### Search Strategy

**Strategy 303105/17**

<table>
<thead>
<tr>
<th>#</th>
<th>Database</th>
<th>Search term</th>
<th>Results</th>
</tr>
</thead>
</table>

### Contents

86 of 86 results on Medline - (((exp IBUPROFEN/ OR (ibuprofen).ti,ab OR (nurofen).ti,ab OR (brufen).ti,ab) AND (exp ACETAMINOPHEN/ OR (paracetamol).ti,ab OR (calpol).ti,ab)) AND (exp FEVER/ OR (fever).ti,ab OR (pyrexia).ti,ab OR (febrile).ti,ab)) [DT 2007-2017] [Human age groups Infant,newborn OR Infant OR Child,preschool OR Child] [Languages English]

2. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms............................. Page 5
4. Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. ........................................................................ Page 6
5. Optimising the management of fever and pain in children. ................................................................................................. Page 6
6. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. ..................................... Page 7
7. Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone. .............. Page 7
8. Combined and alternating paracetamol and ibuprofen therapy for febrile children. ................................................................. Page 7
9. Cochrane in context: Combined and alternating paracetamol and ibuprofen therapy for febrile children. ................................. Page 8
10. Ketoprofen versus paracetamol (acetaminophen) or ibuprofen in the management of fever: results of two randomized, double-blind, double-dummy, parallel-group, repeated-dose, multicentre, phase III studies in children. ................................................ Page 8
11. Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study. .......... Page 8
12. Combined and alternating paracetamol and ibuprofen therapy for febrile children. ................................................................. Page 8
13. Alternating Acetaminophen and Ibuprofen versus Monotherapies in Improvements of Distress and Reducing Refractory Fever in Febrile Children: A Randomized Controlled Trial. ......................................................................................... Page 9
17. Fever management: evaluating the use of ibuprofen and paracetamol. .................................................................................... Page 9
18. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. ................................................................................ Page 9
19. Association of Acetaminophen and Ibuprofen Use With Wheezing in Children With Acute Febrile Illness. Page 15
20. Ibuprofen: pharmacology, efficacy and safety. Page 16
21. A multicenter, randomized, open-label, active-comparator trial to determine the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for treatment of fever in hospitalized pediatric patients. Page 16
24. Does combination treatment with ibuprofen and acetaminophen improve fever control? Page 18
25. A matched case control study with propensity score balancing examining the protective effect of paracetamol against parentally reported apnoea in infants. Page 18
27. Antipyretic Efficacy and Safety of Ibuprofen Versus Acetaminophen Suspension in Febrile Children: Results of 2 Randomized, Double-Blind, Single-Dose Studies. Page 19
28. Is fever treated more promptly than pain in the pediatric emergency department? Page 19
30. Antipyretic effect of ketoprofen. Page 20
32. Ibuprofen in paediatrics: pharmacology, prescribing and controversies. Page 21
33. Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial. Page 21
35. When the child has a fever. Page 22
38. Acute non-oliguric kidney failure and cholestatic hepatitis induced by ibuprofen and acetaminophen: a case report. Page 23
40. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Page 24
41. Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma. Page 24
42. Paracetamol with ibuprofen: Ibuprofen is a marker of soft tissue infection. Page 25
43. Ethnic differences in parental perceptions and management of childhood fever. Page 25
44. Alternating antipyretics for fever reduction in children: an unfounded practice passed down to parents from pediatricians. Page 25
45. Combining paracetamol and ibuprofen for fever in children. Page 26
46. Alternating acetaminophen and ibuprofen for pain in children. Page 26
47. Clinical safety and tolerability of ibuprofen compared with paracetamol in pediatric pain and fever. A systematic review. Page 26
48. Assessment of febrile seizures in children. Page 26
49. Treatment of pediatric fever: Are acetaminophen and ibuprofen equivalent? Page 27
50. Antipyretic treatment of noninfectious fever in children with severe traumatic brain injury ........................................ Page 27
51. ... And which works better on fever--acetaminophen, ibuprofen, or both? .......................................................... Page 27
52. Parental Approach to the Prevention and Management of Fever and Pain Following Childhood Immunizations: A Survey Study ........................................................................................................ Page 27
53. Non-prescription medicines for pain and fever--a comparison of recommendations and counseling from staff in pharmacy and general sales stores. .......................................................... Page 28
54. Management of children's fever by parents and caregivers: Practical measurement of functional health literacy. ........ Page 28
56. Balancing the risks and benefits of the use of over-the-counter pain medications in children ................................ Page 29
57. Alternating acetaminophen with ibuprofen for fever: is this a problem? ............................................................... Page 29
58. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study... Page 29
59. Association between an excess risk of acute kidney injury and concomitant use of ibuprofen and acetaminophen in children, retrospective analysis of a spontaneous reporting system. ........................................................ Page 30
60. Paracetamol is no more likely to exacerbate asthma in children than ibuprofen, shows study. ................................. Page 30
61. Febrile seizures. ........................................................................................................................................ Page 30
62. Question from the clinician: alternating acetaminophen and ibuprofen in the treatment of fever. ....................... Page 31
63. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. .......................... Page 31
64. Febrile seizures. ........................................................................................................................................ Page 31
65. Knowledge, attitudes and misconceptions of primary care physicians regarding fever in children: a cross sectional study... Page 32
66. Symptomatic management of fever by Swiss board-certified pediatricians: results from a cross-sectional, Web-based survey. ........................................................................................................ Page 32
67. Tramadol infusion for the pain management in sickle cell disease: a case report.................................................... Page 33
68. Ibuprofen increases soft tissue infections in children ............................................................................................ Page 33
69. Fever without a localizing source. ......................................................................................................................... Page 33
70. Adherence among Italian paediatricians to the Italian guidelines for the management of fever in children: a cross sectional survey. .................................................................................................... Page 34
71. Acetaminophen and Ibuprofen overdosage ............................................................................................................ Page 34
72. Necrotising fasciitis, dermal infections and NSAIDs: caution ............................................................................... Page 34
73. Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children? ............... Page 34
74. Does acetaminophen in comparison to ibuprofen effectively reduce fevers in children younger than 18 years of age? ...... Page 34
75. Antipyretic treatment for feverish young children in primary care. ....................................................................... Page 35
76. AAP reports on the use of antipyretics for fever in children .................................................................................. Page 35
77. Dipyrone and acetaminophen: correct dosing by parents? ....................................................................................... Page 35
78. Acetaminophen use and asthma in children. ........................................................................................................... Page 35
79. Pediatric rash and joint pain: a case review ............................................................................................................ Page 36
80. Antipyretic therapy for influenza infection--benefit or harm? ................................................................................. Page 36
81. Acetaminophen injection: a review of clinical information .................................................................................... Page 36

83. Ketoprofen pharmacokinetics, efficacy, and tolerability in pediatric patients. ................................................................. Page 37

84. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. ......................... Page 37

85. The association of acetaminophen and asthma prevalence and severity. ................................................................. Page 39


Full search strategy  ........................................................................................................................................................................ Page 40

Authors: Hay, Alastair D; Costelloe, Céire; Redmond, Niamh M; Montgomery, Alan A; Fletcher, Margaret; Hollinghurst, Sandra; Peters, Tim J

Source: BMJ (Clinical research ed.); Sep 2008; vol. 337; p. a1302

Publication Date: Sep 2008

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

PubMed ID: 18765450

Database: Medline

Available at BMJ (Clinical research ed.) from BMJ Journals - NHS

Abstract: OBJECTIVETO investigate whether paracetamol (acetaminophen) plus ibuprofen are superior to either drug alone for increasing time without fever and the relief of fever associated discomfort in febrile children managed at home.DESIGNIndividually randomised, blinded, three arm trial.SETTINGPrimary care and households in England.PARTICIPANTSChildren aged between 6 months and 6 years with axillary temperatures of at least 37.8 degrees C and up to 41.0 degrees C.INTERVENTIONAdvice on physical measures to reduce temperature and the provision of, and advice to give, paracetamol plus ibuprofen, paracetamol alone, or ibuprofen alone.MAIN OUTCOME MEASURESPrimary outcomes were the time without fever (<37.2 degrees C) in the first four hours after the first dose was given and the proportion of children reported as being normal on the discomfort scale at 48 hours. Secondary outcomes were time to first occurrence of normal temperature (fever clearance), time without fever over 24 hours, fever associated symptoms, and adverse effects.RESULTSON an intention to treat basis, paracetamol plus ibuprofen were superior to paracetamol for less time with fever in the first four hours (adjusted difference 55 minutes, 95% confidence interval 33 to 77; P<0.001) and may have been as good as ibuprofen (16 minutes, -7 to 39; P=0.2). For less time with fever over 24 hours, paracetamol plus ibuprofen were superior to paracetamol (4.4 hours, 2.4 to 6.3; P<0.001) and to ibuprofen (2.5 hours, 0.6 to 4.4; P=0.008). Combined therapy cleared fever 23 minutes (2 to 45; P=0.025) faster than paracetamol alone but no faster than ibuprofen alone (~3 minutes, 18 to -24; P=0.8). No benefit was found for discomfort or other symptoms, although power was low for these outcomes. Adverse effects did not differ between groups.CONCLUSIONParents, nurses, pharmacists, and doctors wanting to use medicines to supplement physical measures to maximise the time that children spend without fever should use ibuprofen first and consider the relative benefits and risks of using paracetamol plus ibuprofen over 24 hours.TRIAL REGISTRATIONCurrent Controlled Trials ISRCTN26362730.


Authors: Kanabar, Dipak; Dale, Stephen; Rawat, Mariyam

Source: Clinical therapeutics; Dec 2007; vol. 29 (no. 12); p. 2716-2723

Publication Date: Dec 2007

Publication Type(s): Research Support, Non-u.s. Gov't Comparative Study Journal Article Review

PubMed ID: 18201589

Database: Medline

Available at Clinical therapeutics from ProQuest (Hospital Premium Collection) - NHS Version
BACKGROUND Although many studies have investigated the safety and tolerability of ibuprofen or acetaminophen (paracetamol) use in children, few have specifically examined the association of ibuprofen or acetaminophen and the occurrence of asthma in pediatric populations.

OBJECTIVES The primary objective of this literature review was to ascertain whether ibuprofen use exacerbates the symptoms of asthma or asthma-related adverse events in febrile children, and how it compares with acetaminophen use. The secondary objective was to develop an algorithm that allows for the consideration of ibuprofen treatment in children by health care professionals.

METHODS Twelve electronic databases (MEDLINE, EMBASE, Cochrane Database, DARE, British Nursing Index, CBIB, Derwent Drug File, International Pharmaceutical Abstracts, Pharm-Line, CINAHL, PASCAL, SCZz-SciSearch) were searched from their year of inception to June 2007, to identify English-language articles pertaining to ibuprofen or acetaminophen use in the asthmatic pediatric population. The following search terms were used: asthma, child, pediatric, pediatrics, ibuprofen, Nurofen, Brufen, Motrin, Advil, propionic acid, paracetamol, and acetaminophen.

