

Efficacy and Safety of Acetaminophen vs Ibuprofen for Treating Children's Pain or Fever

A Meta-analysis

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Objective: To summarize studies testing the efficacy and safety of single-dose acetaminophen and ibuprofen for treating children's pain or fever.

Data Sources: Reports were gathered by searching computerized databases (from their inception through May 2002) and registries, relevant journals, and bibliographies of key articles.

Study Selection: Seventeen blinded, randomized controlled trials with children (<18 years) receiving either drug to treat fever or moderate to severe pain.

Data Extraction: Under a fixed-effects model, outcome measures for an initial single dose of ibuprofen vs acetaminophen were the risk ratio for achieving more than 50% of maximum pain relief, effect size for febrile temperature reduction, and risk ratio for minor and major harm.

Data Synthesis: Ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) showed comparable efficacy (3 pain relief trials; 186 children). The risk ratio point-estimates was 1.14 (95% confidence interval [CI], 0.82-1.58) at 2 hours

after receiving the dose, and 1.11 (95% CI, 0.89-1.38) at 4 hours. Ibuprofen (5-10 mg/kg) reduced temperature more than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours after treatment (respective weighted-effect sizes: 0.19 [95% CI, 0.05-0.33], 0.31 [95% CI, 0.19-0.44], and 0.33 [95% CI, 0.19-0.47]) (9 fever trials; 1078 children). For ibuprofen 10 mg/kg (acetaminophen, 10-15 mg/kg), corresponding effect sizes were 0.34 (95% CI, 0.12-0.56), 0.81 (95% CI, 0.56-1.03), and 0.66 (95% CI, 0.44-0.87). There was no evidence the drugs differed from each other (or placebo) in incidence of minor or major harm (17 safety trials; 1820 children).

Conclusions: In children, single doses of ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) have similar efficacy for relieving moderate to severe pain, and similar safety as analgesics or antipyretics. Ibuprofen (5-10 mg/kg) was a more effective antipyretic than acetaminophen (10-15 mg/kg) at 2, 4, and 6 hours post-treatment.

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ACETAMINOPHEN AND IBUPROFEN are widely prescribed in children and are the most frequently used over-the-counter analgesics and antipyretics, yet their relative efficacy and safety is uncertain. For adult analgesia, research has shown ibuprofen treatment to be just as^{1,2} or more^{3,4} effective than acetaminophen. As the pharmacodynamic profile of the drugs may vary with patient age,⁵⁻⁷ generalization of these results to children may be inappropriate.

A clear picture has not yet emerged from studies with children comparing the 2 drugs. Although some studies have concluded ibuprofen to be the superior analgesic⁸ and antipyretic,⁹ literature reviews typically have concluded that the drugs were equally effective but that acetaminophen should be preferred because its safety seemed more assured.^{5,6,10,11} Other commentators have noted the importance of considering contextual variation across

studies before drawing conclusions,¹²⁻¹⁴ ideally by way of meta-analysis.^{15,16}

Heeding this call, we investigated by way of meta-analysis the following 3 questions about acetaminophen and ibuprofen

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for single-dose, short-term use in children: (1) their relative efficacy for treating pain, (2) their relative efficacy for treating fever, and (3) their safety compared with each other and with placebo.

METHODS

DATA SOURCES

We searched the following electronic databases from their inception through May 2002 to identify randomized controlled trials of ibuprofen and acetaminophen for pediatric pain and fever: MEDLINE, EMBASE, Cochrane

Study Characteristics and Outcomes for Pain Relief, Febrile Temperature Reduction, and Safety

