

Antipyretic Efficacy and Safety of Ibuprofen and Acetaminophen in Children

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OBJECTIVE: To evaluate the antipyretic effects and safety of ibuprofen compared with acetaminophen in febrile children.

DATA SOURCES: Searches of MEDLINE (1966–November 2003) and EMBASE (1988–November 2003) were conducted using the terms ibuprofen and acetaminophen. Bibliographies of selected articles were reviewed.

DATA SYNTHESIS: Ibuprofen was significantly more effective than acetaminophen in reducing fever after a single dose. Ibuprofen was found to be more effective after 6 hours, but not after a longer period of time. Studies with multiple doses have also failed to show that one drug is better than the other.

CONCLUSIONS: The efficacy and effectiveness of acetaminophen and ibuprofen in their recommended dosages are similar, with slightly more beneficial effects shown with ibuprofen.

KEY WORDS: acetaminophen, children, ibuprofen.

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REQUEST

How do acetaminophen and ibuprofen compare in terms of antipyretic efficacy in children?

RESPONSE

BACKGROUND

Fever has been estimated to be the primary symptom for 30% of patients seen by pediatricians.¹ Although elevated body temperature is an adaptive physiologic response with important immunologic defense mechanisms,^{2,3} it is also associated with discomfort, increased risk of dehydration, and seizures.² Parental fear of the presumed harmful effects of fever in children is common and based on misconceptions regarding both the role of fever in illness and its management.⁴ The benefits and relative risks of using antipyretic medications are a matter of debate.² Although the use of antipyretics is widely recommended, the treatment and management of fever are often inconsistent in practice and not supported by evidence-based research.^{5,6}

The use of salicylates for their antipyretic effects has decreased over the last few decades because of their suggested role in Reye syndrome.⁷ Over that time, acetaminophen has become the most widely used antipyretic for febrile children despite its association with adverse effects, such as hepatotoxicity, especially in toxic dosages.⁸ Ibuprofen is well tolerated by most patients and recommended for children.^{9,10} Ibuprofen is also associated with adverse effects such as renal toxicity, mainly in patients with preexisting renal disease, allergic reactions, worsening of asthma, gastrointestinal discomfort, and ulceration.⁹

Family physicians and pediatricians are frequently asked by parents of febrile children which of the 2 most commonly used medications—ibuprofen and acetaminophen—is more effective in reducing fever. This review evaluates the current knowledge of the antipyretic effects of ibuprofen compared with acetaminophen and assesses the adverse effects associated with the use of these drugs in children.

DATA SOURCES

A literature search was conducted using MEDLINE (1966–November 2003) and EMBASE (1988–November 2003) using the search terms ibuprofen and acetaminophen.

Author information provided at the end of the text.

We only included studies in English in which the drugs were compared with one another. We limited the studies examined to children from birth to 18 years old and when both medications were administered for the treatment of fever. Bibliographies of selected articles were also examined to include all relevant investigations.

EFFICACY

To date, 14 studies have compared the antipyretic effects of ibuprofen and acetaminophen^{2,9-21}; 11 of these were randomized controlled trials^{2,9-12,14-19} (Table 1). Several of these studies compared more than one dosage of ibuprofen with acetaminophen.^{2,9,13,15,17-20} A variety of outcome measures were used to compare the antipyretic effects of ibuprofen and acetaminophen including AUC of percentage reduction of

temperature with respect to time,^{2,9,11,15,17} change in temperature over time,^{10,12,14,16,19,20} and duration^{9,10,12,14,19} and extent of temperature reduction after a single dose of medication.^{10,12,14}

Single-Dose Studies

Single-dose antipyretic efficacy of ibuprofen compared with acetaminophen remains controversial. Several studies have reported that ibuprofen was significantly more effective than acetaminophen in reducing fever. Greater antipyresis and longer duration of that effect was shown while using ibuprofen, as measured by AUC of percentage reduction of temperature.^{2,11,15,17}

In a double-blind triple-dummy study, children from the emergency department or responders to a newspaper ad were found to have temperatures decreases more after ad-