RESULTS Of 472 articles retrieved, 3 were relevant for the development of the algorithm. Two were subanalyses of a major randomized controlled trial (RCT), the Boston University Fever Study. Therefore, some overlap should be noted. The third article was another RCT. Other studies and review articles identified were used for the discussion. Findings from the literature analysis indicated that the use of ibuprofen in the pediatric population does not exacerbate asthma morbidity. Two of the studies demonstrated that ibuprofen was associated with a lower risk for asthma morbidity in febrile children with or without asthma compared with acetaminophen. In one study, ibuprofen use was associated with a lower relative risk for hospitalization (0.63) and outpatient visits (0.56) for asthma compared with acetaminophen. In the second study, acetaminophen use was associated with the exacerbation of wheezing in febrile children. This observation was corroborated by the findings of other studies that revealed an increased risk for asthma, wheezing, and other atopic outcomes with acetaminophen use.

CONCLUSION The evidence reviewed in this article suggests a low risk for asthma-related morbidity associated with ibuprofen use in children and a possible protective and therapeutic effect compared with acetaminophen. The findings also suggest that acetaminophen use in children is associated with an increased risk for wheezing. The pediatric algorithm developed might serve as a guide for health care professionals in assessing suitability for ibuprofen use in children.
OBJECTIVES: The main aim of this review was to compare the tolerability and safety between ibuprofen and paracetamol when used as anti-pyretic and analgesic agents in children up to 18 years of age. METHODS: MEDLINE (1950 to November 2008), EMBASE (1980 to November 2008), The Cochrane Library (2007, Issue 3), ACP Journal Club (1991 to November 2007) and Pascal (1987 to November 2007) were searched for randomised controlled trials (RCTs) (comparing ibuprofen and/or paracetamol with placebo), controlled observational studies and large case series comprising more than 1000 participants. MAIN OUTCOME MEASURES: Adverse events (AEs) requiring discontinuation of medication; systemic reactions related to ibuprofen or paracetamol; serious AEs that are fatal, life-threatening or require hospitalisation; and serious AEs not requiring hospitalisation. RESULTS: A total of 24 RCTs examined either ibuprofen and/or paracetamol versus placebo for AE data. Twelve other studies meeting our criteria were also included for AE data. Meta-analysis of systemic reactions demonstrated that tolerability and safety of ibuprofen was similar to placebo, as was paracetamol: ibuprofen versus placebo relative risk (RR) 1.39 (95% CI: 0.92, 2.10); paracetamol versus placebo RR 1.57 (95% CI 0.74, 3.33). A total of 2937 systemic AEs occurred in 21,305 patients taking ibuprofen compared with 1,466 systemic AEs in 11,164 patients taking paracetamol: RR 1.03 (95% CI 0.98, 1.10). There was no significant difference between the two groups. Narrative analysis of AE data identified conflicting evidence regarding hepatic injury with paracetamol and group A streptococcal infections with ibuprofen or paracetamol treatment. CONCLUSIONS: Ibuprofen, paracetamol and placebo have similar tolerability and safety profiles in terms of gastrointestinal symptoms, asthma and renal adverse effects. While the study data investigated here may not reflect over-the-counter use, these results are still relevant in the context of any safety concerns relating to general ibuprofen or paracetamol treatment in children.


OBJECTIVES: The main aim of this review was to compare the tolerability and safety between ibuprofen and paracetamol when used as anti-pyretic and analgesic agents in children up to 18 years of age. METHODS: MEDLINE (1950 to November 2008), EMBASE (1980 to November 2008), The Cochrane Library (2007, Issue 3), ACP Journal Club (1991 to November 2007) and Pascal (1987 to November 2007) were searched for randomised controlled trials (RCTs) (comparing ibuprofen and/or paracetamol with placebo), controlled observational studies and large case series comprising more than 1000 participants. MAIN OUTCOME MEASURES: Adverse events (AEs) requiring discontinuation of medication; systemic reactions related to ibuprofen or paracetamol; serious AEs that are fatal, life-threatening or require hospitalisation; and serious AEs not requiring hospitalisation. RESULTS: A total of 24 RCTs examined either ibuprofen and/or paracetamol versus placebo for AE data. Twelve other studies meeting our criteria were also included for AE data. Meta-analysis of systemic reactions demonstrated that tolerability and safety of ibuprofen was similar to placebo, as was paracetamol: ibuprofen versus placebo relative risk (RR) 1.39 (95% CI: 0.92, 2.10); paracetamol versus placebo RR 1.57 (95% CI 0.74, 3.33). A total of 2937 systemic AEs occurred in 21,305 patients taking ibuprofen compared with 1,466 systemic AEs in 11,164 patients taking paracetamol: RR 1.03 (95% CI 0.98, 1.10). There was no significant difference between the two groups. Narrative analysis of AE data identified conflicting evidence regarding hepatic injury with paracetamol and group A streptococcal infections with ibuprofen or paracetamol treatment. CONCLUSIONS: Ibuprofen, paracetamol and placebo have similar tolerability and safety profiles in terms of gastrointestinal symptoms, asthma and renal adverse effects. While the study data investigated here may not reflect over-the-counter use, these results are still relevant in the context of any safety concerns relating to general ibuprofen or paracetamol treatment in children.
Abstract

OBJECTIVES To establish the relative clinical effectiveness and cost-effectiveness of paracetamol plus ibuprofen compared with paracetamol and ibuprofen separately for time without fever, and the relief of fever-associated discomfort in young children who can be managed at home. DESIGN The trial design was a single-centre (multisite), individually randomised, blinded, three-arm trial comparing paracetamol and ibuprofen together with paracetamol or ibuprofen separately. SETTING There were three recruitment settings, as follows: 'local' where research nurses were recruited from NHS primary care sites; 'remote' where NHS sites notified the study of potentially eligible children; and 'community' where parents contacted the study in response to local media advertisements. PARTICIPANTS Children aged between 6 months and 6 years with fever > or = 37.8 degrees C and < or = 41 degrees C due to an illness that could be managed at home. INTERVENTIONS The intervention was the provision of, and advice to give, the medicines for up to 48 hours: paracetamol every 4-6 hours (maximum of four doses in 24 hours) and ibuprofen every 6-8 hours (maximum of three doses in 24 hours). Every parent received two bottles, with at least one containing an active medicine. Parents, research nurses and investigators were blinded to treatment allocation by the use of identically matched placebo medicines. The dose of medicine was determined by the child's weight: paracetamol 15 mg/kg and ibuprofen 10 mg/kg per dose.

RESULTS For additional time without fever in the first 4 hours, use of both medicines was superior to use of paracetamol alone [adjusted difference 55 minutes, 95% confidence interval (CI) 33 to 77 minutes; p < 0.001] and may have been as good as ibuprofen [adjusted difference 16 minutes, 95% CI -6 to 39 minutes; p = 0.2]. Both medicines together cleared the fever 23 minutes [95% CI 2-45 minutes; p = 0.015] faster than paracetamol alone, but no faster than ibuprofen alone [adjusted difference -3 minutes, 95% CI 24-18 minutes; p = 0.8]. For additional time without fever in the first 24 hours, both medicines were superior to paracetamol [adjusted difference 4.4 hours, 95% CI 2.4-6.3 hours; p < 0.001] or ibuprofen [adjusted difference 2.5 hours, 95% CI 0.6-4.5 hours; p = 0.008] alone. No reduction in discomfort or other fever-associated symptoms was found, although power was low for these outcomes. An exploratory analysis showed that children with higher discomfort levels had higher mean temperatures. No difference in adverse effects was observed between treatment groups. The recommended maximum number of doses of paracetamol and ibuprofen in 24 hours was exceeded in 8% and 11% of children respectively. Over the 5-day study period, paracetamol and ibuprofen together was the cheapest option for the NHS due to the lower use of health-care services: 14 pounds [standard deviation (SD) 23 pounds] versus 20 pounds (SD 38 pounds) for paracetamol and 18 pounds (SD 40 pounds) for ibuprofen. Both medicines were also cheaper for parents because the lower use of health care services resulted in personal saving on travel costs and less time off work: 24 pounds (SD 46 pounds) versus 26 pounds (SD 63 pounds) for paracetamol and 30 pounds (SD 91 pounds) for ibuprofen. This more than compensated for the extra cost of medication. However, statistical evidence for these differences was weak due to lack of power. Overall, a quarter of children were 'back to normal' by 48 hours and one-third by day 5. Five (3%) children were admitted to hospital, two with pneumonia, two with bronchiolitis and one with a severe, but unidentified 'viral illness'.

CONCLUSIONS Young children who are unwell with fever should be treated with ibuprofen first, but the relative risks (inadvertently exceeding the maximum recommended dose) and benefits (extra 2.5 hours without fever) of using paracetamol plus ibuprofen over 24 hours should be considered. However, if two medicines are used, it is recommended that all dose times are carefully recorded to avoid accidentally exceeding the maximum recommended dose. Manufacturers should consider supplying blank charts for this purpose. Use of both medicines should not be discouraged on the basis of cost to either parents or the NHS. Parents and clinicians should be aware that fever is a relatively short-lived symptom, but may have more serious prognostic implications than the other common symptom presentations of childhood.

7. Systematic review of studies comparing combined treatment with paracetamol and ibuprofen, with either drug alone.

Authors Purssell, Edward
Source Archives of disease in childhood; Dec 2011; vol. 96 (no. 12); p. 1175-1179
Publication Date Dec 2011
Publication Type(s) Comparative Study Journal Article Review
PubMedID 21868405
Database Medline
Available at Archives of disease in childhood from BMJ Journals - NHS
Available at Archives of disease in childhood from ProQuest (Hospital Premium Collection) - NHS Version
OBJECTIVETo evaluate the evidence surrounding the use of combinations of paracetamol and ibuprofen in the treatment of fever.

DESIGNSystematic narrative review of randomised controlled trials using the UK Economic and Social Research Council guidance on the conduct of narrative synthesis.

SETTINGInpatient, outpatient and home care.

PATIENTSChildren with fever.

MAIN OUTCOME MEASURES

The effect of combination treatments of paracetamol and ibuprofen on fever and comfort, and identification of side effects.

RESULTS Seven studies were identified, six of which provided useful data for the evaluation of the effect of treatment on temperature. Overall these studies showed limited benefit from the combined treatment until around 4 h, after which there was a statistically but only marginally clinically significant benefit. Two studies contained data directly relating to comfort; these suggest a marginal benefit from the combined treatment, but the clinical significance of this was limited. There was no evidence of greater side effects or toxicities associated with the combined treatment. However, it is important to note that these studies were small, short term, and not conducted in the normal setting in which these treatments are given.

CONCLUSIONS There is little evidence of any benefit or harm from the combined treatment compared with the use of each drug alone. In the absence of such benefit, there is little to recommend the unnecessary use of polypharmaceutical methods to treat a symptom that does not require treatment, when effective monotherapies exist.


Authors
Wong, Tiffany; Stang, Antonia S; Ganshorn, Heather; Hartling, Lisa; Maconochie, Ian K; Thomsen, Anna M; Johnson, David W

Source
Evidence-based child health: a Cochrane review journal; Sep 2014; vol. 9 (no. 3); p. 675-729

PubMed ID
25236309

Database
Medline

Abstract
BACKGROUND Health professionals frequently recommend fever treatment regimens for children that either combine paracetamol and ibuprofen or alternate them. However, there is uncertainty about whether these regimens are better than the use of single agents, and about the adverse effect profile of combination regimens. OBJECTIVE To assess the effects and side effects of combining paracetamol and ibuprofen, or alternating them on consecutive treatments, compared with monotherapy for treating fever in children.