Source	Model	Mean Age, y	% Girls	Dosage, mg/kg		No. of Patients*	
				Acetaminophen	Ibuprofen	Acetaminophen	Ibuprofen
Pain							
McGaw et al, ⁸ 1987	Pain (dental)	14	62	7§	4	43	41
Moore et al, ²⁶ 1985	Pain (dental)	8	30	10§	6	11	14
Schachtel and Thoden, ²⁷ 1993	Pain (sore throat)	9	51	15	10	38	39
Overall	NA	NA	NA	NA	NA	92	94
Fever							
Kauffman et al, ⁹ 1992	Fever (temp)	6	73	10	10	8	8
Wilson et al, ¹³ 1991	Fever (trb)	3	NA	12.5	10	51	47
Wong et al, ¹⁴ 2001	Fever (trb)	3	46	12	5 or 10#	191	185
Walson et al, ²² 1989	Fever (temp)	6	53	10	10	32	25
Autret et al, ²⁸ 1994	Fever (trb)	2	42	10	7.5	74	77
McIntyre and Hull, ²⁹ 1996	Fever (trb)	2	41	12.5	5	66	69
Starha et al, ³⁰ 1994	Fever (temp)	5	NA	10	10	26	36
Van Esch et al, ³¹ 1995	Fever (temp)	2	27	10	5	36	34
Vauzelle-Kevroedan et al, ³² 1997	Fever (temp)	4	49	10	10	55	58
Walson et al, ³³ 1992	Fever (trb)	6	52	15	10	16	15
Overall	NA	NA	NA	NA	NA	539	539
10 mg/kg ibuprofen only**	NA	NA	NA	NA	NA	172	174
Safety only††							
Bertin et al, ¹⁷ 1991	Otitis media	8	44	10	10	78	77
Bertin et al, ¹⁸ 1994	Sore throat	3	56	10	10	73	71
Hämäläinen et al, ¹⁹ 1997	Migraine	11	50	15	10	88	88
Sidler et al, ²⁰ 1990	Fever	NA	NA	10	10	21	25
Overall	NA	NA	NA	NA	NA	905‡‡	915‡‡

Abbreviations: CI, confidence interval; NA, not applicable; temp, fever outcome measure was between-drug difference in temperature at given time point; trb, fever outcome was between-drug difference in temperature reduction from baseline.

*After attrition, at 4 hours (6 hours for Walson et al²²).

†Risk ratio values greater than 1 indicate a greater likelihood of minor (major) harm for ibuprofen than for acetaminophen treatment.

‡For pain, the risk ratio values greater than 1 indicate a greater likelihood of achieving more than 50% of the maximum pain relief with ibuprofen than with acetaminophen treatment. For fever, the values given are reported as febrile temperature reduction effect size (95% CI).

§The exact dosage was 240 mg/d for children younger than 8 years and 360 mg/d for children aged 8 years and older.

||The exact dosage was 200 mg/d.

¶Outcomes were estimated from a figure rather than a table.

#The exact dosage was 5 mg/kg if the initial temperature was less than 39.2°C; or 10 mg/kg otherwise.

**The mean effect size for analysis comparing 10 mg/kg of ibuprofen with 10 mg/kg or more of acetaminophen.

††Studies that examined safety that were not already included in the pain for fever analysis.

‡‡The number of patients included in the minor harm analysis. For the major harm analysis, there were 899 participants in the acetaminophen arm and 914 in the ibuprofen arm.

Library, Biological Abstracts, Biological Abstracts/RRM, CINAHL, Dissertation Abstracts International, EBM Reviews-Best Evidence, EBM Reviews-Database of Abstracts of Reviews of Effectiveness, ERIC, Expanded Academic ASAP, General Science Abstracts, Health Reference Center Academic, Health Source Plus, HealthStar, Oxford Pain Relief Database, PsychInfo, and Web of Science. We used combinations of the following search terms: "clinical trial," "RCT," "random*," "trial," "study," "ibuprofen," "Brufen," "propionic acid," "acetaminophen," and "paracetamol." Hand searches of reference lists of located studies, as well as relevant review articles, Web sites, textbooks, and 4 key medical journals, did not yield any additional reports. No relevant data sets were obtained from approaches to pharmaceutical companies marketing the drugs, or from requests placed on the international Pediatric Pain listserv.

