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

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Acetaminophen has become the non-narcotic of choice for children because of concerns regarding the connection between acetylsalicylic acid exposure and Reye's syndrome. Ibuprofen, recently granted over-the-counter status for children over two years of age, offers another choice for treatment. The efficacy and safety of both drugs have been studied in numerous clinical trials. This paper reviews the published evidence about the efficacy and safety of acetaminophen and ibuprofen with regard to treating fever and mild to moderate pain in children.

Key Words: *Acetaminophen, Fever, Ibuprofen, Pain*

L'acétaminophène et l'ibuprofène dans la prise en charge de la fièvre et de la douleur bénigne à modérée chez l'enfant

RÉSUMÉ : L'acétaminophène est devenu le non-narcotique d'élection pour les enfants en raison des inquiétudes quant au lien entre l'exposition à l'acide acétylsalicilique et le syndrome de Reye. L'ibuprofène, qui a récemment été autorisée en vente libre pour les enfants de plus de deux ans, constitue une autre possibilité de traitement. On a examiné l'efficacité et l'innocuité des deux médicaments dans de nombreuses études cliniques. Le présent article révise les observations publiées quant à l'efficacité et à l'innocuité de l'acétaminophène et de l'ibuprofène pour ce qui est du traitement de la fièvre et de la douleur bénigne à modérée chez l'enfant.

Until the early 1980s, acetylsalicylic acid (ASA) was the most commonly used analgesic/antipyretic; however, evidence associating ASA exposure with Reye's syndrome led to its contraindication in young children in a number of countries, including Canada. As a result, acetaminophen (APAP) became the non-narcotic analgesic/antipyretic of choice in children. Most recently, ibuprofen has achieved over-the-counter status, but unlike APAP, it is not labelled for use in children under the age of two years because of insufficient clinical experience.

The efficacy and tolerability of both APAP and ibuprofen have been studied in many well-designed clinical trials in recent years, so that choices can be guided by good evidence. In addition, there has been close scrutiny of the adverse effects of these drugs, with the result that epidemiological evidence is also available to allow better understanding of both dose-related and idiosyncratic reactions.

TREATMENT OF FEVER IN CHILDREN

There is abundant evidence that uncomplicated fever is a relatively harmless but important immunological defence mechanism (1), and this knowledge has been used to support arguments against treating fever. It has also been suggested that lowering temperature may obliterate valuable diagnostic signs which may allow better patient evaluation. However, no correlation between etiology and either fever severity or pattern of temperature increase has been demonstrated (2), and it is generally agreed that use of antipyretics does not prolong illness or adversely affect outcome (3). Furthermore, the fact that fever responds to antipyretics cannot be used to distinguish between serious and uncomplicated disease (4).

Although consideration of the physiological role of fever raises the question of the appropriateness of any treatment, many clinicians favour the use of antipyretics when needed to alleviate distressful symptoms and to

This continuing education document summarizes a more comprehensive review of clinical studies that is available on the internet at the Canadian Paediatric Society site <www.cps.ca>

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avoid the debilitating effect of increased metabolic rate in the absence of adequate intake of protein, fluid and electrolytes. There is more agreement about the use of antipyretics in the management of children prone to febrile seizures, which occur in 2% to 5% of those under the age of five years. Although there are no supporting clinical studies and prophylaxis in high risk children has been shown to be ineffective (5), the Committee on Infectious Diseases of the American Academy of Pediatrics suggests that children with a family history of a convulsive disorder might benefit from prophylactic APAP 15 mg/kg at the time of diphtheria, polio and tetanus vaccination, repeated every 4 h for three doses (6).

Treatment of fever includes physical measures such as tepid sponging and fanning. Although these measures can reduce temperature rapidly, the effect often adds to the child's discomfort without achieving adequate control. In addition or alternatively, pharmacotherapy can be initiated with either APAP or ibuprofen.

Clinical studies

The safety and efficacy of APAP and ibuprofen have been studied in at least 30 clinical trials since 1976, and the majority of the more recent studies included both APAP and ibuprofen treatment groups. Table 1 summarizes studies published after 1988. Despite this body of work, comparisons among studies are complicated by the great variety of outcome measures. The number of measures per study varies from one to more than 10, and it comes as no surprise that statistically significant differences often emerge from this maze of variables. In the pursuit of equieffective doses of ibuprofen and APAP in these studies, one or more among six doses of each drug have been compared in a total of 17 different combinations. The challenge is to determine whether there are clinically detectable and important differences among treatments.