SEARCH METHODS In September 2013, we searched Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; and International Pharmaceutical Abstracts (2009-2011). SELECTION CRITERIA We included randomized controlled trials comparing alternating or combined paracetamol and ibuprofen regimens with monotherapy in children with fever. DATA COLLECTION AND ANALYSIS One review author and two assistants independently screened the searches and applied inclusion criteria. Two authors assessed risk of bias and graded the evidence independently. We conducted separate analyses for different comparison groups (combined therapy versus monotherapy, alternating therapy versus monotherapy, combined therapy versus alternating therapy).

MAIN RESULTS Six studies, enrolling 915 participants, are included. Compared to giving a single antipyretic alone, giving combined paracetamol and ibuprofen to febrile children can result in a lower mean temperature at one hour after treatment (MD -0.27 °Celsius, 95% CI -0.45 to -0.08, two trials, 163 participants, moderate quality evidence). If no further antipyretics are given, combined treatment probably also results in a lower mean temperature at four hours (MD -0.70 °Celsius, 95% CI -1.05 to -0.35, two trials, 196 participants, moderate quality evidence), and in fewer children remaining or becoming febrile for at least four hours after treatment (RR 0.08, 95% CI 0.02 to 0.42, two trials, 196 participants, moderate quality evidence). Only one trial assessed a measure of child discomfort (fever associated symptoms at 24 hours and 48 hours), but did not find a significant difference in this measure between the treatment regimens (one trial, 156 participants, evidence quality not graded). In practice, caregivers are often advised to initially give a single agent (paracetamol or ibuprofen), and then give a further dose of the alternative if the child’s fever fails to resolve or recurs. Giving alternating treatment in this way may result in a lower mean temperature at one hour after the second dose (MD -0.60 °Celsius, 95% CI -0.94 to -0.26, two trials, 78 participants, low quality evidence), and may also result in fewer children remaining or becoming febrile for up to three hours after it is given (RR 0.25, 95% CI 0.11 to 0.55, two trials, 109 participants, low quality evidence). One trial assessed child discomfort (mean pain scores at 24, 48 and 72 hours), finding that these mean scores were lower, with alternating therapy, despite fewer doses of antipyretic being given overall (one trial, 480 participants, low quality evidence) Only one small trial compared alternating therapy with combined therapy. No statistically significant differences were seen in mean temperature, or the number of febrile children at one, four or six hours (one trial, 40 participants, very low quality evidence).

There were no serious adverse events in the trials that were directly attributed to the medications used. AUTHORS’ CONCLUSIONS There is some evidence that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy alone. However, the evidence for improvements in measures of child discomfort remains inconclusive. There is insufficient evidence to know which of combined or alternating therapy might be more beneficial. Future research needs to measure child discomfort using standardized tools, and assess the safety of combined and alternating antipyretic therapy.

Authors: Wong, Tiffany; Stang, Antonia S; Ganshorn, Heather; Hartling, Lisa; Maconochie, Ian K; Thomsen, Anna M; Johnson, David W

Source: Evidence-based child health : a Cochrane review journal; Sep 2014; vol. 9 (no. 3); p. 730-732

Publication Date: Sep 2014

Publication Type(s): Comparative Study, Randomized Controlled Trial, Multicenter Study, Journal Article, Clinical Trial, Phase III

PubMedID: 25236310

Database: Medline

Abstract:

BACKGROUND: Health-care professionals frequently recommend fever treatment regimens for children who either combine paracetamol and ibuprofen or alternate them. However, there is uncertainty about whether these regimens are better than using single agents and about the adverse effect profile of combination regimens.

OBJECTIVES: To assess the results and side effects of combining paracetamol and ibuprofen, or alternating them in consecutive treatments, compared with monotherapy for treating fever in children.

SEARCH METHODS: In September 2013, we searched Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS and International Pharmaceutical Abstracts (2009-2011). SELECTION CRITERIA: We included randomized controlled trials that compared alternating or combined paracetamol and ibuprofen regimens with monotherapy in children with fever.

DATA COLLECTION AND ANALYSIS: One review author and two assistants independently screened the searches and applied the inclusion criteria. Two authors assessed risk of bias and graded the evidence independently. We conducted various analyses for different comparison groups (combined therapy versus monotherapy, alternating therapy versus monotherapy and combined therapy versus alternating therapy).

MAIN RESULTS: Six studies, enrolling 915 participants, are included. Compared to administering a single antipyretic alone, administering combined paracetamol and ibuprofen to febrile children can result in a lower mean temperature at 1 hour after treatment (mean difference -0.27°C, 95% confidence interval -0.45 to -0.08, two trials, 163 participants, moderate quality evidence). If no further antipyretics are given, combined treatment probably also results in a lower mean temperature at 4 hours (mean difference -0.70°C, 95% confidence interval -1.05 to -0.35, two trials, 196 participants, moderate quality evidence), and in fewer children remaining or becoming febrile for at least 4 hours after treatment (relative risk 0.08, 95% confidence interval 0.02 to 0.42, two trials, 196 participants, moderate quality evidence). Only one trial assessed a measure of child discomfort (fever, associated symptoms at 24 and 48 hours), but did not find a significant difference in this measure between the treatment regimens (one trial, 156 participants, evidence quality not graded).

In practice, caregivers are often advised to initially provide a single agent (paracetamol or ibuprofen), and then provide a further dose of the alternative if the child’s fever fails to resolve or recurs. Giving alternating treatment in this manner may result in a lower mean temperature at 1 hour after the second dose (mean difference -0.60°C, 95% confidence interval -0.94 to -0.26, two trials, 78 participants, low quality evidence), and may also result in fewer children remaining or becoming febrile for up to 3 hours after it is given (relative risk 0.25, 95% confidence interval 0.11 to 0.55, two trials, 109 participants, low quality evidence). One trial assessed child discomfort (mean pain scores at 24, 48 and 72 hours), finding that these mean scores were lower, with alternating therapy, despite fewer doses of antipyretic being given overall (one trial, 480 participants, low quality evidence) Only one small trial compared alternating therapy with combined therapy. No statistically significant differences were seen in mean temperature or in the number of febrile children at 1, 4 or 6 hours (one trial, 40 participants, very low quality evidence). In all the trials, there were no serious adverse events that were directly attributed to the medications used.

AUTHORS’ CONCLUSIONS: There is some evidence that both combined and alternating antipyretic therapies may be more effective at reducing temperatures than monotherapy alone. However, the evidence for improvements in measures of child discomfort remains inconclusive. There is insufficient evidence to decide which of combined or alternating therapy might be more beneficial. Future research needs to measure child discomfort using standardized tools, and assess the safety of combined and alternating antipyretic therapies.


Authors: Kokki, Hannu; Kokki, Merja

Source: Clinical drug investigation; 2010; vol. 30 (no. 6); p. 375-386

Publication Date: 2010

Publication Type(s): Comparative Study, Randomized Controlled Trial, Multicenter Study, Journal Article, Clinical Trial, Phase III

PubMedID: 20380479

Database: Medline

Available at Clinical drug investigation from SpringerLink - Medicine
Available at Clinical drug investigation from ProQuest (Hospital Premium Collection) - NHS Version
**Abstract**

Fever is a common symptom in children and one of the major concerns of parents of younger and preschool-age children. To compare the efficacy and safety of ketoprofen with that of paracetamol (acetaminophen) and ibuprofen in the treatment of febrile conditions in children. Two prospective, randomized, double-blind, double-dummy, repeated-dose, multicentre, phase III studies with two parallel groups in each study were conducted in primary-care outpatient clinics. Children aged 6 months to 6 years presenting with a febrile condition and an oral body temperature of \( \geq 38.8 \) degrees C or rectal temperature of \( \geq 39 \) degrees C were eligible for inclusion. Patients were randomized to receive either ketoprofen syrup 0.5 mg/kg, ibuprofen suspension 5 mg/kg or paracetamol suspension 15 mg/kg every 6 hours by the oral route. The primary outcome measure was the change in temperature at 3 hours (H3), compared with baseline (H0). All three treatments provided similar mean maximum decreases of 1.4-1.5 degrees C in body temperature at H3 compared with H0. Use of ketoprofen was not associated with any increased risk of adverse events compared with the two reference compounds. Ketoprofen 0.5 mg/kg appeared to be equivalent to the standard antipyretic doses of the reference products ibuprofen 5 mg/kg and paracetamol 15 mg/kg. Ketoprofen at the 0.5 mg/kg dose should be an effective and safe option for symptomatic management of fever in children.

11. Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study.

**Authors**

Autret-Leca, Elisabeth; Gibb, Iain A; Goulder, Michael A

**Source**

Current medical research and opinion; Sep 2007; vol. 23 (no. 9); p. 2205-2211

**Publication Date**

Sep 2007

**Publication Type(s)**

Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article

**PubMedID**

17686209

**Database**

Medline

**Abstract**

OBJECTIVEThe main objective of this study was to compare the single-dose efficacy of 15 mg/kg paracetamol (acetaminophen) versus 10 mg/kg ibuprofen in a general practice setting.METHODSChildren from the age of 3 months to 12 years with a fever of non-serious origin were randomized to receive either ibuprofen or paracetamol. The first dose was given double-blind, using a double-dummy technique. Tympanic temperature was measured at baseline and over the following 8 hours. The second and subsequent doses were administered open-label for up to 3 days by parents at home. At the end of the double-blind and the open-label periods, parents were asked to subjectively rate the efficacy of the product and state whether they would treat their child with the product again. The primary endpoint of the study was the area under the temperature reduction curve expressed as an absolute difference from baseline, from 0 to 6 hours (AUC(0-6)). Secondary efficacy endpoints included a variety of objective and subjective measures.RESULTSNo statistically significant differences in the primary endpoint or any of the objective secondary endpoints were observed. Both agents were equally well tolerated. Compared with parents in the paracetamol group, significantly more parents in the ibuprofen group rated the drug as very efficacious, and reported that they would use the drug again in both the double-blind and open-label phases of the study.CONCLUSIONIbuprofen at a dose of 10 mg/kg and paracetamol at a dose of 15 mg/kg have equivalent efficacy and tolerability; parental opinion in favor of ibuprofen could be explained by additional benefits of ibuprofen that were not measured in this trial and helped allay their anxiety over the treatment of their child.


**Authors**

Wong, Tiffany; Stang, Antonia S; Ganshorn, Heather; Hartling, Lisa; Maconochie, Ian K; Thomsen, Anna M; Johnson, David W

**Source**

The Cochrane database of systematic reviews; Oct 2013 (no. 10); p. CD009572

**Publication Date**

Oct 2013

**Publication Type(s)**

Research Support, Non-u.s. Gov't Meta-analysis Journal Article Review

**PubMedID**

24174375

**Database**

Medline

Available at The Cochrane database of systematic reviews from Cochrane Collaboration (Wiley)
Abstract

BACKGROUND: Health professionals frequently recommend fever treatment regimens for children that either combine paracetamol and ibuprofen or alternate them. However, there is uncertainty about whether these regimens are better than the use of single agents, and about the adverse effect profile of combination regimens.

OBJECTIVE: To assess the effects and side effects of combining paracetamol and ibuprofen, or alternating them on consecutive treatments, compared with monotherapy for treating fever in children.

SEARCH METHODS: In September 2013, we searched Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; and International Pharmaceutical Abstracts (2009-2011).

SELECTION CRITERIA: We included randomized controlled trials comparing alternating or combined paracetamol and ibuprofen regimens with monotherapy in children with fever.

