion and administration errors.

The results of the current review are well aligned with previous guidelines and recommendations (4-6). In 1998, a Canadian Paediatric Society Practice Point on acetaminophen and ibuprofen in the management of fever and mild to moderate pain in children stated, "…the use of alternating doses of [acetaminophen] and ibuprofen or a combination of both drugs has no place outside specialized units" (4). In more recent guidelines, the American Academy of Pediatrics (5) and the National Institute for Health and Clinical Excellence (6), both support the primary goal of treating fever to reduce child discomfort and advise against the routine use of combined and alternating acetaminophen and ibuprofen. Despite these recommendations, combining and alternating antipyretics has come into common practice by many physicians (9) and caregivers (10), and is likely perpetuating 'fever phobia' (11,12).

It is critical to acknowledge that there is insufficient evidence supporting the common practice of combined and alternating antipyretics for childhood fever. At this time, monotherapy with either acetaminophen or ibuprofen, according to caregiver preference, should be considered first-line treatment.

When counselling caregivers of children with fever, health care practitioners have a vital responsibility to reassure caregivers, dispel myths, and provide accurate and consistent verbal and written (13) education regarding:

- fever as a natural and favourable biological response;
- fever as a symptom of underlying illness;
- antipyretic monotherapy to relieve discomfort of their child; and
- recognizing symptoms and signs requiring urgent medical attention.

This new evidence in the context of the pervasive practice of combined and alternating antipyretics for fever suggests a critical opportunity for physicians to systemically recommit to evidence-based medicine through the deimplementation (14) of this ineffective and potentially harmful practice until more robust evidence is available.

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