INCLUSION AND EXCLUSION CRITERIA

We included studies with participants younger than 18 years receiving either drug for treatment of fever or moderate to severe pain, randomly allocated to treatment arms in a blinded design. Otherwise relevant studies were excluded if any prior or concurrent medication was a potential confound (eg, lido-

caine, codeine, and others), if the data were already included in another study, or if insufficient data were provided to calculate a value for the relevant outcome measures. The latter criterion resulted in the exclusion of 3 studies from the pain analysis¹⁷⁻¹⁹ and 1 from the fever analysis²⁰ (but did not prohibit their inclusion in the safety analysis), and in the exclusion of 1 study from the safety analysis.²¹

For multidose studies, we included only the data for the first dose in the pain and fever analyses. No study included more than 1 acetaminophen treatment arm, but 4 studies used 2 ibuprofen treatment arms at different dosages.^{9,13,20,22} To preserve independence of effect sizes,²³ we included only the ibuprofen treatment arm at the higher dosage, which was less than or equal to the corresponding acetaminophen dosage.

DATA EXTRACTION AND OUTCOME DEFINITIONS

The independent coders (D.A.P. and T.P.) were blinded to identifying information about the author, institutional affiliation, financial support, source, and year of publication until the meta-analyses were completed. Outcome variables were independently coded with a median agreement across coded variables of 100% (median, $\kappa=0.99$; minimum, $\kappa=0.75$).²⁴ Disagreements were resolved by discussion.

Safety Assessment Interval, h	Maximum No. of Doses	Safety Risk Ratio (95% CI)†		Time, h ‡		
		Minor Harm	Major Harm	2	4	6
4	1	1.05 (.07 to 16.22)	1.05 (0.02 to 53.60)	1.25 (0.75 to 2.07)	1.14 (0.80 to 1.62)	NA
4	1	0.80 (0.2 to 37.43)	0.80 (0.02 to 37.34)	1.31 (0.70 to 2.47)	1.14 (0.83 to 1.55)	NA
6	1	2.93 (0.12 to 69.64)	2.85 (0.12 to 67.97)	0.91 (0.51 to 1.62)¶	0.97 (0.54 to 1.76)¶	NA
NA	NA	NA	NA	1.14 (0.82 to 1.58)	1.11 (0.89 to 1.38)	NA
24	1	1.00 (0.02 to 45.13)	1.00 (0.02 to 45.13)	0.37 (–0.71 to 1.46)¶	1.06 (–0.11 to 2.23)¶	1.20 (0.00 to 2.39)¶
12	1	1.00 (0.02 to 49.28)	1.0 (0.02 to 49.28)	0.00 (–0.40 to .40)¶	0.99 (0.57 to 1.42)¶	1.21 (0.78 to 1.65)¶
342	1	4.13 (0.47 to 36.61)	0.97 (0.14 to 6.81)	0.01 (–0.19 to 0.22)	–0.03 (–0.24 to 0.17)	0.04 (–0.17 to 0.24)
8	1	1.03 (0.37 to 2.86)	7.97 (0.43 to 147.82)	0.97 (0.40 to 1.53)	0.86 (0.30 to 1.42)	0.57 (0.03 to 1.12)
72	12	1.78 (0.62 to 5.07)	1.50 (0.26 to 8.73)	NA	0.29 (–0.03 to .62)	NA
72	3	0.60 (0.30 to 1.20)	0.85 (0.33 to 2.23)	NA	0.08 (–0.26 to .42)	NA
24	1	0.73 (0.02 to 35.64)	0.73 (0.02 to 35.64)	1.09 (0.54 to 1.64)	1.74 (1.13 to 2.35)	1.42 (0.84 to 1.99)
72	12	0.79 (0.31 to 2.05)	1.06 (0.02 to 51.84)	0.46 (–0.03 to 0.94)	0.49 (0.00 to 0.97)	0.31 (–0.17 to 0.79)
6	1	0.19 (0.01 to 3.81)	0.93 (0.02 to 46.31)	0.00 (–0.37 to 0.37)	.25 (–0.13 to 0.62)	0.00 (–0.38 to 0.38)
24	4	NA	0.36 (0.02 to 5.46)	NA	NA	0.16 (–0.58 to 0.90)
NA	NA	NA	NA	0.19 (0.05 to 0.33)	0.31 (0.19 to 0.44)	0.33 (0.19 to 0.47)
NA	NA	NA	NA	0.34 (0.12 to 0.56)	0.81 (0.56 to 1.03)	0.66 (0.44 to 0.87)
48	6	1.69 (0.42 to 6.82)	1.01 (0.02 to 50.41)	NA	NA	NA
48	6	1.71 (0.43 to 6.91)	1.03 (0.02 to 51.11)	NA	NA	NA
5	1	0.89 (0.36 to 2.19)	1.00 (0.02 to 49.84)	NA	NA	NA
24	3	0.42 (0.04 to 4.31)	0.27 (0.01 to 6.27)	NA	NA	NA
NA	NA	0.96 (0.68 to 1.36)	1.00 (0.55 to 1.82)	NA	NA	NA