Efficacy studies

In the earliest studies, the tendency was to use the same relatively low doses of APAP and ibuprofen, and, overall, there was no difference in temperature reduction. Starting in 1988, doses of APAP 10 mg/kg and ibuprofen 5 to 10 mg/kg were compared (7-12,20). The antipyretic effect of 5 mg/kg ibuprofen was not different; however, higher ibuprofen doses (7.5 to 10 mg/kg) tended to have significantly greater efficacy than this dose of APAP, at least at some time points. Doses of 10 mg/kg of both drugs were compared in three large studies: one found no difference (7), and in the others, ibuprofen was found to be more effective than APAP (9,11).

APAP 12.5 mg/kg has been compared with ibuprofen 5 to 10 mg/kg in three studies (13,14,16). One showed that 8 mg/kg ibuprofen caused greater temperature reduction (13,14), and two demonstrated that ibuprofen 5 mg/kg was not different from APAP 12.5 mg/kg (13,16). A 1976 study showed that ibuprofen 6 mg/kg was as effective as APAP 12.5 mg/kg (15).

APAP 15 mg/kg has been compared with ibuprofen 2.5 to 10 mg/kg in three studies (17-19). At this dose, APAP was superior to low doses of ibuprofen (2.5 to 5 mg/kg) but equivalent to higher doses (7.5 to 10 mg/kg). One study showed that a dose of 8 mg/kg ibuprofen was superior to APAP 15 mg/kg, but at only one time point (19).

The effects of multiple doses of APAP and ibuprofen in children are probably more important than temperature decreases due to single doses, particularly from the point of view of possible drug accumulation and side effects. However, there are only four studies of multiple doses on which to base a consideration of effective pharmacotherapy (10,12,16,18). Although the studies provide some support for single dose recommendations, there is only weak evidence on which to base optimal dosing intervals. With increasing concern about drug accumulation and overdosing with therapeutic intent, much could be learned from additional rigorously designed studies.

At one time it was not uncommon to treat resistant fevers with alternating doses of ASA and APAP, although there were and are no clinical studies supporting this practice, either using these two drugs or with the combination of APAP and ibuprofen. Considering that these drugs have different half lives, alternating therapy should only be used in specialized units under professional supervision, after consideration of possible risks and benefits of exposing a child to two drugs. The practice of decreasing the dosing interval from 4 to 2 h for resistant fevers is also ill-advised.

TREATMENT OF MILD TO MODERATE PAIN IN CHILDREN

The causes of mild to moderate pain in children can be classified broadly as those involving infection, those related to minor surgery and those that fall into neither category. The few clinical studies of APAP and ibuprofen in children have struggled to find objective measures of pain capable of reliably distinguishing between active treatment and placebo. Assessment is further complicated because the inclusion of a placebo control is sometimes not possible for perceived ethical reasons. Certainly such a design is not appropriate when there is a significant risk of pain. Information about 11 of the more recent studies is included in Table 1.

Of five studies of pain associated with bilateral myringotomy and tube placement, two showed that neither drug in doses shown to be effective in fever differed from placebo (21,22). Three studies without placebo groups concluded that there was no difference between drugs tested (23-25). A study of otitis media showed that ibuprofen 10 mg/kg provided more relief of ear pain than placebo, but at only one time point (17).

When the pain of tonsillopharyngitis was the target, the two drugs were shown to have equal activity and to be better than placebo in two studies (26,27). Similarly, in tonsillectomy pain, another two studies without placebo

TABLE 1: Clinical studies of antipyretic/analgesic drugs, including acetaminophen and/or ibuprofen, for fever and mild to moderate pain in children