DATA COLLECTION AND ANALYSIS: One review author and two assistants independently screened the searches and applied inclusion criteria. Two authors assessed risk of bias and graded the evidence independently. We conducted separate analyses for different comparison groups (combined therapy versus monotherapy, alternating therapy versus monotherapy, combined therapy versus alternating therapy).

MAIN RESULT: Six studies, enrolling 915 participants, are included. Compared to giving a single antipyretic alone, giving combined paracetamol and ibuprofen to febrile children can result in a lower mean temperature at one hour after treatment (MD -0.27 °Celsius, 95% CI -0.45 to -0.08, two trials, 163 participants, moderate quality evidence). If no further antipyretics are given, combined treatment probably also results in a lower mean temperature at four hours (MD -0.70 °Celsius, 95% CI -1.05 to -0.35, two trials, 196 participants, moderate quality evidence), and in fewer children remaining or becoming febrile for at least four hours after treatment (RR 0.08, 95% CI 0.02 to 0.42, two trials, 196 participants, moderate quality evidence). Only one trial assessed a measure of child discomfort (fever associated symptoms at 24 hours and 48 hours), but did not find a significant difference in this measure between the treatment regimens (one trial, 156 participants, evidence quality not graded). In practice, caregivers are often advised to initially give a single agent (paracetamol or ibuprofen), and then give a further dose of the alternative if the child’s fever fails to resolve or recurs. Giving alternating treatment in this way may also result in a lower mean temperature at one hour after the second dose (MD -0.60 °Celsius, 95% CI -0.94 to -0.26, two trials, 78 participants, low quality evidence), and may also result in fewer children remaining or becoming febrile for up to three hours after it is given (RR 0.25, 95% CI 0.11 to 0.55, two trials, 109 participants, low quality evidence). One trial assessed child discomfort (mean pain scores at 24, 48 and 72 hours), finding that these mean scores were lower, with alternating therapy, despite fewer doses of antipyretic being given overall (one trial, 480 participants, low quality evidence). Only one small trial compared alternating therapy with combined therapy. No statistically significant differences were seen in mean temperature, or the number of febrile children at one, four or six hours (one trial, 40 participants, very low quality evidence). There were no serious adverse events in the trials that were directly attributed to the medications used.

AUTHORS’ CONCLUSIONS: There is some evidence that both alternating and combined antipyretic therapy may be more effective at reducing temperatures than monotherapy alone. However, the evidence for improvements in measures of child discomfort remains inconclusive. There is insufficient evidence to know which of combined or alternating therapy might be more beneficial. Future research needs to measure child discomfort using standardized tools, and assess the safety of combined and alternating antipyretic therapy.

13. Alternating Acetaminophen and Ibuprofen versus Monotherapies in Improvements of Distress and Reducing Refractory Fever in Febrile Children: A Randomized Controlled Trial.

Authors: Luo, Shuanghong; Ran, Mengdong; Luo, Qihong; Shu, Min; Guo, Qin; Zhu, Yu; Xie, Xiaoping; Zhang, Chongfan; Wan, Chaomin

Source: Paediatric drugs; Oct 2017; vol. 19 (no. 5); p. 479-486

Publication Date: Oct 2017

Publication Type: Comparative Study Randomized Controlled Trial Journal Article

PubMedID: 28523589

Database: Medline

Available at Paediatric drugs from SpringerLink - Medicine
BACKGROUND
No evidence can be found in the medical literature about the efficacy of alternating acetaminophen and ibuprofen treatment in children with refractory fever. OBJECTIVE Our objective was to assess the effect of alternating acetaminophen and ibuprofen therapy on distress and refractory fever compared with acetaminophen or ibuprofen as monotherapy in febrile children.

METHODS
A total of 474 febrile children with axillary temperature ≥38.5 °C and fever history ≤3 days in a tertiary hospital were randomly assigned to receive either (1) alternating acetaminophen and ibuprofen (acetaminophen 10 mg/kg per dose with shortest interval of 4 h and ibuprofen 10 mg/kg per dose with shortest interval of 6 h and the shortest interval between acetaminophen and ibuprofen ≥2 h; n = 158), (2) acetaminophen monotherapy (10 mg/kg per dose with shortest interval of 4 h; n = 158), or (3) ibuprofen monotherapy (10 mg/kg per dose with shortest interval of 6 h; n = 158). The mean Non-Communicating Children's Pain Checklist (NCCPC) score was measured every 4 h, and axillary temperatures were measured every 2 h. RESULTS In total, 471 children were included in an intention-to-treat analysis. No significant clinical or statistical difference was found in mean NCCPC score or temperature during the 24-h treatment period in all febrile children across the three groups. Although the proportion of children with refractory fever for 4 h and 6 h was significantly lower in the alternating group than in the monotherapy groups (4 h: 11.54% vs. 26.58% vs. 21.66%, respectively [p = 0.003]; 6 h: 3.85% vs. 10.13% vs. 17.83%, respectively [p < 0.001]), the mean NCCPC score of children with refractory fever for 4 or 6 h was not lower than those in either of the monotherapy groups. The number of patients who developed persistent high body temperature was consistent across all study groups. CONCLUSIONS Alternating acetaminophen and ibuprofen can reduce the proportion of children with refractory fever, but if one cycle of alternating therapy cannot reduce febrile distress as defined by NCCPC score, two or more cycles of alternating therapy may have minimal to no clinical efficacy in some cases. The trial was registered with the Chinese Clinical Trial Registry as ChiCTR-TRC-13003440 and the WHO Registry Network as U1111-1146-6714.

OBJECTIVES
To estimate the cost to the NHS and to parents and carers of treating febrile preschool children with paracetamol, ibuprofen, or both, and to compare these costs with the benefits of each treatment regimen.

DESIGN
Cost consequences analysis and cost effectiveness analysis conducted as part of a three arm, randomised controlled trial.

PARTICIPANTS
Children between the ages of 6 months and 6 years recruited from a population of 3,000 patients attending primary care throughout the trial area.

INTERVENTIONS
The three arms were: (1) alternating acetaminophen and ibuprofen (acetaminophen 10 mg/kg per dose with shortest interval of 4 h and ibuprofen 10 mg/kg per dose with shortest interval of 6 h and the shortest interval between acetaminophen and ibuprofen ≥2 h), (2) acetaminophen monotherapy (acetaminophen 10 mg/kg per dose with shortest interval of 4 h), and (3) ibuprofen monotherapy (ibuprofen 10 mg/kg per dose with shortest interval of 6 h).

RESULTS
In total, 471 children were included in an intention-to-treat analysis. No significant clinical or statistical difference was found in mean NCCPC score or temperature during the 24-h treatment period in all febrile children across the three groups. Although the proportion of children with refractory fever for 4 h and 6 h was significantly lower in the alternating group than in the monotherapy groups (4 h: 11.54% vs. 26.58% vs. 21.66%, respectively [p = 0.003]; 6 h: 3.85% vs. 10.13% vs. 17.83%, respectively [p < 0.001]), the mean NCCPC score of children with refractory fever for 4 or 6 h was not lower than those in either of the monotherapy groups. The number of patients who developed persistent high body temperature was consistent across all study groups. CONCLUSIONS Alternating acetaminophen and ibuprofen can reduce the proportion of children with refractory fever, but if one cycle of alternating therapy cannot reduce febrile distress as defined by NCCPC score, two or more cycles of alternating therapy may have minimal to no clinical efficacy in some cases. The trial was registered with the Chinese Clinical Trial Registry as ChiCTR-TRC-13003440 and the WHO Registry Network as U1111-1146-6714.


BACKGROUND Many pediatricians recommend, and many parents administer, alternating or combined doses of ibuprofen and acetaminophen for fever. Limited data support this practice with standard US doses. OBJECTIVE This study compared the antipyretic effect of 3 different treatment regimens in children, using either ibuprofen alone, ibuprofen combined with acetaminophen, or ibuprofen followed by acetaminophen over a single 6-hour observation period. METHODS Febrile episodes from children aged 6 to 84 months were randomized into the 3 treatment groups: a single dose of ibuprofen at the beginning of the observation period; a single dose of ibuprofen plus a single dose of acetaminophen at the beginning of the observation period; or ibuprofen followed by acetaminophen 3 hours later. Ibuprofen was administered at 10 mg/kg; acetaminophen at 15 mg/kg. Temperatures were measured hourly for 6 hours using a temporal artery thermometer. The primary outcome was temperature difference between treatment groups. Adverse-event data were not collected in this single treatment period study. RESULTS Sixty febrile episodes in 46 children were assessed. The mean (SD) age of the children was 3.4 (2.2) years, and 31 (51.7%) were girls. Differences among temperature curves were significant (P < 0.001; the combined and alternating arms had significantly better antipyresis compared with the ibuprofen-alone group at hours 4 to 6 (hour 4, P < 0.005; hours 5 and 6, P < 0.001). All but one of the children in the combined and alternating groups were afebrile at hours 4, 5, and 6. In contrast, for those receiving ibuprofen alone, 30%, 40%, and 50% had temperatures >38.0 °C at hours 4, 5, and 6, respectively (hour 4, P = 0.002; hours 5 and 6, P < 0.001). CONCLUSION During a single 6-hour observation period for these participating children, combined and alternating doses of ibuprofen and acetaminophen provided greater antipyresis than ibuprofen alone at 4 to 6 hours. ClinicalTrials.gov identifier: NCT00267293.
Abstract

BACKGROUND Acute otitis media (AOM) is one of the most common childhood infectious diseases and a significant reason for antibiotic prescriptions in children worldwide. Pain from middle ear infection and pressure behind the eardrum is the key symptom of AOM. Ear pain is central to children’s and parents’ experience of the illness. Because antibiotics provide only marginal benefits, analgesic treatment including paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) is regarded as the cornerstone of AOM management in children.

OBJECTIVES Our primary objective was to assess the effectiveness of paracetamol (acetaminophen) or NSAIDs, alone or combined, with placebo or no treatment in relieving pain in children with AOM. Our secondary objective was to assess the effectiveness of NSAIDs compared with paracetamol in children with AOM.

METHODS We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 7, July 2016; MEDLINE (Ovid, from 1946 to August 2016), Embase (from 1947 to August 2016), CINAHL (from 1981 to August 2016), LILACS (from 1982 to August 2016) and Web of Science (from 1955 to August 2016) for published trials. We screened reference lists of included studies and relevant systematic reviews for additional trials. We searched WHO ICTRP, ClinicalTrials.gov, and the Netherlands Trial Registry (NTR) for completed and ongoing trials (search date 19 August 2016).

SEARCH STRATEGY We included randomised controlled trials (RCTs) comparing the effectiveness of paracetamol or NSAIDs, alone or combined, for pain relief in children with AOM. We also included trials of paracetamol or NSAIDs, alone or combined, for children with fever or upper respiratory tract infections (URTIs) if we were able to extract subgroup data on pain relief in children with AOM either directly or after obtaining additional data from study authors. Data collection and analysis were independently assessed methodological quality of the included trials and extracted data. We used the GRADE approach to rate the overall quality of evidence for each outcome of interest.