Pain

The outcome measure for pain relief was the risk ratio for achieving at least 50% of maximum pain relief with ibuprofen vs acetaminophen treatment. To determine the risk ratio, we estimated from area under the curve statistics for pain relief vs time the proportion of participants showing at least 50% of maximum pain relief for each treatment arm. This was done following guidelines and regression equations provided by McQuay and Moore.²⁵ The risk ratio was computed by dividing the proportion for the ibuprofen treatment arm by that for the acetaminophen treatment arm.

Fever

Half of the fever studies reported efficacy in terms of the mean between-drug difference in temperature at 2, 4, and 6 hours after treatment, whereas the remainder described it in terms of the mean between-drug difference in temperature reduction from baseline at these time points (**Table**). By converting these outcomes into standardized effect sizes, using the method of Hedges³⁴ to correct for small sample bias, we were able to include all 10 studies in a single analysis. In each study, differences across treatment arms in baseline temperature were negligible.

Safety

The main outcome measure for safety was the risk ratio for minor and major harm for ibuprofen vs acetaminophen treatment. We defined minor harm as the occurrence of an adverse event not leading to withdrawal from the study (eg, nausea, sweating, or cutaneous rash).³⁵ The risk ratio for minor harm was computed by dividing the number of minor harm events per patient for the ibuprofen treatment arm by the corresponding figure for the acetaminophen treatment arm.

We defined major harm as the withdrawal of a patient from the study owing to an adverse event (eg, abdominal pain, vomiting, or hypothermia).³⁵ The risk ratio for major harm was computed by dividing the proportion of patients experiencing major harm in the ibuprofen treatment arm by the corresponding proportion in the acetaminophen treatment arm. We also computed risk ratios for minor and major harm for each drug compared with placebo.

DATA ANALYSIS

We analyzed data under a fixed-effects inverse-variance model. To determine whether outcomes were consistent across studies, we calculated a homogeneity statistic, Q , which has an approximate χ^2 distribution with $k-1$ df, where k is the number of outcomes.²³ For example, k was 3 for the pain analysis, because each of the 3 studies contributed 1 outcome. Where we rejected the null hypothesis of homogeneity (using a criterion of $P < .05$), we used the method of Hedges^{23,34} to examine whether effect sizes varied according to particular study characteristics such as dosage.

RESULTS

TRIALS

Of 127 studies of potential relevance, 17 met the inclusion criteria, providing 3 data sets for the pain relief analysis,^{8,26,27} 10 data sets for the fever reduction analysis,^{9,13,14,22,28-33} and 17 data sets for the safety analysis.^{8,9,13,14,17-20,22,26-33}

Studies were typically single-dose, randomized, double-blinded trials of 10 mg/kg of each drug, published between 1985 and 2002, with approximately 40 participants in each condition (Table). All dosages for

each drug fell within the recommended range for clinical practice.

PAIN

A risk ratio of 1 indicates the drugs were equally effective for achieving 50% of maximum pain relief. Risk ratios greater than 1 indicate that ibuprofen was superior to acetaminophen treatment.

