

## Evidence that alternate dosing of paracetamol and ibuprofen in children with fever may reduce temperature: other benefits uncertain

A recently published systematic review provides evidence that the use of alternating, or combined, antipyretics (paracetamol and ibuprofen) may reduce body temperature in children with febrile illness. However, there was inconclusive evidence as to whether either practice would improve overall discomfort of the child. The aim should be to treat the underlying cause of the fever. Practice recommendations for the use of antipyretic medicines in children with febrile illness therefore remain unchanged.

Febrile illness is reported to be the number one reason that parents take their children to a General Practitioner; 20 – 40% of parents report a child having a fever each year.<sup>1</sup> Paracetamol and ibuprofen are both indicated for the treatment of pain, and fever with discomfort in children.<sup>2</sup> Current guidelines are clear in that each of these medicines should only be used as an antipyretic in children for the purposes of reducing distress and discomfort, rather than temperature reduction alone, and that the two medicines should not be combined, i.e. not given simultaneously.<sup>1</sup> However, guidelines are less clear about the role of alternate dosing of antipyretics in the treatment of fever with discomfort. Alternate dosing involves starting with one antipyretic medicine and administering the second if the child's discomfort is not sufficiently reduced within one to four hours of treatment.<sup>3</sup> NICE guidelines state that alternating doses of paracetamol and ibuprofen may be considered, but only if a child's distress persists or recurs before the next dose of medicine is due.<sup>1</sup>

A 2013 Cochrane review of six studies, involving 915 children, is the first systematic review reporting evidence of effectiveness of alternating, or combined, paracetamol and ibuprofen for temperature reduction, compared with antipyretic monotherapy.<sup>3</sup> The children included in the studies were between the ages of six months and 14 years, with the majority of children being at the younger end of this scale.<sup>3</sup> Fever was defined as a temperature greater than 37.8°C and was presumed to be of infectious origin in all children.<sup>3</sup> Three studies compared alternating paracetamol and ibuprofen treatment to ibuprofen alone, and two studies compared alternating treatment to paracetamol alone.<sup>3</sup> Three studies assessed combined treatment versus ibuprofen alone, and two

studies focused on combined treatment versus paracetamol alone.<sup>3</sup> No significant adverse effects were reported in any of the included studies. The review was limited by the small number of participants in some studies, variations in dosing regimens and the frequency and type of assessment that was conducted on the children.

The review concluded that there was low quality evidence suggesting that alternating treatment was more effective at lowering body temperature for the first three hours after the second dose, compared to either paracetamol or ibuprofen alone.<sup>3</sup> However, it was uncertain if alternating treatment was more effective at improving comfort in febrile children compared to antipyretic monotherapy.<sup>3</sup>

The Cochrane review also found moderate evidence that giving both paracetamol and ibuprofen together is likely to be more effective at lowering body temperature in children with febrile illness for the first four hours after treatment.<sup>3</sup> However, the one trial that assessed child comfort did not detect a benefit of combined treatment over treatment with either medicine alone.<sup>3</sup>

Treatment of the underlying cause is central to the management of febrile children. A symptom-based approach to treatment has the potential to mask signs of serious illness, e.g. meningococcal disease. Furthermore, the increased temperature of fever can suppress bacterial growth and slow viral replication. Paracetamol and ibuprofen should therefore not be prescribed for the sole purpose of reducing body temperature in febrile children.<sup>1</sup> The role of antipyretics in the treatment of febrile children is to improve comfort, in order to ensure the child maintains adequate intake of fluids and food, thus reducing the risk of fever-associated complications.

Many General Practitioners are already safely advising parents with distressed children to use alternate dosing, if antipyretic monotherapy initially fails to improve child comfort. The regimen that was used by the largest study in the review was to alternate doses of paracetamol and ibuprofen every four hours.<sup>4</sup> This is a reasonable approach to take in select children, depending on any contraindications to treatment. Ibuprofen

is contraindicated in children with hypersensitivity to aspirin or any other non-steroidal anti-inflammatory drug (NSAID), in children with heart failure, and in children with a history of gastrointestinal bleeding or ulceration.<sup>2</sup> It should also be remembered that the use of NSAIDs in children at recommended doses is associated with an increased risk of acute kidney injury (AKI).<sup>5</sup> Acute illness and volume depletion further increase the risk of AKI in children therefore ibuprofen should be used cautiously in children with fever. Paracetamol is generally considered to be a safer treatment option in children, although it does have the potential to cause hepatotoxicity, e.g. if overdosed or used in a child with dehydration or existing hepatic impairment.

None of the studies included in the Cochrane review reported any significant adverse effects from combined or alternate dosing of paracetamol and ibuprofen, however, adverse effects were not a primary focus of these studies. Due to their mechanisms of action, using paracetamol and ibuprofen together theoretically increases the risk of renal and hepatic toxicity. Until further safety data emerges, alternate dosing of antipyretics should only be done cautiously in select children. To minimise dosing errors, parents should be encouraged to write down the medicine, the dose, when it was given as well as the earliest time the next dose can be given; assuming the child continues to experience fever-related discomfort. This is especially important if there is more than one child in the household being treated.

Until more data is available on the safety and benefits of combined (simultaneous) dosing of paracetamol and ibuprofen the recommendation to avoid this practice in children remains.

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#### References

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