MAIN RESULTS We included three RCTs (327 children) which were assessed at low to moderate risk of bias. One RCT included 219 children with AOM, and used a three-arm, parallel group, double-blind design to compare paracetamol versus ibuprofen versus placebo. All children also received antibiotics and those with fever > 39 °C could have received paracetamol (30 mg to 60 mg) additionally to the studied treatments. Another RCT involved 156 febrile children (26 of whom had AOM). The study design was a three-arm, parallel group, double-blind design and compared paracetamol versus ibuprofen versus ibuprofen plus paracetamol. The third RCT included 889 children with respiratory tract infections (82 of whom had AOM). This study applied a 3 x 2 x 2 factorial, open-label design and compared paracetamol versus ibuprofen versus ibuprofen plus paracetamol. Study participants were randomised to one of the three treatment groups as well as two dosing groups (regular versus as required) and two steam inhalation groups (steam versus no steam). Authors of two RCTs provided crude subgroup data on pain relief in children with AOM. We used data from the remaining trial to inform comparison of paracetamol versus placebo (148 children) and ibuprofen versus placebo (146 children) assessments. Data from all included RCTs informed comparison of ibuprofen versus paracetamol (183 children); data from the two RCTs informed comparison of ibuprofen plus paracetamol versus paracetamol alone (71 children). We found evidence, albeit of low quality, that both paracetamol and ibuprofen as monotherapies were more effective than placebo in relieving pain at 48 hours (paracetamol versus placebo; proportion of children with pain 10% versus 25%, RR 0.38, 95% CI 0.17 to 0.85; number needed to treat to benefit (NNTB) 7; ibuprofen versus placebo; proportion of children with pain 7% versus 25%, RR 0.28, 95% CI 0.11 to 0.70; NNTB 6). Very low quality evidence suggested that adverse events did not significantly differ between children treated with either paracetamol, ibuprofen or placebo. We found insufficient evidence of a difference between ibuprofen and paracetamol in relieving ear pain at 24 hours (2 RCTs, 39 children; RR 0.83, 95% CI 0.59 to 1.18; very low quality evidence), 48 to 72 hours (3 RCTs, 183 children; RR 0.91, 95% CI 0.54 to 1.54; low quality evidence) and four to seven days (2 RCTs, 38 children; RR 0.74, 95% CI 0.17 to 3.23; very low quality evidence). Data on the effectiveness of ibuprofen plus paracetamol versus paracetamol alone came from two RCTs that provided crude subgroup data for 71 children with AOM. The small sample provided imprecise effect estimates and we were consequently unable to draw any firm conclusions (very low quality evidence).

AUTHORS’ CONCLUSIONS Despite explicit guideline recommendations on its use, current evidence on the effectiveness of paracetamol or NSAIDs, alone or combined, in relieving pain in children with AOM is limited. Low quality evidence indicates that both paracetamol and ibuprofen as monotherapies are more effective than placebo in relieving short-term ear pain in children with AOM. There is insufficient evidence of a difference between ibuprofen and paracetamol in relieving short-term ear pain in children with AOM, whereas data on the effectiveness of ibuprofen plus paracetamol versus paracetamol alone were insufficient to draw any firm conclusions. Further research is needed to provide insights into the role of ibuprofen as adjunct to paracetamol, and other analgesics such as anaesthetic eardrops, for children with AOM.

19. Association of Acetaminophen and Ibuprofen Use With Wheezing in Children With Acute Febrile Illness.

Authors Matok, Ilan; Elizur, Arnon; Perlman, Amichai; Ganor, Shani; Levine, Hagai; Kozer, Eran

Source The Annals of pharmacotherapy; Mar 2017; vol. 51 (no. 3); p. 239-244

Publication Date Mar 2017

Publication Type(s) Journal Article

PubMedID 27794128

Database Medline
BACKGROUND Many infants and children receive acetaminophen and/or ibuprofen during febrile illness. Previously, some studies have linked acetaminophen and ibuprofen use to wheezing and exacerbation of asthma symptoms in infants and children. OBJECTIVE To assess whether acetaminophen or ibuprofen use are associated with wheezing in children presenting to the emergency department (ED) with febrile illness. METHOD This was a cross-sectional study of children who presented with fever to the pediatric ED between 2009 and 2013. The data were collected from questionnaires and from the children's medical files. Patients with wheezing in the ED were compared with nonwheezing patients. Associations between medication use and wheezing were assessed using univariate and multivariate analyses. The multivariate analysis adjusted for potential confounding variables (ie, age, atopic dermatitis, allergies, smoking, antibiotics use, etc) via propensity scores. RESULTS During the study period, 534 children admitted to the ED met our inclusion criteria, of whom 347 (65%) were included in the study. The use of acetaminophen was similar in children diagnosed with wheezing compared with those without wheezing (n = 39, 81.3%, vs n = 229, 82.7%, respectively). Ibuprofen use was significantly lower in children diagnosed with wheezing (n = 22, 52.4%, vs n = 168, 69.4%, respectively). In multivariate analysis, acetaminophen was not associated with a higher rate of wheezing during acute febrile illness (adjusted odds ratio [OR] = 0.76, 95% CI = 0.24–2.39), whereas ibuprofen was associated with a lower risk of wheezing (adjusted OR = 0.36, 95% CI = 0.13–0.96). CONCLUSIONS Our study suggests that acetaminophen and ibuprofen are not associated with increased risk for wheezing during acute febrile illness.

20. Ibuprofen: pharmacology, efficacy and safety.

Authors Rainsford, K D
Source Inflammopharmacology; Dec 2009; vol. 17 (no. 6); p. 275-342
Publication Date Dec 2009
Publication Type(s) Journal Article Review
PubMedID 1994916
Database Medline

Abstract OBJECTIVE This review attempts to bring together information from a large number of recent studies on the clinical uses, safety and pharmacological properties of ibuprofen. Ibuprofen is widely used in many countries for the relief of symptoms of pain, inflammation and fever. The evidence for modes of action of ibuprofen are considered in relation to its actions in controlling inflammation, pain and fever, as well as the adverse effects of the drug. SUMMARY OF OUTCOMES At low doses (800-1,200 mg day(-1)) which in many countries are considered in relation to its actions in controlling inflammation, pain and fever, as well as the adverse effects of the drug. SUMMARY OF OUTCOMES At low doses (800-1,200 mg day(-1)) which in many countries are low doses (800-1,200 mg day(-1)) which in many countries are approved for non-prescription (over-the-counter) sale ibuprofen has a good safety profile comparable with paracetamol. Its analgesic activity is linked to its anti-inflammatory effects and is related to reduction in the ex vivo production in blood of cyclo-oxygenase (COX)-1 and COX-2 derived prostanoids. Higher prescription doses (circa 1,800-2,400 mg day(-1)) are employed long-term for the treatment of rheumatic and other more severe musculo-skeletal conditions. Recent evidence from large-scale clinical trials with the newer coxibs, where ibuprofen was as a comparator, have confirmed earlier studies which have shown that ibuprofen has comparable therapeutic benefits with coxibs and other NSAIDs. For long-term usage (6+ months) there are greater numbers of drop-outs due to reduced effectiveness of therapy, a feature which is common with NSAIDs. Spontaneous reports of adverse events and adverse drug reactions (ADRs) in clinical trials from long-term coxib comparator studies, as well as in epidemiological studies, shows that ibuprofen has relatively low risks for gastro-intestinal (GI), hepato-renal and other, rarer, ADRs compared with other NSAIDs and coxibs. A slightly higher risk of cardiovascular (CV) events has been reported in some, but not all studies, but the risks are in general lower than with some coxibs and diclofenac. The possibility that ibuprofen may interfere with the anti-platelet effects of aspirin, though arguably of low grade or significance, has given rise to caution on its use in patients that are at risk for CV conditions that take aspirin for preventing these conditions. Paediatric use of ibuprofen is reviewed and the main results are that the drug is relatively safe and effective as a treatment of acute pain and fever. It is probably more effective than paracetamol as an antipyretic. CONCLUSIONS This assessment of the safety and benefits of ibuprofen can be summarized thus: (1) Ibuprofen at OTC doses has low possibilities of serious GI events, and little prospect of developing renal and associated CV events. Ibuprofen OTC does not represent a risk for developing liver injury especially the irreversible liver damage observed with paracetamol and the occasional liver reactions from aspirin. (2) The pharmacokinetic properties of ibuprofen, especially the short plasma half-life of elimination, lack of development of pathologically related metabolites (e.g. covalent modification of liver proteins by the quinine-imine metabolite of paracetamol or irreversible acetylation of biomolecules by aspirin) are support for the view that these pharmacokinetic and notably metabolic effects of ibuprofen favour its low toxic potential. (3) The multiple actions of ibuprofen in controlling inflammation combine with moderate inhibition of COX-1 and COX-2 and low residence time of the drug in the body may account for the low GI, CV and renal risks from ibuprofen, especially at OTC doses.

21. A multicenter, randomized, open-label, active-comparator trial to determine the efficacy, safety, and pharmacokinetics of intravenous ibuprofen for treatment of fever in hospitalized pediatric patients.

Authors Khalil, Samia N; Hahn, Barry J; Chumpitazi, Corrie E; Rock, Amy D; Kaelin, Byron A; Macias, Charles G
Abstract
BACKGROUND Oral antipyretics are commonly used to treat pediatric patients who develop fevers. However, patients presenting to the emergency department or undergoing surgery are frequently unable to tolerate oral antipyretics. Rectal formulations are available; however, this route of administration is unpredictable. The main objectives of this randomized controlled study was to evaluate the efficacy and safety of single or multiple doses of intravenous ibuprofen to acetaminophen (oral or suppository) in pediatric patients with fever and to assess plasma ibuprofen concentrations.

METHODS This multi-center study was conducted in hospitalized patients, ≤ 16 years, with a new onset of fever ≥ 38.3°C. Patients were randomly assigned to receive either 10 mg/kg intravenous ibuprofen or acetaminophen. Study drug was administered at hour 0, and thereafter every 4 h as needed, up to 5 days. The primary outcome was to evaluate the effect of a single dose of intravenous ibuprofen compared to acetaminophen in reducing temperature in the first 2 h after administration. Data were compared using an analysis of variance model for continuous measurements and Cochran-Mantel-Haenszel test of general association for categorical data. A two-sided testing was used and a p-value ≤ 0.05 was considered significant.

RESULTS A total of 103 patients received study medication. Intravenous ibuprofen resulted in a greater reduction in temperature as measured by the area under the change from baseline at 2 h (p = 0.005) and 4 h (<0.001); in a greater reduction in change from baseline temperature compared to treatment with acetaminophen, and it reduced fever throughout a 24 h dosing period. There were no differences in safety parameters or serious adverse events. CONCLUSIONSA single 10 mg/kg dose of intravenous ibuprofen provided a significant reduction of temperature for febrile pediatric patients compared to those that received 10 mg/kg acetaminophen at 2 h and 4 h post-treatment. A reduction in temperature was also demonstrated over 24 h; however the reduction was not considered statically significant. Intravenous ibuprofen provides an effective option for reducing fever in hospitalized pediatric patients.

TRIAL REGISTRATION The study was registered on ClinicalTrials.gov on 26 October 2009, Study Identifier: NCT01002573.


Authors Kanabar, Dipak J
Source Inflammopharmacology; Feb 2017; vol. 25 (no. 1); p. 1-9
Publication Date Feb 2017
Publication Type(s) Journal Article Review
PubMedID 28063133
Database Medline

Abstract The antipyretic analgesics, paracetamol, and non-steroidal anti-inflammatory agents NSAIDs are one of the most widely used classes of medications in children. The aim of this review is to determine if there are any clinically relevant differences in safety between ibuprofen and paracetamol that may recommend one agent over the other in the management of fever and discomfort in children older than 3 months of age.