The point-estimate of the weighted mean was 1.14 (95% confidence interval [CI], 0.82-1.58) after 2 hours, and 1.11 (95% CI, 0.89-1.38) after 4 hours (Table). Although the point-estimates were in favor of ibuprofen treatment, the 95% confidence intervals also contained risk ratios in favor of acetaminophen treatment. There was no evidence that the risk ratio varied in magnitude across the individual studies ($P > .30$ for the Q-test of heterogeneity at 2 and 4 hours).

FEVER

An effect size of 0 indicates that the drugs were equally effective for reducing febrile temperature. Effect sizes greater than 0 indicate that ibuprofen was superior to acetaminophen treatment.

All point-estimates of the mean weighted-effect sizes for comparisons between ibuprofen and acetaminophen were positive (ie, favoring ibuprofen), with values of 0.19 (95% CI, 0.05-0.33) at 2 hours, 0.31 (95% CI, 0.19-0.44) at 4 hours, and 0.33 (95% CI, 0.19-0.47) at 6 hours (Table). The 95% CIs for each of these point-estimates were fairly narrow and did not contain 0. Since this analysis included 3 studies with low (5-mg/kg) dosages of ibuprofen (cf acetaminophen, 10-12.5 mg/kg), we performed a more focused analysis that included only those studies comparing 10 mg/kg of ibuprofen to 10 mg/kg or more of acetaminophen. The point-estimates in favor of ibuprofen were approximately twice as large in these analyses (Table), bounded by fairly narrow 95% CIs.

SAFETY

The median duration of adverse effects assessment was 48 hours after commencing treatment, but there was considerable variability across studies, ranging from 4 hours to 14 days. There was also considerable variability in the method of assessment of adverse effects: 1 study relied on spontaneous participant reports; 3 studies each used participant diaries or direct questioning by the investigator; and the assessment method was not reported in the remaining 10 studies.

For the minor and major harm analyses, a risk ratio of 1 indicates that the drugs did not differ in safety. Risk ratios greater than 1 indicate that ibuprofen was less safe than acetaminophen, and values less than 1 indicate the converse.

The point-estimate for the risk ratio was 0.96 (0.68-1.36) for minor harm and 1.00 (0.55-1.82) for major harm (Table). As the 95% CIs contained values on either side of 1.00, these data provide no clear evidence that the drugs differed from each other in safety. There was also no evi-

dence that the risk ratio varied in magnitude across the individual studies (P values for the Q-test of heterogeneity were $> .70$ for each comparison).

Nine studies^{8,9,13,17-19,22,26,27} reported minor and major harm data for a placebo arm. As a supplementary analysis, we used these data to compute risk ratios for minor and major harm compared with placebo. For minor harm, the risk ratio for acetaminophen vs placebo was 0.79 (95% CI, 0.42-1.48); the risk ratio for ibuprofen vs placebo was 1.17 (95% CI, 0.68-2.03). For major harm, the risk ratio for acetaminophen vs placebo was 0.90 (95% CI, 0.25-3.29); the risk ratio for ibuprofen vs placebo was 1.51 (95% CI, 0.45-5.05). Although for both minor and major harm the risk ratio point-estimates were close to 1 for both drug-placebo comparisons, the width of the 95% CIs suggests that these data are inconclusive as to safety, especially for major harm. In summary, these data do not provide any evidence to suggest that treatment with ibuprofen and acetaminophen are less safe than each other or placebo.

COMMENT

PAIN

In the context of postextraction dental pain and sore throat pain in children, 3 small but otherwise good quality trials did not provide any evidence that ibuprofen (4-10 mg/kg) and acetaminophen (7-15 mg/kg) differ in their relative efficacy. Point-estimates at 2 and 4 hours after treatment were in a direction slightly favoring ibuprofen, but 95% CIs were wide enough to also include values that favored acetaminophen.

