

Alternating acetaminophen and ibuprofen for pain in children

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Abstract

Question Because pain is a very common condition in children, such as after musculoskeletal injuries, many parents ask whether they can alternate over-the-counter analgesics to treat their children's pain. While some guidelines advise against this, it is common practice. Should alternating acetaminophen and ibuprofen be recommended for treating pain in children?

Answer Children who have unresolved pain despite the use of either ibuprofen or acetaminophen should have their medication regimen reviewed to ensure they are receiving the medication at an adequate dose and interval. If monotherapy has failed, a short trial of an alternating regimen could be implemented. However, there is a lack of evidence for safety with long-term use of alternating ibuprofen and acetaminophen.

Alterner l'acétaminophène et l'ibuprofène pour la douleur chez l'enfant

Résumé

Question Les problèmes de douleur sont très fréquents chez les enfants, par exemple après une blessure musculosquelettique. De nombreux parents demandent s'ils peuvent alterner les analgésiques en vente libre pour traiter leurs enfants. Certains guides de pratique conseillent de ne pas le faire, mais c'est pratique courante. Devrait-on recommander d'alterner l'acétaminophène et l'ibuprofène pour traiter la douleur chez les enfants?

Réponse Il faudrait revoir le régime pharmacologique des enfants dont la douleur n'est pas soulagée malgré l'utilisation de l'ibuprofène ou de l'acétaminophène pour assurer qu'ils reçoivent une dose adéquate à intervalles appropriés. Si la monothérapie ne fonctionne pas, un essai de courte durée d'un régime en alternance pourrait être effectué. Toutefois, il n'y a pas de données probantes suffisantes concernant la sécurité de l'utilisation en alternance à long terme de l'ibuprofène et de l'acétaminophène.

Ibuprofen and acetaminophen are the most commonly used over-the-counter analgesics^{1,2} and antipyretics in children.^{3,4} The American Academy of Pediatrics and the National Institute for Health and Clinical Excellence have advised parents against routinely alternating or simultaneously using acetaminophen and ibuprofen.^{5,6} Despite these recommendations, alternating doses of acetaminophen and ibuprofen is still practised by many parents⁷ and health professionals⁸ in the management of pain in children.⁹

The use of ibuprofen and acetaminophen in the pediatric population has been a topic of research for more than 30 years. There is a lack of evidence for the safety of using either of these medications for prolonged periods,⁴ and studies to date offer only short-term safety information.^{3,10} The general perception of safety of over-the-counter analgesics might contribute to inappropriate dosing and a failure to recognize children at increased risk of side effects or adverse events from these medications.¹¹ Most studies on safety and efficacy of acetaminophen and ibuprofen in children have extensively focused

on their role as antipyretic agents. A meta-analysis of 19 randomized controlled studies assessing safety of ibuprofen compared with acetaminophen as sole therapy in children demonstrated no significant difference in number of adverse events between children receiving either medication (odds ratio 0.82, 95% CI 0.6 to 1.2).⁹

Theoretical benefits and risks

The mechanism of action of acetaminophen remains unclear. Both acetaminophen and ibuprofen are metabolized by separate pathways in the liver and eliminated by the kidneys. Approximately 5% to 10% of acetaminophen is metabolized by oxidation to the hepatotoxic and nephrotoxic compound *N*-acetyl-*p*-benzoquinoneimine (NAPQI). Conjugation of NAPQI with glutathione produces a nontoxic metabolite for excretion in the kidney.¹¹

The analgesic effect of nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, is primarily via inhibition of prostaglandin biosynthesis. The reduction in prostaglandins results in decreased production of glutathione and reduced renal perfusion. When therapy combines

acetaminophen and ibuprofen, there is a theoretical increased risk of hepatic and renal toxicity as a result of the accumulation of oxidized by-products (NAPQI) of acetaminophen metabolism.¹² While this theory has not been clinically substantiated, recent case studies in the literature document children with reversible renal failure temporally related to use of both acetaminophen and ibuprofen at apparent therapeutic doses.¹³

The benefits of using an NSAID and acetaminophen concurrently or alternately have been suggested owing to the potential for synergism of antinociceptive effects and also the convenience of having a further analgesic for pain that has not responded to a single agent or dose. The potential for synergism between an NSAID and acetaminophen has been described by isobolographic analysis in experimental animal pain models.¹⁴ While recent systematic reviews demonstrate analgesic advantage when combining acetaminophen and an NSAID when compared with either as a single agent in postoperative pain management in adult and pediatric patients,¹⁵ it is unclear whether this is synergism or rather the effect of dual analgesic therapy.

Is alternating safe?

Acetaminophen has a peak plasma concentration at 30 minutes compared with 60 minutes for ibuprofen. In studies of antipyretic effects, acetaminophen has a peak effect at approximately 2 hours and ibuprofen at 3 hours. The recommended dosing intervals are every 6 and every 8 hours for acetaminophen and ibuprofen respectively¹⁰; thus, theoretically they might be alternated every 3 hours.¹¹ However, many children are undertreated,^{16,17} with more than 50% of parents shown to give an incorrect dose of these analgesics.^{17,18} In one study, following tonsillectomy, children's documented pain severity did not correlate with provision of analgesia at home (postoperative day 2, $P=.43$; day 3, $P=.95$; week 1, $P=.25$; week 2, $P=.81$). Despite 86% of children reporting severe pain postoperatively (day 2), one-quarter of children were receiving one dose of analgesia or none at all.¹⁶ Thus, in many cases an optimal single therapeutic regimen is better than implementing an alternating plan.^{16,18} Ensuring safe dosing and administration is vital in all regimens to avoid increased risk of adverse events, particularly in the face of the ranges of formulations and the knowledge gap of parents at times.


Evidence for alternating medications

In 2010, authors of a systematic review of postoperative analgesia in adults and children concluded that the combination of acetaminophen and an NSAID provided superior analgesia than either drug alone following a range of orthopedic, ear, nose and throat, gynecologic, and dental procedures.¹⁵ However, the true magnitude of possible benefit is uncertain, as these studies were

too heterogeneous for quantitative statistical comparison.¹⁵ The generalizability of the findings is limited by the brief duration of therapy and follow-up, and the small sample sizes ($N=40$ to 246) used in these studies.

When comparing alternating versus single-drug therapy for febrile children, authors of another systematic review reported that small sample sizes ($n=18$ to 155 per treatment group) and short duration of follow-up in available studies resulted in a lack of statistical power to make any general recommendations regarding safety.¹⁹ Of note, there were no reports of side effects in these studies.

Conclusion

Despite ibuprofen and acetaminophen being frequently alternated for the treatment of pain in children, the evidence of both safety and efficacy is lacking. Studies of children with fever report no increase in adverse events; however, these studies have short duration of therapy and have limited follow-up periods. Physicians should ensure children are receiving the appropriate dose and interval therapy of a single agent. Short-term use of an alternating regimen can be considered for pain unresponsive to monotherapy. 

Competing interests

None declared

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