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DRUG NEWS

Alternating or Combining Acetaminophen and Ibuprofen for Pediatric Fever

Pearls for Practice:

- Several myths regarding fever and treatment of fever continue to be believed by caregivers.
- Fever is a therapeutic biological response and the decision to treat fever should not be based on temperature alone.
- Evidence is lacking to support alternating or combining acetaminophen and ibuprofen in order to achieve clinically meaningful results for fever; monotherapy should be recommended.

Background

Fever is part of the human host defence mechanism that impedes the proliferation of viruses and bacteria and provides the optimal temperature in the body's acute-phase reaction.[1] Fever is often accompanied by symptoms of the underlying illness and discomfort, which is a source of parents' and caregivers' anxiety also known as 'fever phobia'.[1] Many physicians and caregivers favour treatment of fever with antipyretics to minimize the child's distress, avoid complications of dehydration, and avoid the effects of poor nutrition.[1-3] The decision to normalize the body temperature may also arise from a fear of seizure development resulting from rapid increases in temperature.[1-3] However, antipyretics do not prevent febrile convulsions and should not be used prophylactically for this condition.[4] It has also been claimed that patients with underlying cardiac and pulmonary disorders may be at more risk from fever because of increased metabolic demands; however there are no studies that show antipyretics benefit patients with cardiopulmonary disease by reducing metabolic demand.[5]

The idea of alternating or sometimes combining acetaminophen and ibuprofen for fever seems to now appear more commonly in the literature, and as such, presumably is contributing to increased practice among health care providers.[6] However, there is uncertainty regarding the efficacy and the safety of this practice in comparison to using either acetaminophen or ibuprofen alone.[6]

Efficacy

A major limitation to evaluating efficacy is the choice of outcome used in the literature. Fever is neither linearly correlated with severity of the underlying condition, nor is it harmful.[7] As such, temperature measurement provides little value, yet all of the randomized studies assessing the use of alternating or combined antipyretic regimens for fever in children used temperature reduction as the primary outcome.[8-13] Arguably a more meaningful outcome to measure is child discomfort. However, discomfort in children is often poorly defined, difficult to assess, and dismissed in the literature. For instance, of the six trials, discomfort was assessed in only two trials[9,13]

A Cochrane Review has been published that evaluated the six aforementioned studies, which enrolled a total of 915 participants.[6] While the review concluded use of alternating or combining acetaminophen and ibuprofen likely results in a statistically significant reduction in core temperature at 1 hour (-0.27°C, 95% CI -0.45 to -0.08) and 4 hours (-0.70°C, 95% CI -1.05 to -0.35) compared to monotherapy, these differences are unlikely clinically significant, and therefore not particularly meaningful parameters.

Understandably, no conclusions could be made regarding the effect on comfort given the limited data. The only RCT that measured child discomfort as a primary outcome included 156 children between 6 months and 6 years with axillary temperatures of at least 37.8°C and up to 41.0°C.[9] Participants were randomized into three groups: acetaminophen plus ibuprofen; acetaminophen alone; or ibuprofen alone. The study addressed fever-associated symptoms as a measure of discomfort at 48 hours after initiating the antipyretic regimen. Caregivers were provided a scale to score their child at particular time points; the scale spanned from 1 point (child is asleep) to 5 points (crying, very distressed, hard to settle/agitated). The scale is quite descriptive and clear though validation is unknown. No significant difference in discomfort level was found between the treatment regimens.

The only other study reporting on comfort was another randomized, double-blind, parallel-group trial that included 464 children 6 to 36 months old with fever.[13] The children were randomized into three groups: acetaminophen alone (Group A); ibuprofen alone (Group B); or both in an alternating dosage regimen (Group C). Although a significant reduction in children's stress levels was observed in group C, a major limitation needs to be highlighted. Stress was measured with the Non-Communicating Children's Pain Checklist (NCCPC). This tool was designed for children 3 to 18 years old who are unable to speak because of cognitive (mental/intellectual) impairments or disabilities.[14] As the population in this study was otherwise healthy infants 6 to 36 months old, this potentially inappropriate choice of scales calls into question the validity of the results.

Safety

It has been reported that up to 50% of acetaminophen or ibuprofen doses administered to children for fever are incorrect.[15] Alternating acetaminophen and ibuprofen can be confusing to caregivers, potentially leading to incorrect dosing of either product. For instance in one study, of 14 children given both agents, only one child was given the correct dose of both medications.[15] Supratherapeutic doses may be more common when both acetaminophen and ibuprofen are administered (43%) compared to either given alone (15% acetaminophen, 14% ibuprofen) though this is based on small numbers of patients.[15] One promising observation is that of the four trials in the Cochrane review that reported on adverse events, no serious adverse events attributable to the medications were observed.[6]

Conclusion

The current evidence of alternating or combining antipyretics versus monotherapy for the treatment of fever in children suggests temperature may be marginally reduced further by using two antipyretics; however, no clear data demonstrate an improvement in children's comfort using these regimens. As antipyretic dosing errors are common, the simplest regimens should be recommended until such time that a clear, clinically meaningful advantage of more complicated regimens can be demonstrated. **The recommended first line treatment of fever in children is antipyretic monotherapy with <u>either</u> ibuprofen or acetaminophen**.

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