Table 1. Studies Comparing the Antipyretic Effect of Ibuprofen and Acetaminophen

Reference	Design	Setting	Pts. (n, age)	Acetaminophen (mg/kg)	Ibuprofen (mg/kg)	Findings
Single-dose						
Walson et al. (1989) ²	R, DB, followed for 8 h	ED and clinics	118, 2–11 y	10	5, 10	ibuprofen 10 mg/kg produced rapid, longer-lasting fever control than acetaminophen
Sheth et al. (1980) ¹⁰	R, open, followed for 12 h	hospital	22, 2–8 y	8	7	rate, duration of, and maximum temperature reduction similar between the groups
Autret et al. (1997) ¹¹	R, DB, followed for 6 h	outpatients (private practitioners)	348, 6–24 mo	10	7.5	ibuprofen significantly more effective than acetaminophen in reducing fever
Vauzelle-Kervroedan et al. (1997) ¹²	R, DB, MC, followed for 6 h	outpatients (private practitioners)	116, 8 mo–12 y	10	10	time to lowest temperature, as well as extent, rate, and duration of temperature reduction similar between 2 groups (drugs given in Sparklets)
Amdekar et al. (1985) ¹⁴	R, open, followed for 8 h	hospital	39, 2–12 y	8	7	rate, degree, and duration of temperature reduction similar between the groups
Kauffman et al. (1992) ¹⁵	R, DB, PC, followed for 8 h	ED	37, 2–12 y	10	7.5, 10	ibuprofen 10 mg/kg produced a significant decrease in temperature early after dose, greater maximum, and longer duration of temperature reduction than acetaminophen
Wilson et al. (1991) ¹⁷	R, DB, PC, followed for 6 h	outpatients or inpatients	178, 3 mo–12 y	12.5	5, 10	ibuprofen 10 mg/kg significantly more effective than acetaminophen in reducing fever
Wong et al. (2001) ¹⁸	R, DB, followed for 6 h	hospital and outpatient clinic	555, 6 mo–6 y	12	5–10	ibuprofen significantly better than acetaminophen for “temperature normalization”
Simila et al. (1976) ²⁰	open, followed for 6 h	hospital	79, 3 mo–13 y	12.5	0.5, 6	ibuprofen 6 mg/kg and acetaminophen had similar antipyretic effects
Joshi et al. (1990) ²¹	open, MC, followed for 2 h	hospital	175, 4 mo–12 y	8	7	similar action in temperature reduction
Multiple-dose						
Walson et al. (1992) ⁹	R, DB, followed for 48 h	hospital	64, 6 mo–12 y	15	2.5, 5, 10	ibuprofen 10 mg/kg and acetaminophen produced greater reduction of fever than acetaminophen after 6 h but not after 12 h
Sidler et al. (1990) ¹³	DB, followed for 24 h	hospital	71, 6 mo–13 y	10	7, 10	rate of temperature reduction at 3 h significantly greater with ibuprofen 10 mg/kg
McIntyre et al. (1996) ¹⁶	R, DB, followed for 36 h	inpatients	150, 2 mo–12 y	12.5	5	ibuprofen and acetaminophen equally effective in reducing fever
Single and multiple dose						
Wilson et al. (1984) ¹⁹	open, followed for 11 h	inpatients and outpatients with pathology	30, 2 mo–10 y	125/250/500 mg per dose (by age)	50/100/200 mg 1 dose (by age)	ibuprofen induced greater reduction in temperature for a longer time

DB = double-blind; ED = emergency department; MC = multicenter; PC = placebo-controlled; R = randomized.

ministration of ibuprofen 10 mg/kg than when given acetaminophen 10 mg/kg ($p < 0.05$).² Both drugs were better than placebo ($p < 0.05$). Ibuprofen 5 mg/kg had no beneficial effect over acetaminophen. In an open, randomized study, ibuprofen created a higher AUC up to 6 hours after treatment compared with acetaminophen ($p < 0.05$).¹¹ Ibuprofen caused a larger mean reduction in temperature 4 hours ($p = 0.003$) and 6 hours ($p = 0.019$) after administration, but not after 1 hour ($p > 0.05$). Another study showed that ibuprofen 10 mg/kg resulted in a longer duration of antipyresis compared with acetaminophen.¹⁷ A randomized, double-blind, double-dummy study with a small sample size found ibuprofen to give a higher median AUC than acetaminophen up to 8 hours after administration ($p = 0.05$).¹⁵ Fever subsided faster, maximal reduction in temperature was larger, and duration of antipyretic effect was longer with ibuprofen. The magnitude of the differences in mean temperatures between the 2 drugs was found to vary over time, with the differences being greatest between 3–8 hours and 16–24 hours after administration.¹³