FEVER

In the context of single doses of ibuprofen, 5 to 10 mg/kg, vs acetaminophen, 10 to 15 mg/kg, ibuprofen was the superior antipyretic. This relative superiority was more pronounced at 4 and 6 hours after treatment (cf 2 hours), with effect sizes in the order of 0.30 (cf 0.20). A more intuitive way to gauge the practical value of effect sizes is to consider them in binomial effect size display format, in which the effect size is a measure of the percentage of people likely to have shown improvement from a given treatment.^{36,37} Following this metric, at 4 and 6 hours after treatment approximately 15% more children were likely to have a febrile temperature reduction with ibuprofen than with acetaminophen.

Restricting the analysis to 10 mg/kg of ibuprofen vs 10 to 15 mg/kg of acetaminophen roughly doubled the effect sizes in favor of ibuprofen. Four hours after treatment, the effect size was 0.81, which is large and corresponds to a 38% increase in the number of children likely to have a febrile temperature reduction with ibuprofen compared with acetaminophen. Ninety-five percent confidence intervals surrounding point-estimates for mean weighted-effect sizes were relatively narrow in these analyses and did not contain values less than or equal to 0 that would have favored acetaminophen. These findings are consistent with a recent meta-analysis of a smaller sample of trials that were not all randomized or blinded³⁸ that concluded that ibuprofen was a more efficacious antipy-

retic than acetaminophen in terms of maximum temperature reduction and the length of antipyretic action.

SAFETY

There was no evidence that the drugs differ from each other or placebo in safety. Rather, these data were inconclusive on this point. Point-estimates for minor and major harm for the risk ratios for ibuprofen vs acetaminophen were close to the neutral value of 1, but 95% CIs were wide enough to contain values indicating one drug's being safer than the other. Given that adverse events from either drug or placebo were rare in the current sample, a large-scale randomized trial (or its equivalent as several smaller studies) would be required to detect any small but real differences in safety. The only large-scale randomized trial addressing this issue used risk of hospitalization as the measure of safety and, thus, did not meet our safety meta-analysis inclusion criteria. It was found across 84 192 febrile children taking acetaminophen (12 mg/kg) vs ibuprofen (5 to 10 mg/kg) in a single dose or short-term repeated doses, that safety did not differ according to drug.²¹ Interpreting these results along with our own, we conclude that there does not appear to be any evidence that ibuprofen and acetaminophen differ from each other in terms of major harm events, but more research is required to draw firmly the same conclusion for minor harm events.

LIMITATIONS AND IMPLICATIONS FOR RESEARCH

We included only published reports in our meta-analysis because our literature search did not locate any unpublished studies. It is possible that this led to a publication bias (at the study level, in favor of either drug) insofar as studies with null findings were less likely to have been published. As acknowledged in the "Methods" section, we also excluded a few studies because we could not extract relevant outcomes from the reported data. For the single fever study we excluded on this basis²⁰ and for 1 of the 3 pain studies,¹⁹ ibuprofen was found to be superior to acetaminophen on the particular outcome measure used. The second pain study reported a trend for ibuprofen to be superior to acetaminophen.¹⁸ The third study did not directly compare the 2 drugs but reported that pain relief was greater than that for placebo for the ibuprofen treatment arm but not the acetaminophen treatment arm.¹⁷ The basic direction of effect in these excluded data was thus consistent with our results.

Reporting the main outcome measures in more detail in the original studies would have enabled more fine-grained analyses, especially for the safety data, where sometimes only the number of adverse events was reported rather than the number of patients experiencing particular adverse events. In terms of sheer number of studies, more data have been gathered addressing the antipyretic properties of the drugs, as opposed to their analgesic properties. We suggest that it would be useful for future studies to investigate the kinds of pain for which these drugs are typically indicated, such as headache, cold and flu pain, muscular aches, and menstrual cramps. Participants should be sampled from the broader global com-

munity of children for whom these drugs are acquired on an over-the-counter basis, in contrast to the prior research focus on accessible clinical samples from North America and Europe that may not be adequately representative. Researchers have not studied children younger than 2 years; especially infants younger than 6 months.