First author (year)	Reference number	Study design	Number of patients (evaluable)	Dose (mg/kg) APAP	IBUP	Other
Aksoylar et al (1997)	19	Fever, open label	224 (201)	15	8	ASA: 15 Sponging
Autret et al (1997)	20	Fever, open label, multiple dose	351 (326)	10	7.5	ASA: 10
Vauzelle-Kervroedan et al (1997)	7	Fever, double-blind	120 (116)	10	10	
McIntyre et al (1996)	16	Fever, double-blind, multiple dose	150	12.5	5	
Van Esch et al (1995)	12	Fever, double-blind, multiple dose	70	10	5	
Autret et al (1994)	10	Fever, double-blind, multiple dose	154 (151)	10	7.5	
Schnaiderman et al (1993)	5	Febrile seizures	104	15-20*		
Schachtel et al (1993)	17	Fever and sore throat pain, double-blind	116 (39 with fever)	15	10	Placebo
Walson et al (1992)	18	Fever, double-blind, multiple dose	64 (61)	15	2.5, 5, 10	
Kauffman et al (1992)	8	Fever, double-blind	38 (37)	10	7.5, 10	Placebo
Kelley et al (1992)	14	Fever, open label	39	10 to 15	8	
Wilson et al (1991)	13	Fever, dose-ranging, modified double-blind	178	12.5	5, 10	Placebo
Sidler et al (1990)	11	Fever, double-blind	90	10	7, 10	
Walson et al (1989)	9	Fever, double-blind, stratified	127 (118)	10	5, 10	Placebo
Derkay et al (1998)	22	BM&T pain, observer blinded	200 (182)	10†	10	Placebo
Bennie et al (1997)	21	BM&T pain, double-blind	43	15	10	Placebo
Hamalainen et al (1997)	30	Migraine pain, double blind, crossover	106 (88)	15	10	
St Charles et al (1997)	28	Tonsillectomy pain, open label, stratified	110	Up to 15‡	5, 10	
Bean-Lijewski et al (1997)	23	BM&T pain, double-blind	132 (125)	15		Ketorolac: 1
Tobias et al (1995)	24	BM&T pain, double-blind	50	15‡		
Holloway and Logan (1992)	29	Tonsillectomy pain, double-blind	60	12	10	Placebo
Watcha et al (1992)	25	BM&T pain, double-blind	90	10		Ketorolac: 1 Placebo
Schachtel and Thoden (1991)	26	Ear pain, double-blind	88		10	Placebo
Bertin et al (1991)	27	Sore throat, double-blind, multiple dose	231	10	10	Placebo

*Additional studies performed before 1988 are in the full-length article. * Acetaminophen (APAP) 15 to 20 mg/kg every 4 h versus as required; †APAP 10 mg/kg plus codeine 1 mg/kg; ‡APAP with and without codeine. ASA Acetylsalicylic acid; BM&T Bilateral myringotomy and tube placement; IBUP Ibuprofen*

controls showed no difference between APAP and ibuprofen (28,29).

Finally, one study of headache in children revealed no clear difference between the two drugs, although both gave more relief than placebo (30).

A measure of overall patient status was included in five of the studies reviewed. Three showed that ibuprofen 10 mg/kg was somewhat better than APAP at doses of 10 or 12.5 mg/kg, whereas in the other two, observers did not distinguish between the two drugs given at full doses.

Pending the availability of more evidence, it can be concluded only that the non-narcotic analgesics, APAP and ibuprofen, in doses shown to be effective in reducing fever, may provide some relief of mild to moderate pain in children.

SAFETY OF ACETAMINOPHEN AND IBUPROFEN

APAP and ibuprofen safety data from clinical trials

The safety of APAP and ibuprofen in therapeutic dosages in prospective studies has recently been reviewed in depth, with the conclusion that both drugs are remarkably safe as used in clinical trials (31) and that there are no statistically significant differences between APAP and ibuprofen in reports of adverse events in any organ system, irrespective of the type or frequency of event. In particular, there are no reports of hepatotoxicity with APAP or gastrointestinal bleeding or renal impairment with ibuprofen.

APAP safety

Recently, the hazard of overdosing with therapeutic intent has been demonstrated with respect to APAP-induced hepatotoxicity in children in two studies (32,33). Heubi et al (32) collected 47 such cases through a search of the published literature and Food and Drug Administration files, and reported a mortality rate of 55%, with half the deaths in children less than two years old. In about half of the 47 cases, adult APAP preparations had been substituted for paediatric use with incorrect quantity adjustment.

The experience with APAP-induced hepatotoxicity in Quebec and Ontario since 1990 has been quite different (personal communication). One death has been associated with an APAP overdose in the province of Quebec in the paediatric age group in the past 10 years. Of a total of 370 liver transplants performed in children during the years 1986 to 1996 in the two provinces, none were due to APAP-induced liver damage. The reason for these differences from the experience in the United States is not evident, but may be found in an investigation of patient demographics.

Information on hepatotoxicity must be viewed within the context of the millions of children treated with APAP every day. Although the chances of misadventure are very remote, it is important to recognize the patient at risk. Kearns et al (34) have suggested that the susceptible patient is likely a child who is less than two years of age, has been taking 90 mg/kg/day or more APAP for more than one day, and who is acutely malnourished and dehydrated. Others have concluded that the upper dosage limit is 125 to 150 mg/kg/day when taken for two to four days (35). In addition to a greater appreciation of the characteristics of the patient at risk for APAP hepatotoxicity, a better understanding of multiple dose pharmacokinetics is clearly needed.

It has been estimated that 96 APAP-containing preparations are available in the United States without prescription, of which 22 are in liquid form and presumably intended for paediatric use (34). Physican awareness, direct caregiver education and improved product labelling are all needed to promote the appropriate use of APAP.