Authors Walsh, Anne; Edwards, Helen; Fraser, Jenny
Source Journal of paediatrics and child health; Sep 2007; vol. 43 (no. 9); p. 601-606
Publication Date Sep 2007
Publication Type(s) Journal Article
PubMedID 17608647
Database Medline
Abstract

AIM: To report Australian parents' medication (paracetamol, ibuprofen and homeopathic) use in childhood fever management. METHODS: A cross-sectional survey of 401 Queensland parents of children aged between 6 months and 5 years recruited through advertising (48.4%), face-to-face (26.4%) and snowball (24.4%) methods was conducted. A 17-item instrument was developed; construct and content validity were determined by an expert panel; and item reliability by test-retest with nine parents. Areas targeted were medication use and influences on and barriers to medication use.

RESULTS: Most participants were female, had tertiary education and lived in a major city (mean age 34.6 years). Reducing children's fever with over-the-counter medications was common (91%): 94% of parents reported using paracetamol and 77% reported using ibuprofen. A few (3.7%) used homeopathic remedies. Dosage was determined by weight (86.3%), age (84.3%), temperature (32.4%), illness severity (31.4%) and lethargy (20.9%). Frequency was determined by instructions on the medication label (55.3%), temperature (40.6%) and well-being (27.7%). Ibuprofen was administered too frequently by 31.5% (four hourly by 22.8%), and paracetamol by 3.8%. Fifty-two per cent had alternated medications, 65.8% of these for temperatures below 38.5 degrees C. Decisions to alternate were influenced by information from doctors/hospitals (49.5%) and children remaining febrile post-antipyretic (41.7%). Most parents reported over-the-counter medications as potentially harmful (73.2%), citing liver (38.2%), stomach (26.4%) and kidney (18.6%) damage and overdose (35.7%) as concerns. When medications were refused or spat out (44.0%), parents used force (62.4%), different methods (29.5%) or suppositories (20.8%).

CONCLUSIONS: Most parents used over-the-counter medications to reduce fever, often below 38.5 degrees C. The belief that these medications were harmful was overridden by fears of harmful outcomes from fever.

24. Does combination treatment with ibuprofen and acetaminophen improve fever control?

Authors: Malya, Rohith R
Source: Annals of emergency medicine; May 2013; vol. 61 (no. 5); p. 569-570
Publication Date: May 2013
Publication Type(s): Editorial Review
PubMedID: 23522609
Database: Medline
Abstract: Combination treatment with ibuprofen and acetaminophen is beneficial over either agent alone for sustained fever reduction in children older than 6 months.

25. A matched case control study with propensity score balancing examining the protective effect of paracetamol against parentally reported apnoea in infants.

Authors: Walsh, Paul; Shanholzer, Lucas; Loewe, Mark; Trinh, Kim; McNulty, Ben; Rothenberg, Stephen J
Source: Resuscitation; Apr 2012; vol. 83 (no. 4); p. 440-446
Publication Date: Apr 2012
Publication Type(s): Comparative Study Journal Article
PubMedID: 22178799
Database: Medline
Abstract: BACKGROUND: Central apnoea occurs in infants and if not detected leads to death. Central apnoea is a prostaglandin E(2) (PGE2) mediated effect that is susceptible to pharmacologic manipulation in animal models. Paracetamol and ibuprofen are centrally and peripherally acting PGE2 inhibitors, respectively. AIM: To determine if infants who had received paracetamol or ibuprofen are relatively protected from apnoea. METHODS: We performed a matched case control study using propensity score balancing to adjust for non-random drug assignment. We included infants from prospective studies of central apnoea and bronchiolitis. We matched on age, prematurity and fever to adjust for the infants' underlying risk of apnoea. The primary outcome measure was odds of exposure to paracetamol or ibuprofen by apneic infants compared to their controls. RESULTS: Forty-two apneic and 729 non-apneic infants were identified. Infants with apnoea were younger than those without, median age 6.5 versus 12.2 weeks and were more likely to be premature. These differences were balanced using matching. Differences between those who did and did not receive paracetamol were satisfactorily balanced using the propensity score. Ibuprofen was used too infrequently to analyse it further. In the unadjusted analysis fewer apneic infants had had prior paracetamol use 5/42 (12%) versus 211/729 (29%) or prior ibuprofen use 1/42 (2%) versus 51/729 (7%). In the adjusted analysis paracetamol was protective against apnoea; OR 0.30 (95% CI 0.11, 0.78). CONCLUSIONS: Prior paracetamol use was protective against apnoea in infants. We could not demonstrate an effect for ibuprofen.


Authors: Wysocki, Jacek; Center, Kimberly J; Brzostek, Jerzy; Majda-Stanislawska, Ewa; Szymanski, Henryk; Szenborn, Leszek; Czajka, Hanna; Hasiec, Barbara; Dziduch, Jerzy; Jackowska, Teresa; Witor, Anita; Kopeńska, Elżbieta; Konior, Ryszard; Giardina, Peter C; Sundaraiyer, Vani; Patterson, Scott; Gruber, William C; Scott, Daniel A; Gurtman, Alejandra
Source: Vaccine; Apr 2017; vol. 35 (no. 15); p. 1926-1935
Publication Date: Apr 2017
27. Antipyretic Efficacy and Safety of Ibuprofen Versus Acetaminophen Suspension in Febrile Children: Results of 2 Randomized, Double-Blind, Single-Dose Studies.

**Authors:** Jayawardena, Shyamalie; Kellstein, David

**Source:** Clinical pediatrics; Oct 2017; vol. 56 (no. 12); p. 1120-1127

**Abstract:** Two blinded single-dose studies randomized children 6 months to 11 years old with fever to receive ibuprofen (IBU) pediatric suspension 7.5 mg/kg or acetaminophen (APAP) suspension 10 to 15 mg/kg. The primary efficacy parameter was time-weighted sum of temperature differences (TWSTD) from baseline through 8 hours for each study. Secondary end points included TWSTD from baseline through 6 hours, time to onset and duration of temperature control, and proportion with temperature control. Studies were pooled for post hoc analyses of efficacy and adverse event end points. The primary efficacy parameter significantly favored IBU over APAP in study 1 and the pooled analysis (both P < .001), but was not significant in study 2. Onset of temperature control significantly favored IBU in study 2 (P = .007). Individual and pooled secondary efficacy outcomes supported significant advantages (P < .05) of IBU over APAP. IBU pediatric suspension provided greater temperature reduction versus acetaminophen in febrile children, with a comparable safety profile.

28. Is fever treated more promptly than pain in the pediatric emergency department?

**Authors:** Dvorkin, Ronald; Bair, Jacob; Patel, Hardik; Glantz, Sanford; Yens, David P; Rosalia, Anthony; Marguilies, Jeffrey

**Source:** The Journal of emergency medicine; Mar 2014; vol. 46 (no. 3); p. 327-334

**Abstract:** Fever can be treated with a higher priority than pain in the pediatric emergency department (ED) population. OBJECTIVE The primary objective was to assess whether patients with a fever are treated with acetaminophen or ibuprofen more promptly than they are treated for pain. METHODS A retrospective descriptive study was performed on all patients between the ages of 3 and 19 years who received acetaminophen or ibuprofen in the pediatric ED from February 1, 2010 to January 31, 2011. The time interval from arrival to treatment with acetaminophen or ibuprofen was compared to the time interval from arrival to treatment with saline. RESULTS Pediatric patients with fever (n = 1097) received ibuprofen or acetaminophen a median of 54.0 min (interquartile range [IQR], 35.4-89.3 min) after arrival. The corresponding median time for afebrile patients (n = 1861) that received the same medications was 83.2 min (IQR, 52.7-136.1). The difference between medians was 24.6 min (95% confidence interval 21.3-27.9 min). CONCLUSIONS Fever is treated more promptly than pain in the pediatric ED. This difference is associated with prevailing and largely unfounded concerns about fever and the undertreatment of pain (oligoanalgesia).

**Authors** Kanabar, Dipak

**Source** Drugs in R&D; Jun 2014; vol. 14 (no. 2); p. 45-55

**Publication Date** Jun 2014

**Publication Type(s)** Research Support, Non-u.s. Gov't Journal Article Review

**PubMedID** 24916274

**Database** Medline

**Abstract** Fever is a common symptom of childhood infections that in itself does not require treatment. The UK's National Institute for Health and Care Excellence (NICE) advises home-based antipyretic treatment for low-risk feverish children only if the child appears distressed. The recommended antipyretics are ibuprofen or paracetamol (acetaminophen). They are equally recommended for the distressed, feverish child; therefore, healthcare professionals, parents and caregivers need to decide which of these agents to administer if the child is distressed. This narrative literature review examines recent data on ibuprofen and paracetamol in feverish children to determine any clinically relevant differences between these agents. The data suggest that these agents have similar safety profiles in this setting and in the absence of underlying health issues, ibuprofen seems to be more effective than paracetamol at reducing NICE's treatment criterion, 'distress' (as assessed by discomfort levels, symptom relief, and general behavior).

30. Antipyretic effect of ketoprofen.

**Authors** Celebi, S; Hacimustafaoglu, M; Aygun, D; Arisoy, E S; Karali, Y; Akgoz, S; Citak Kurt, A N; Seringec, M

**Source** Indian journal of pediatrics; Mar 2009; vol. 76 (no. 3); p. 287-291

**Publication Date** Mar 2009

**Publication Type(s)** Randomized Controlled Trial Journal Article

**PubMedID** 19129989

**Database** Medline

**Abstract** OBJECTIVE The aim of this study was to investigate the efficacy and side effect profile of ketoprofen as well as compliance with respect to the taste of the drug and compare these parameters with those of acetaminophen and ibuprofen. METHOD A total of 301 patients between 1-14 years of age who applied to emergency rooms of three medical centers with the complaint of fever that required antipyretic therapy were included in the study. Fever was measured with the aid of a tympanic thermometer (Braun Kronberg 6014) and followed for 4-6 hours. The measurement was repeated at 30, 60, 120 minutes, and again 4-6 hours after the initial assessment. RESULTS The mean age of the patients was 47.8+/-41.1 months. The patients randomly received 15 mg/kg/dose of acetaminophen (n=112 group 1), 0.5 mg/kg/dose of ketoprofen (n=105, group 2), or 10 mg/kg/dose of ibuprofen (n=84, group 3). Fever was 38.4+/-0.7 degrees C, 38.4+/-0.7 degrees C, and 38.5+/-0.5 degrees C at 30 minutes; 38.0+/-0.7 degrees C, 37.9+/-0.7 degrees C, and 38.0+/-0.6 degrees C at 60 minutes (p>0.05); 37.7+/-0.6 degrees C, 37.6+/-0.7 degrees C, and 37.7+/-0.5 degrees C at 120 minutes (p>0.05); 37.5+/-0.7 degrees C, 37.3+/-0.6 degrees C, and 37.4+/-0.6 degrees C at 4-6 hours after admission (p>0.05). The fever was significantly lower at 30, 60, and 120 minutes in all groups (p<0.05). Early vomiting after medication (<6 hours) was observed in 3.8%, 13.5%, and 9.6% whereas late vomiting (6-48 hours) occurred in 1.3%, 2.7%, and 5.8% respectively (p>0.05). Bad taste was expressed by 5.1%, 12.2%, and 5.8% early (<6 hours), and 3.9%, 8.1%, and 3.8% late (6-48 hours) (p>0.05). There were no differences between age groups for antipyretic effect, taste and adverse effect in three drugs (p>0.05). CONCLUSION All three drugs were similar in terms of efficacy, adverse effects, and compliance within 48 hours of therapy. These results suggest that ketoprofen may be used for antipyresis as an alternative to acetaminophen and ibuprofen.