Further issues that may be interesting for future research include the potentially differing time courses in efficacy of the 2 drugs (especially in light of evidence suggesting nonlinear pharmacodynamic profiles)^{13,39} and the net therapeutic benefit of regular repeated doses for either pain or fever, given that the prevalence of persistent or frequently recurring pain in older children and adolescents is estimated to be 15% to 20%.^{40,41}

CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

Ibuprofen and acetaminophen are the most widely available over-the-counter drugs on the market for relief of pain and fever. We conducted the present research because we saw no consensus in the health care literature as to their relative efficacy and safety in the pediatric population.

On the basis of evidence published up to May 2002, we draw the following general conclusions: (1) ibuprofen, 4 to 10 mg/kg, is as effective a pediatric analgesic as acetaminophen, 7 to 15 mg/kg; (2) ibuprofen, 5 to 10 mg/kg, especially a 10-mg/kg dosage, is a more efficacious pediatric antipyretic than acetaminophen, 10 to 15 mg/kg; and (3) there is no indication that the drugs differ in safety from each other or from placebo. More research is required, especially on the categories of pain for which the drugs are typically marketed as pediatric medications, using heterogeneous community samples, and for multidose regimens lasting more than a few hours.

Until such evidence is accrued, and all other things being equal, the logical implication for practice of the present meta-analyses is that when pediatric antipyresis is appropriate, 5 to 10 mg/kg of ibuprofen should be generally preferred over 10 to 15 mg/kg of acetaminophen for short-term use. For pediatric analgesia, these data do not support a clear preference for one drug over the other; both were more effective than placebo and equally safe at the studied dosages.

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What This Study Adds

Ibuprofen and acetaminophen are the most widely available over-the-counter drugs for relief of pain and fever, yet their safety and efficacy is uncertain. Literature reviews typically have concluded that the drugs were equally effective but that acetaminophen should be preferred because its safety seemed more assured.

We performed a systematic meta-analytic review of randomized controlled trials assessing the efficacy and/or safety of single-doses of ibuprofen and acetaminophen for short-term treatment of children's pain or fever. Contrary to the conclusions of prior literature reviews, the results did not indicate any difference between the drugs in analgesic efficacy, nor in safety, but did indicate ibuprofen to be the superior antipyretic.