Ibuprofen safety

Possible adverse events due to ibuprofen are, as for other nonsteroidal anti-inflammatory drugs (NSAIDs), related to inhibition of cyclo-oxygenase and prostaglandin production, and include gastrointestinal bleeding, renal impairment, asthma and hepatic toxicity. Of these, minor gastrointestinal side effects are the most commonly reported in clinical trials, but it is notable that there are no reports in any controlled study, in adults or children, of any sign or symptom of gastrointestinal bleeding (31).

In adults, the most common severe adverse effect of intentional overdosing is renal dysfunction, but this is rarely fatal even after very high ibuprofen doses (36). In a prospective study of more than 83,000 children treated prospectively for fever with APAP or ibuprofen, there were no hospitalizations for renal failure, and milder renal impairment was unlikely because blood urea nitrogen and creatinine levels were within normal range (38).

Several reports have suggested an association between severe soft tissue superinfections and the use of NSAIDs. In particular, ibuprofen was implicated when its use in children with varicella was linked with the subsequent development of invasive group A streptococcal infections (38,39). This concern prompted a retrospective cohort study in which data from over 7000 children with varicella were examined (40). An association was not established by this study because, although children given ibuprofen were about three times more likely to develop a superinfection, the 95% confidence interval was such that the association was not statistically significant. Nevertheless, NSAIDs have been shown to alter some immunological processes, and 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.

Because ASA may be associated with Reye's syndrome and ibuprofen is a NSAID, there is at least the theoretical risk of a similar relationship for ibuprofen. The occurrence of this syndrome was monitored prospectively in the more than 56,000 children who received ibuprofen in the study by Lesko and Mitchell (37). No children were hospitalized with evidence of this syndrome in the four weeks following drug use.

CONCLUSIONS

Clinical studies show that, 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. Information on dosing intervals relies on pharmacokinetic rather than multiple-dose efficacy studies: 4 to 6 h for APAP and 6 to 8 h for ibuprofen. Recommended doses of these drugs are more effective than placebo in approximately half the children tested. Consideration should be given to using these drugs before resorting to more potent agents.

Evaluators of the safety of APAP and ibuprofen must bear in mind the millions of children who receive these drugs every day worldwide and the fact that use of APAP has been far more extensive than ibuprofen. At this point, it appears unlikely that a serious risk such as the associa-

tion between ASA and Reye's syndrome will surface for APAP. However, the same cannot yet be said with the same degree of certainty for ibuprofen, and until adverse event data collected over a period of years prove conclusively that rare serious events are not associated with ibuprofen, APAP must remain the drug of choice. Ibuprofen should be reserved for second-line therapy, and then used on an episode by episode basis.

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Acetaminophen and ibuprofen

Answer the following questions by circling the letter of the correct answer. Answers can be found on the inside back cover.

1. Which of the following statements about fever are true:
   (a) if uncomplicated, fever is relatively harmless and is an important immunological defence mechanism
   (b) severity and/or pattern does not correlate with etiology
   (c) treatment with antipyretics does not prolong illness or adversely affect outcome
   (d) response to antipyretics does not distinguish between serious and uncomplicated disease
   (e) prophylaxis with acetaminophen 15 mg/kg may be of benefit in children with a family history of convulsive disorder at the time of diphtheria, polio and tetanus vaccination every 4 h for three doses
2. Significant antipyresis can be achieved with single doses of
   (a) acetaminophen 10 to 15 mg/kg
   (b) acetaminophen 5 to 8 mg/kg
   (c) ibuprofen 5 to 10 mg/kg
   (d) ibuprofen 12 to 15 mg/kg
3. Appropriate dosing intervals are
   (a) alternate every 2 h acetaminophen and ibuprofen
   (b) acetaminophen 4 to 6 h
   (c) alternate every 4 h acetaminophen and ibuprofen
   (d) ibuprofen 6 to 8 h
4. Which of the following statements about the use of acetaminophen and ibuprofen in pain relief are true?
   (a) acetaminophen may provide relief of mild to moderate pain
   (b) ibuprofen may provide relief of mild to moderate pain
   (c) acetaminophen and ibuprofen are more effective than placebo in about half of the children tested
   (d) acetaminophen and ibuprofen should be considered before more potent agents
   (e) some studies have been hampered by the lack of placebo controls
5. Acetaminophen must be recommended over ibuprofen because of the following safety issues.
   (a) vastly greater experience with acetaminophen
   (b) good controlled studies comparing the safety of the two drugs
   (c) insufficient use of ibuprofen to rule out rare serious events
   (d) association of ibuprofen with Reye's syndrome
   (e) none of the above; there is no preference of acetaminophen over ibuprofen