**Authors** Pierce, Catherine A; Voss, Bryan

**Source** The Annals of pharmacotherapy; Mar 2010; vol. 44 (no. 3); p. 489-506

**Publication Date** Mar 2010

**Publication Type(s)** Meta-analysis Comparative Study Journal Article Review

**PubMedID** 20150507

**Database** Medline
OBJECTIVE To evaluate the analgesic and antipyretic efficacy and safety of ibuprofen compared to acetaminophen in children and adults.

DATA SOURCES Literature searches were performed using PubMed/MEDLINE (through August 2009) and EMBASE (through January 2008) and were restricted to the English language. In PubMed/MEDLINE, search terms used were ibuprofen, acetaminophen, paracetamol, clinical trials, and randomized controlled trials. EMBASE search terms included ibuprofen and acetaminophen, restricted to human and clinical trials.

STUDY SELECTION AND DATA EXTRACTION All English-language articles identified from the data sources were reviewed. Multiple review articles were studied for any pertinent references and this yielded additional articles. Only articles that directly compared ibuprofen and acetaminophen were eligible for this review.

DATA SYNTHESIS Eighty-five studies that directly compared ibuprofen to acetaminophen were identified; 54 contained analgesic efficacy data, 35 contained antipyretic/temperature reduction data, and 66 contained safety data (some articles contained more than 1 type of data). Qualitative review of the literature revealed that, for the most part, ibuprofen was more efficacious than acetaminophen for the treatment of pain and fever in both pediatric and adult populations, and that these 2 drugs were equally safe. Meta-analyses on the subset of randomized clinical trial articles that reported sufficient quantitative information to calculate either an odds ratio (adverse event [AE]) or standardized mean difference (pain and fever) confirmed the qualitative results for adult (standardized mean difference [SMD] 0.69; 95% CI 0.57 to 0.81) and pediatric (SMD 0.28; 95% CI 0.10 to 0.46) pain at 2 hours postdose and pediatric fever (SMD 0.26; 95% CI 0.10 to 0.41) at 4 hours postdose. Conclusions regarding adult fever/temperature reduction could not be made due to a lack of evaluable data. The combined odds ratio for the proportion of adult subjects experiencing at least 1 AE slightly favored ibuprofen; however, the difference was not statistically significant (1.12; 95% CI 1.00 to 1.25). No significant difference between drugs in AE incidence was found for pediatric patients (0.82; 95% CI 0.60 to 1.12).

CONCLUSIONS Ibuprofen is as or more efficacious than acetaminophen for the treatment of pain and fever in adult and pediatric populations and is equally safe.

32. Ibuprofen in paediatrics: pharmacology, prescribing and controversies.

Authors Moriarty, Camilla; Carroll, Will

Source Archives of disease in childhood. Education and practice edition; Dec 2016; vol. 101 (no. 6); p. 327-330

Publication Date Dec 2016

Publication Type(s) Journal Article

PubMedID 27458064

Database Medline

Available at Archives of disease in childhood. Education and practice edition from BMJ Journals - NHS

Abstract Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug. The oral formulation is widely used in paediatric practice and after paracetamol it is one of the most common drugs prescribed for children in hospital. The treatment of fever with antipyretics such as ibuprofen is controversial as fever is the normal response of the body to infection and unless the child becomes distressed or symptomatic, fever alone should not be routinely treated. Combined treatment with paracetamol and ibuprofen is commonly undertaken but almost certainly is not helpful. This article aims to describe the indications and mode of action of the drug, outline its pharmacokinetics and highlight the important key messages regarding its use in clinical practice.

33. Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial.

Authors Falup-Pecurariu, Oana; Man, Sorin C; Neamtu, Mihai L; Chicin, Gratiana; Baciu, Ginel; Pitic, Carmen; Cara, Alexandra C; Neculau, Andrea E; Burlea, Marin; Brinza, Ileana L; Schnell, Cristina N; Sas, Valentina; Lupu, Valeriu V; Francois, Nancy; Swinnen, Kristien; Borys, Dorota

Source Human vaccines & immunotherapeutics; Mar 2017; vol. 13 (no. 3); p. 649-660

Publication Date Mar 2017

Publication Type(s) Research Support, Non-u.s. Gov't Randomized Controlled Trial Clinical Trial, Phase Iv Multicenter Study Journal Article

PubMedID 27541270

Database Medline

Available at Human vaccines & immunotherapeutics from Europe PubMed Central - Open Access
Prophylactic paracetamol administration impacts vaccine immune response: this study (www.clinicaltrials.gov: NCT01235949) is the first to assess PHID-CV immunogenicity following prophylactic ibuprofen administration. In this phase IV, multicenter, open-label, randomized, controlled, non-inferiority study in Romania (November 2010-December 2012), healthy infants were randomized 3:3:1:1:1:1 to prophylactically receive immediate, delayed or no ibuprofen (IIBU, DIBU, NIBU) or paracetamol (IPARA, DPARA, NPARA) after each of 3 primary doses (PHID-CV at age 3/4/5 months co-administered with DTPa-HBV-IPV/Hib at 3/5 and DTPa-IPV/Hib at 4 months) or booster dose (PHID-CV and DTPa-HBV-IPV/Hib; 12-15 months). Non-inferiority of immune response one month post-primary vaccination in terms of percentage of infants with anti-pneumococcal antibody concentrations ≥0.2 µg/mL (primary objective) was demonstrated if the upper limit (UL) of the 98.25% confidence interval of difference between groups (NIBU vs IIBU, NIBU vs DIBU) was <10% for >7/10 serotypes. Immunogenicity and reactogenicity/safety were evaluated, including confirmatory analysis of difference in fever incidences post-primary vaccination in IBU or DIBU group compared to NIBU. Of 850 infants randomized, 812 were included in the total vaccinated cohort. Non-inferiority was demonstrated for both comparisons (UL was <10% for 9/10 vaccine serotypes; exceptions: 6B [NIBU], 23F [IIBU]). However, fever incidence post-primary vaccination in the IIBU and DIBU groups did not indicate a statistically significant reduction. Prophylactic administration (immediate or delayed) of paracetamol decreased fever incidence but seemed to reduce immune response to PHID-CV, except when given only at booster. Twenty-seven serious adverse events were reported for 15 children; all resolved and were not vaccination-related.


Authors
Pereira, Gracian Li; Dagostini, Josiane Magda Camarotto; Pizzol, Tatiane da Silva Dal

Source
Jornal de pediatria; Jul 2012; vol. 88 (no. 4); p. 289-296

Abstract
OBJECTIVE To summarize the existing evidence on the efficacy of therapy with alternating antipyretics compared to monotherapy in the management of fever in children. SOURCES MEDLINE, EMBASE, Cochrane Library, LILACS, SciELO, IBECS, Web of Science, Clinical Trials, Google Scholar and references of the articles found. The review included randomized clinical trials published until December 2011, in which one of the arms was the alternating antipyretics therapy to treat fever in children younger than 12 years, treated on an outpatient basis. Data selection and extraction were performed independently by two reviewers. The quality of the studies was assessed according to CONSORT items. SUMMARY OF THE FINDINGS The selected studies showed great heterogeneity of participants, temperature for fever diagnosis, interventions (dose and dosing intervals) and assessed outcomes. The treatment groups ranged from 38 to 464 children. The studies compared paracetamol and ibuprofen alternated with paracetamol and/or ibuprofen. Only one study used different doses from the 15 mg/kg for paracetamol and 10 mg/kg for ibuprofen, but the dosing intervals varied considerably. The alternate use with dipyrone or acetylsalicylic acid was not assessed by any of the studies. Overall, the articles pointed to a tendency of lower mean temperatures in groups with alternating therapy. Few adverse effects were reported. CONCLUSION Although there was a tendency towards the reduction of mean temperatures with alternating antipyretics compared to the use of one antipyretic alone, there is not enough evidence to say that alternating antipyretic therapy is more effective than monotherapy.

35. When the child has a fever.

Authors
BMJ Group

Source
Drug and therapeutics bulletin; Mar 2008; vol. 46 (no. 3); p. 17-21

Abstract
Fever in a child is usually due to a self-limiting viral infection, with recovery occurring quickly without intervention. However, fever may also be the presenting feature of severe illnesses such as meningitis, septicaemia, urinary tract infections and pneumonia, and trying to exclude such causes is a key part of management. In a review 17 years ago, we concluded that there was no evidence that reducing fever improved the outcome of childhood infections, but that it probably alleviated distress and discomfort caused by fever. We also advised that parents should give paracetamol only if the child seemed uncomfortable or had previously had a febrile convulsion, and said that tepid sponging may further comfort the child, while recognising evidence that it added little to the effect of paracetamol alone. Does this advice still hold?

BACKGROUND
In 2009, the Italian Pediatric Society developed national guidelines for management of fever in children for health care providers and parents/caregivers; an update of these guidelines was scheduled after 2 years.

OBJECTIVE
This article summarizes the update of Italian guidelines on managing fever in children, focusing specifically on measuring body temperature and using antipyretic agents.

METHODS
Relevant publications in English and Italian were identified through searches of MEDLINE and the Cochrane Database of Systematic Reviews from January 1, 2008, to May 1, 2012. On the basis of consensus of a multidisciplinary expert panel, evidence levels and strength of recommendations were reviewed.

RESULTS
Axillary temperature measurement using a digital thermometer is recommended in children younger than 4 weeks. In the hospital or ambulatory care setting, axillary temperature measurement using a digital or infrared thermometer (tympanic, skin contact, or nocontact) is recommended in children older than 4 weeks. Paracetamol and ibuprofen are the only antipyretic drugs recommended for use in children; however, combined or alternating use of these agents is not recommended.

CONCLUSIONS
Recent scientific evidence mainly supports previous recommendations. The aim of the present article was to support pediatric knowledge and stimulate application of guidelines in daily clinical practice.
OBJECTIVE To evaluate the literature examining prophylactic use of acetaminophen and ibuprofen for prevention of adverse reactions associated with childhood immunization.

DATA SOURCES Articles were identified via MEDLINE/PubMed/EMBASE (1966-March 2007) using the following key terms: vaccination, immunization, diphtheria-tetanus toxoids-whole pertussis (DTwP), diphtheria-tetanus-toxoid, whole pertussis, diphtheria-tetanus toxoids-acellular pertussis (DTaP), acellular pertussis, Haemophilus influenzae type B, inactivated poliovirus, pneumococcal 7-valent conjugate, measles, mumps, rubella, meningococcal C-conjugate, varicella zoster, hepatitis B, influenza, pneumococcal polysaccharide, adverse reactions, analgesics, antipyretics, acetaminophen, ibuprofen, infant, and child.

STUDY SELECTION AND DATA EXTRACTION No limitations were placed on article selection.