REFERENCES

- Furey SA, Waksman JA, Dash BH. Nonprescription ibuprofen: side effect profile. *Pharmacotherapy*. 1992;12:403-407.
- Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P. Ibuprofen and acetaminophen in the relief of acute pain: a randomized, double-blind, placebo-controlled study. *J Clin Pharmacol*. 1989;29:1026-1030.
- Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an anti-inflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med*. 1991;325:87-91.
- Packman B, Packman E, Doyle G, et al. Solubilized ibuprofen: evaluation of onset, relief, and safety of a novel formulation in the treatment of episodic tension-type headache. *Headache*. 2000;40:561-567.
- Drwal-Klein LA, Phelps SJ. Antipyretic therapy in the febrile child. *Clin Pharm*. 1992;11:1005-1021.
- Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs*. 2001;3:817-858.
- Tanaka E. In vivo age-related changes in hepatic drug-oxidizing capacity in humans. *J Clin Pharm Ther*. 1998;23:247-255.
- McGaw T, Raborn W, Grace M. Analgesics in pediatric dental surgery: relative efficacy of aluminum ibuprofen suspension and acetaminophen elixir. *ASDC J Dent Child*. 1987;54:106-109.
- Kauffman RE, Sawyer LA, Schaunbaum ML. Antipyretic efficacy of ibuprofen vs acetaminophen. *AJDC*. 1992;146:622-625.
- Renn E. The antipyretic use of acetaminophen versus ibuprofen in a pediatric care setting. *P&T*. 2000;25:395-397.
- Canadian Paediatric Society. *Position Paper DT98-01 of the Drug Therapy and Hazardous Substances Committee*. Ottawa, Ontario: Canadian Paediatric Society; 2000.
- El-Chaar G. Efficacy and safety of acetaminophen vs ibuprofen in the febrile child. *Child Hosp Q*. 1995;6:139-142.
- Wilson JT, Brown D, Kearns GL, et al. Single-dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children. *J Pediatr*. 1991;119:803-811.
- Wong A, Sibbald A, Ferrero F, et al. Antipyretic effects of dipyron versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. *Clin Pediatr (Phila)*. 2001;40:313-324.
- Carley S. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary: paracetamol or ibuprofen in febrile children. *J Acad Emerg Med*. 1999;16:137-39.
- Hayward J, Veale B. Paracetamol for children: high time for systematic reviews of the evidence. *Aust Fam Physician*. 1999;28:105.
- Bertin L, Pons G, d'Athis P, et al. Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. *J Pediatr*. 1991;119:811-814.
- Bertin L, Pons G, d'Athis P, et al. A randomized, double-blind, multicenter controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fundam Clin Pharmacol*. 1994;10:387-392.
- Hämäläinen ML, Hoppu K, Valkela E, et al. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. *Neurology*. 1997;48:103-107.
- Sidler J, Frey B, Baerlocher K. A double-blind comparison of ibuprofen and paracetamol in juvenile pyrexia. *Br J Clin Pract Suppl*. 1990;70:22-25.
- Lesko SM, Mitchell AA. An assessment of safety and pediatric ibuprofen: a practitioner based randomized clinical trial. *JAMA*. 1995;273:929-933.
- Walson PD, Galletta G, Braden NJ, Alexander L. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther*. 1989;46:9-17.
- Cooper H, Hedges LV, eds. *Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994.
- Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:27-46.
- McQuay HJ, Moore RA. *An Evidence-Based Resource for Pain*. Oxford, England: Oxford University Press; 1998.
- Moore PA, Acs G, Hargreaves JA. Postextraction pain relief in children: a clinical trial of liquid analgesics. *Int J Clin Pharmacol*. 1985;23:173-177.
- Schachtel BP, Thoden WR. A placebo-controlled model for assaying systemic analgesics in children. *Clin Pharmacol Ther*. 1993;53:593-601.
- Autret E, Breart G, Jonville AP, Courcier S, Lassale C, Goehrs JM. Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. *Eur J Clin Pharmacol*. 1994;46:197-201.
- McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Arch Dis Child*. 1996;74:164-167.
- Starha J, Coupek P, Kopečna L, Brazdova L, Vintrova O. Ibuprofen as an antipyretic drug in childhood. *Cesko-Slov Pediatr*. 1994;49:424-427.
- Van Esch A, Van Steensel-Moll HA, Steyerberg EW, Offringa M, Habbema JD, Derksen-Lubsen G. Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. *Arch Pediatr Adolesc Med*. 1995;149:632-637.
- Vauzelle-Kervroedan F, d'Athis P, Pariente-Khayat A, Devregeas S, Olive G, Pons G. Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. *J Pediatr*. 1997;131:683-687.
- Walson PD, Galletta G, Chomilo F, Braden NJ, Sawyer LA, Scheinbaum ML. Comparison of multidose ibuprofen and acetaminophen therapy in febrile children. *AJDC*. 1992;146:626-632.
- Hedges LV. Fitting categorical models to effect sizes from a series of experiments. *J Educ Stat*. 1982;7:119-137.
- McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med*. 1997;126:712-720.
- Rosenthal R, Rubin DB. A simple, general purpose display of magnitude of experimental effect. *J Educ Psychol*. 1982;74:166-169.
- Rosnow RL, Rosenthal R. Effect sizes for experimenting psychologists. *Can J Exp Psychol*. 2003;57:221-237.
- Pursell E. Treating fever in children: paracetamol or ibuprofen? *Br J Community Nurs*. 2002;7:316-320.
- Wilson JT, Brown RD, Bocchini JA Jr, Kearns GL. Efficacy, disposition and pharmacodynamics of aspirin, acetaminophen and choline salicylate in young febrile children. *Ther Drug Monit*. 1982;4:147-180.
- Goodman JE, McGrath PJ. The epidemiology of pain in children and adolescents: a review. *Pain*. 1991;46:247-264.
- Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, et al. Pain in children and adolescents: a common experience. *Pain*. 2000;87:51-58.