Other studies found no significant difference in the single-dose antipyretic effect of ibuprofen and acetaminophen as measured by change in temperature over time,^{10,12,14,20,21} duration of temperature reduction,^{12,14} and extent of temperature reduction.^{10,12,14} Ibuprofen 10 mg/kg decreased temperature by $\geq 1^\circ\text{C}$ in 90% ($n = 26$) of children aged 5 months to 13 years compared with 79% ($n = 23$) given acetaminophen 10 mg/kg.¹³ However, this difference was not statistically significant ($p > 0.05$). In the largest multinational trial to date, 555 children were assessed.¹⁸ Ibuprofen 5 or 10 mg/kg (based on temperature lower or higher than 39°C , respectively) reduced the temperature by $\geq 1.5^\circ\text{C}$ in 83% of the children compared with only 77% who received acetaminophen ($p = \text{NS}$).

When ibuprofen and acetaminophen were administered in 10-mg/kg dosages in the Sparklets formulation, the time difference between drug administration and the lowest observed temperature was not significantly different between the drugs (3.6 vs 3.65 h).¹² In addition, temperature reduction was similar (1.65 and 1.5°C), as were rate of reduction (0.52 and $0.51^\circ\text{C}/\text{h}$) and duration of temperature $< 38.5^\circ\text{C}$ (3.79 vs 3.84 h).

Multidose Studies

The effect of multiple doses of ibuprofen was compared with that of acetaminophen in 2 randomized, double-blind trials and one open, comparative study.^{9,16,19} One of the studies¹⁶ used a low dose of both antipyretics (acetaminophen 12.5 mg/kg and ibuprofen 5 mg/kg) and found mean changes of -1.8 and -1.6°C at 4 hours, respectively, after treatment ($p = 0.39$). There were no significant differences in the distribution of times until temperature decreased to $< 37.5^\circ\text{C}$ ($p = 0.25$) and the time until the second dose of an antipyretic was given ($p = 0.44$). An open-label trial with only 30 patients and dose based on age rather than weight found a steeper regression line corresponding to the decrease in temperature over 12 hours after administration

of ibuprofen although the difference seems to be relatively small (p value not reported).¹⁹ Another study using recommended dosages of both drugs (ibuprofen 10 mg/kg, acetaminophen 15 mg/kg) found ibuprofen to induce a larger reduction in mean percent decrease in temperature up to 6 hours after administration (73.2% vs 65.9%).⁹ The AUC of percent temperature reduction over time was only borderline significant ($p = 0.03$). This difference appeared to disappear when measured at 0–12 hours ($p = 0.06$), 0–24 hours ($p = 0.07$), or 0–48 hours ($p = 0.13$).

ADVERSE EFFECTS

Current literature regarding the adverse effects associated with ibuprofen and acetaminophen use in children is limited. In one large study aiming to compare the incidence of serious adverse clinical events leading to admission to the hospital among children < 2 years old, 27 065 children were followed.²² During a 4-week follow-up period, the risk of hospitalization due to illness in children treated for a median of 3 days was 1.4% and did not vary by antipyretic treatment. The risk of hospitalization with gastrointestinal bleeding among children who were randomly assigned to the ibuprofen group was 17 per 100 000 (95% CI 3.5 to 49 per 100 000). This was not significantly greater than the risk among children given acetaminophen.

Much information has been published on the adverse effects of each medication separately.^{23,24} The number of children with mild adverse events did not differ significantly between acetaminophen and placebo or acetaminophen and physical methods for reducing temperature,²³ and the risk for hospitalization due to gastrointestinal bleeding, renal failure, or anaphylaxis was not increased following short-term use of ibuprofen.²⁴

Studies comparing the adverse effects of ibuprofen and acetaminophen are sparse. While some trials concluded that the proportion of patients who experienced adverse events was not significantly different between treatment groups,^{2,16,22} several studies have reported no adverse effects related to antipyretic use.^{14,15,20} Other studies have reported adverse effects in 0–26.6% of febrile children treated with ibuprofen compared with 0.9–19% treated with acetaminophen.^{2,9,11–13} Patients in the ibuprofen group reported at least one adverse event more than with the use of acetaminophen,¹¹ with gastrointestinal symptoms and sweating being the most common.^{2,9,11} In contrast, febrile children treated with acetaminophen experienced hypothermia, abdominal pain, agitation, and/or nervousness (18.8%).⁹ Vomiting was also reported as a common adverse effect with the use of acetaminophen (1.7–6.7%).^{12,13} Limitations of these findings include small sample sizes in most studies (< 100), and the methods in which the adverse effects were monitored were not reported.^{9,13–15,20}

