CANADIAN PAEDIATRIC SOCIETY PRACTICE POINT

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Acetaminophen and ibuprofen in the management of fever and mild to moderate pain in children

With evidence of an association between acetylsalicylic acid (ASA) use and Reye's syndrome in young children, nonprescription therapeutic choices for managing fever and mild to moderate pain are limited to acetaminophen (APAP) and ibuprofen. Whereas APAP has been available without prescription for many years, ibuprofen achieved this status more recently and, because of insufficient clinical experience, it is not labelled for over-the-counter use in children under the age of two years.

As with all drugs, parents, physicians and other caregivers should base their therapeutic choice on careful consideration of the relative safety and efficacy of the products. The statements that follow have been distilled from the extensive literature on the subject.

- In febrile children with temperatures less than 41°C, significant antipyresis can be achieved with single doses of APAP of 10 to 15 mg/kg and with ibuprofen doses of 5 to 10 mg/kg. Recommended dosing intervals, 4 to 6 h for APAP and 6 to 8 h for ibuprofen, rely on pharmacokinetic rather than multiple-dose efficacy studies.
- Based on evidence from the limited number of placebo controlled studies, it can be concluded only that these drugs, in doses shown to be effective in reducing fever, may provide some relief of mild to moderate pain in children.
- It appears unlikely that a serious risk such as the link between ASA and Reye's syndrome will surface for APAP. However, the same cannot yet be said with an equivalent degree of certainty for ibuprofen. Until adverse event data collected over a number of years prove conclusively that rare serious events are not associated with ibuprofen, APAP must remain the drug of first choice. While likely to be safe and efficacious, ibuprofen should be reserved for second-line therapy, and then used on an episode by episode basis.

The efficacy and safety of APAP and ibuprofen have been studied in many well-designed clinical trials in recent years, so that choices can be informed by good evidence. In addition, there has been close scrutiny for adverse effects, so that epidemiological evidence is also available to allow better understanding of dose-related reactions.

EFFICACY OF APAP AND IBUPROFEN

Although there is abundant evidence that uncomplicated fever is a relatively harmless but important immunological defence mechanism, many clinicians favour the use of antipyretics when needed to alleviate distressful symptoms. Most agree that antipyretics should be used in children prone to febrile seizures, although prophylaxis in high risk cases has been shown to be ineffective.

APAP and ibuprofen have been studied in at least 30 clinical trials since 1976. In these, one or more among six doses of each drug have been compared in a total of 17 different combinations. Direct comparison among studies is complicated by this diversity of doses as well as by

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the variety of outcome measures. Although the ultimate challenge is to determine whether there are clinically detectable and important differences among treatments, measures of overall patient status are conspicuously absent from the great majority of studies. Also problematic is the relative lack of multiple dose efficacy studies, although the few studies available do provide some evidence to support currently recommended dosages, but do not address concerns about drug accumulation.

The few clinical studies of APAP and ibuprofen in mild to moderate pain have encountered difficulty in finding objective measures capable of reliably distinguishing between active treatment and placebo. In pain due to otitis media, tonsillopharyngitis and headache, the two drugs are equieffective, and most studies show they are superior to placebo when given in recommended dosages. In pain associated with bilateral myringotomy and tube placement, and with tonsillectomy, placebo controlled studies have been unable to show a significant effect of either drug.

SAFETY OF APAP AND IBUPROFEN

As demonstrated by the numerous prospective clinical studies, both APAP and ibuprofen are remarkably safe in therapeutic doses. In particular, there are no reports of the most serious side effects, hepatotoxicity for APAP and gastrointestinal bleeding and renal toxicity for ibuprofen. There is at least the theoretical risk of a link between ibuprofen and Reye's syndrome, but there was no evidence of this syndrome in a prospective, APAP-controlled study in which 56,000 (66%) children received ibuprofen.

Overdosing may occur in therapeutic intent situations and the consequences of APAP-induced hepatotoxicity can be fatal, as reported in two series of cases in the United States. However, a similar finding has not been documented in the provinces of Quebec and Ontario, where none of the liver transplants in children between 1986 and 1996 was performed because of APAP-induced damage.

Although the chances of misadventure are very remote, it is important to recognize the patient at risk. The susceptible patient is likely the child who is under two years old, has received 120 mg/kg/day or more APAP for more than one day, and who is acutely malnourished and dehydrated. There are, however, isolated reports of liver toxicity at dosages of less than 100 mg/kg/day. The practice of decreasing the dosing interval from 4 to 2 h for resistant fevers is ill-advised, and the use of alternating doses of APAP and ibuprofen or a combination of both drugs has no place outside specialized units.

Several reports have suggested an association between severe soft tissue superinfections and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). In particular, ibuprofen was implicated when its use in children with varicella was linked with invasive group A streptococcal infections. An association was not established by a large retrospective cohort study; however, a larger series is required to rule out the possibility with complete confidence. It has been suggested that NSAIDs should be used judiciously in cases of local complications of varicella to avoid masking clinical features that might be useful in early recognition of superinfection.

In conclusion, both APAP and ibuprofen have reasonable efficacy and safety profiles for over-the-counter use. However, given the substantially greater volume of safety data available for APAP, it remains the first choice for therapy, while ibuprofen should be reserved for more problematic cases.

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