LIMITATIONS OF STUDIES

Evaluation of the evidence comparing the antipyretic effects of ibuprofen and acetaminophen is complicated by a number of methodologic limitations. One of the most sig-

nificant limitations is the small sample size investigated by most comparison studies to date. Most studies^{2,9,10,12-17,19-21} compared <100 febrile children in each group (range 22–348), which enables the comparison of efficacy but makes the comparison of adverse effects impossible due to the low rate of adverse effects reported. Furthermore, multidosage studies^{9,16} reported a high percentage of withdrawals (64–82%) before completion of the study due to recovery from illness. This makes the comparison of the antipyretic effect beyond a period of 24 hours incomplete.

Patient recruitment varied across the studies. While some studies recruited patients from community health settings, such as pediatric clinics and private practices,^{11,12,22} others used inpatients^{9,10,13,15,16} and both inpatients and outpatients.^{2,17} Groups were not matched at the time of recruitment in any of the studies. Inherent differences between inpatient and outpatient populations regarding severity, as well as the course and management of the illness, make it difficult to analyze findings and draw conclusions from these studies.

The dosages of the antipyretics varied across studies, ranging from 0.5 to 10 mg/kg with ibuprofen and 8 to 15 mg/kg with acetaminophen. Results of studies that used doses lower than those recommended therapeutically were not clinically useful.

SUMMARY

To date, only a few reports compare the antipyretic effect of ibuprofen and acetaminophen in the recommended dosages, with no significant advantage to one over the other. Hence, the antipyretic effectiveness of ibuprofen versus acetaminophen remains controversial.

Ibuprofen was found to be slightly advantageous in few single- and multiple-dose studies, but methodologic flaws make the comparisons debatable. The risk of serious adverse events among children receiving short-term treatment with either ibuprofen or acetaminophen was small and did not vary by choice of medication. The existing data do not provide any information on the safety of these 2 medications when used for prolonged periods or when used together, regardless of duration.

Further studies are needed to obtain conclusive findings on the comparative efficacy and safety of ibuprofen and acetaminophen in lowering temperature in children. These studies should also include evaluations of use in specific pediatric populations and assessment of cost effectiveness. In order to obtain conclusive results, larger series will be needed and evaluation of the drugs should be performed using recommended therapeutic dosages and standard outcome measures.

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EXTRACTO

OBJETIVO: Evaluar el efecto antipirético de ibuprofén comparado con acetaminofén en niños con fiebre.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en MEDLINE (1966 al noviembre 2003) y EMBASE (1998 al noviembre 2003) utilizando los términos de búsqueda ibuprofén y acetaminofén y la bibliografía de artículos seleccionados.

SÍNTESIS: Ibuprofén es significativamente más efectivo que acetaminofén en reducir la fiebre luego de 1 dosis. Se encontró que ibuprofén fue más efectivo luego de 6 horas, pero no después de un período mayor de tiempo. Estudios con dosis múltiples tampoco han demostrado que un fármaco es mejor que el otro.

CONCLUSIONES: La eficacia y efectividad de acetaminofén e ibuprofén en sus dosis recomendadas es similar, con un efecto beneficioso un poco mayor con ibuprofén.

Giselle Rivera

RÉSUMÉ

OBJECTIF: Evaluer les effets antipyrétiques de l'ibuprofène par comparaison avec ceux du paracétamol chez des enfants fébriles.

REVUE DE LITTÉRATURE: Littérature de langue anglaise repérée par MEDLINE (depuis 1966) et Embase (depuis 1988) à partir des mots-

clés ibuprofène et acétaminophène, et les références bibliographiques d'articles pertinents.

RÉSUMÉ: Il a été analysé 14 études, dont 11 essais à répartition aléatoire. Les différences dans les critères d'inclusion ou d'évaluation, la faiblesse des effectifs, ou le fort taux de perdus de vue limitent les possibilités de tirer des conclusions valides de certaines de ces études. L'ibuprofène est significativement plus efficace que le paracétamol sur la réduction de la fièvre 6 heures après une prise unique, mais pas après une durée plus longue. Les études après administration de doses multiples n'ont pas montré de supériorité d'un médicament par rapport à l'autre.

CONCLUSIONS: L'efficacité du paracétamol et celle de l'ibuprofène aux doses recommandées sont similaires, avec un léger effet bénéfique pour l'ibuprofène.

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