DATA SYNTHESIS Five articles examining the effects of prophylactic acetaminophen or ibuprofen for adverse effects associated with either DTaP or DTwP vaccine were retrieved. In one randomized controlled trial of children aged 4-6 years given DTaP, no effect of prophylactic acetaminophen 15 mg/kg/dose, up to 450 mg, or ibuprofen 10 mg/kg/dose, up to 300 mg, was found on the incidence of fever, redness, pain, swelling, or itching. In 3 randomized studies of DTwP, either acetaminophen 10-15 mg/kg/dose or ibuprofen 20 mg/kg/24 hours, given in 3 equal doses before or at the time of immunization and every 4-8 hours thereafter for 12 or more hours, reduced fever, pain, fussiness, and local redness in infants 2-7 months of age compared with placebo. Results were not duplicated in older infants/children. No studies investigated use of prophylactic acetaminophen or ibuprofen for any other vaccine.

CONCLUSIONS Use of prophylactic acetaminophen and ibuprofen may reduce the incidence of adverse reactions in young infants receiving DTwP vaccine; however, DTwP has been replaced with DTaP, and no benefits have been demonstrated for this vaccine when evaluated in children aged 4-6 years, or with any other vaccine currently in use. Thus, neither drug can be recommended prophylactically to prevent vaccine-associated adverse reactions. Individuals at high risk for seizures may, however, warrant special consideration.

40. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial.

Authors Strengell, Teemu; Uhari, Matti; Tarkka, Rita; Uusimaa, Johanna; Alen, Reija; Lautala, Pentti; Rantala, Heikki

Source Archives of pediatrics & adolescent medicine; Sep 2009; vol. 163 (no. 9); p. 799-804

Abstract OBJECTIVE To evaluate the efficacy of different antipyretic agents and their highest recommended doses for preventing febrile seizures. DESIGN Randomized, placebo-controlled, double-blind trial. SETTING Five hospitals, each working as the only pediatric hospital in its region. PARTICIPANTS Total of 231 children who experienced their first febrile seizure between January 1, 1997, and December 31, 2003. The children were observed for 2 years. INTERVENTIONS All febrile episodes during follow-up were treated first with either rectal diclofenac or placebo. After 8 hours, treatment was continued with oral ibuprofen, acetaminophen, or placebo.

MAIN OUTCOME MEASURERecurrence of febrile seizures. RESULTS The children experienced 851 febrile episodes, and 89 of these included a febrile seizure. Febrile seizure recurrences occurred in 54 of the 231 children (23.4%). There were no significant differences between the groups in the main measure of effect, and the effect estimates were similar, as the rate was 23.4% (46 of 197) in those receiving antipyretic agents and 23.5% (8 of 34) in those receiving placebo (difference, 0.2; 95% confidence interval, -12.8 to 17.6; P = .99). Fever was significantly higher during the episodes with seizure than in those without seizure (39.7 degrees C vs 38.9 degrees C; difference, 0.8 degrees C; 95% confidence interval, -0.6 degrees C to 0.0 degrees C; P = .01), and this phenomenon was independent of the medication given.

CONCLUSION Use of prophylactic acetaminophen and ibuprofen may reduce the incidence of adverse reactions in young infants receiving DTwP vaccine; however, DTwP has been replaced with DTaP, and no benefits have been demonstrated for this vaccine when evaluated in children aged 4-6 years, or with any other vaccine currently in use. Thus, neither drug can be recommended prophylactically to prevent vaccine-associated adverse reactions. Individuals at high risk for seizures may, however, warrant special consideration.

41. Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma.

Authors Sheehan, William J; Mauger, David T; Paul, Ian M; Moy, James N; Boehmer, Susan J; Szefer, Stanley J; Fitzpatrick, Anne M; Jackson, Daniel J; Bacharier, Leonard B; Cabana, Michael D; Covar, Ronina; Holguin, Fernando; Lemaske, Robert F; Martinez, Fernando D; Pongracic, Jacqueline A; Beigelman, Avraham; Baxi, Sachin N; Benson, Mindy; Blake, Kathryn; Chmiele, James F; Daines, Cori L; Daines, Michael O; Gaffin, Jonathan M; Gentile, Deborah A; Gower, W Adam; Israel, Elliot; Kumar, Harsha V; Lang, Jason E; Lazarus, Stephen C; Lima, John J; Ly, Ngoc; Marbin, Jyothi; Morgan, Wayne J; Myers, Ross E; Olin, J Tod; Peters, Stephen P; Raissy, Hengameh H; Robison, Rachel G; Ross, Kristie; Sorkness, Christine A; Thyne, Shannon M; Wechsler, Michael E; Phipatanakul, Wanda; NIH/NHLBI AsthmaNet

Source The New England journal of medicine; Aug 2016; vol. 375 (no. 7); p. 619-630
Abstract
BACKGROUND Studies have suggested an association between frequent acetaminophen use and asthma-related complications among children, leading some physicians to recommend that acetaminophen be avoided in children with asthma; however, appropriately designed trials evaluating this association in children are lacking. METHODS In a multicenter, prospective, randomized, double-blind, parallel-group trial, we enrolled 300 children (age range, 12 to 59 months) with mild persistent asthma and assigned them to receive either acetaminophen or ibuprofen when needed for the alleviation of fever or pain over the course of 48 weeks. The primary outcome was the number of asthma exacerbations that led to treatment with systemic glucocorticoids. Children in both groups received standardized asthma-controller therapies that were used in a simultaneous, factorially linked trial. RESULTS Participants received a median of 5.5 doses (interquartile range, 1.0 to 15.0) of trial medication; there was no significant between-group difference in the median number of doses received (P = 0.47). The number of asthma exacerbations did not differ significantly between the two groups, with a mean of 0.81 per participant with acetaminophen and 0.87 per participant with ibuprofen over 46 weeks of follow-up (relative rate of asthma exacerbations in the acetaminophen group vs. the ibuprofen group, 0.94; 95% confidence interval, 0.69 to 1.28; P = 0.67). In the acetaminophen group, 49% of participants had at least one asthma exacerbation and 21% had at least two, as compared with 47% and 24%, respectively, in the ibuprofen group. Similarly, no significant differences were detected between acetaminophen and ibuprofen with respect to the percentage of asthma-control days (85.8% and 86.8%, respectively; P = 0.50), use of an albuterol rescue inhaler (2.8 and 3.0 inhalations per week, respectively; P = 0.69), unscheduled health care utilization for asthma (0.75 and 0.76 episodes per participant, respectively; P = 0.94), or adverse events. CONCLUSIONS Among young children with mild persistent asthma, as-needed use of acetaminophen was not shown to be associated with a higher incidence of asthma exacerbations or worse asthma control than was as-needed use of ibuprofen. (Funded by the National Institutes of Health; AVICA ClinicalTrials.gov number, NCT01606319.)

42. Paracetamol with ibuprofen: Ibuprofen is a marker of soft tissue infection.
Authors Moore, Nicholas D
Source BMJ (Clinical research ed.); Oct 2008; vol. 337; p. a2072
Publication Date Oct 2008
Publication Type(s) Letter Comment
PubMedID 18852172
Database Medline

Available at BMJ (Clinical research ed.) from BMJ Journals - NHS

43. Ethnic differences in parental perceptions and management of childhood fever.
Authors Cohee, Lauren M S; Crocetti, Michael T; Serwint, Janet R; Sabath, Bruce; Kapoor, Sumit
Source Clinical pediatrics; Mar 2010; vol. 49 (no. 3); p. 221-227
Publication Date Mar 2010
Publication Type(s) Comparative Study Multicenter Study Journal Article
PubMedID 19448132
Database Medline

To explore knowledge and management of childhood fever among ethnically diverse parents and identify opportunities for educational intervention, we administered a cross-sectional survey to a convenience sample of 487 parents of children enrolled in 2 urban hospital-based pediatric clinics. Outcomes included parental definition of fever, level of concern, and management of fever. Latino parents were least likely to identify a temperature as nonfebrile from 97-100.3 degrees F (adjusted odds ratios [AOR] 0.06) or identify a fever as a temperature from 100.4-107 degrees F (AOR 0.52). African Americans were least likely to believe that fever can cause death or brain damage (AOR 0.4). African Americans were more likely to dose ibuprofen more frequently than recommended (AOR 1.97). All ethnicities are equally likely to treat normal temperatures and dose acetaminophen too frequently. Therefore continued education of all families about fever is necessary, and there are opportunities to develop ethnically sensitive strategies to target educational interventions.

44. Alternating antipyretics for fever reduction in children: an unfounded practice passed down to parents from pediatricians.
Authors Wright, Ashley D; Liebelt, Erica L
Source Clinical pediatrics; Mar 2007; vol. 46 (no. 2); p. 146-150
Publication Date Mar 2007
Publication Type(s) Journal Article
A convenience sample of parents/caregivers completed a 10-question survey on their patterns of antipyretic therapy administration to determine if antipyretics were alternated, how often, who advised them to do this, and how they learned to dose the antipyretic. Of the 256 caregivers (93%) who completed the survey, 67% responded that they alternated acetaminophen and/or ibuprofen. The frequency varied: every 2 hours (9%), every 3 hours (16%), every 4 hours (43%), every 6 hours (23%) and other (8%). Of these, 81% stated that their health care provider/pediatrician advised them to alternate acetaminophen and/or ibuprofen; 8% stated that nobody advised them. Only 61% received written instructions on how to dose antipyretics from their health care provider. Most caregivers of young children reported alternating acetaminophen and ibuprofen for fever reduction in their children. There was a wide variability of the dosing interval. Most learned this practice from their pediatrician/health care provider.

45. Combining paracetamol and ibuprofen for fever in children.
Authors: Purssell, Edward
Source: BMJ (Clinical research ed.); Sep 2008; vol. 337; p. a1590
Publication Date: Sep 2008
Publication Type(s): Letter Comment
PubMedID: 18784169
Database: Medline
Available at BMJ (Clinical research ed.) from BMJ Journals - NHS

46. Alternating acetaminophen and ibuprofen for pain in children.
Authors: Smith, Christine; Goldman, Ran D
Source: Canadian family physician Medecin de famille canadien; Jun 2012; vol. 58 (no. 6); p. 645-647
Publication Date: Jun 2012
Publication Type(s): Journal Article
PubMedID: 22700733
Database: Medline
Available at Canadian family physician Medecin de famille canadien from EBSCO (MEDLINE Complete)
Abstract
QUESTION
Because pain is a very common condition in children, such as after musculoskeletal injuries, many parents ask whether they can alternate over-the-counter analgesics to treat their children's pain. While some guidelines advise against this, it is common practice. Should alternating acetaminophen and ibuprofen be recommended for treating pain in children?
ANSWER
Children who have unresolved pain despite the use of either ibuprofen or acetaminophen should have their medication regimen reviewed to ensure they are receiving the medication at an adequate dose and interval. If monotherapy has failed, a short trial of an alternating regimen could be implemented. However, there is a lack of evidence for safety with long-term use of alternating ibuprofen and acetaminophen.

47. Clinical safety and tolerability of ibuprofen compared with paracetamol in pediatric pain and fever. A systematic review.
Authors: Kleijnen, J
Source: Minerva pediatrica; Dec 2009; vol. 61 (no. 6); p. 757
Publication Date: Dec 2009
Publication Type(s): Comparative Study Journal Article Review
PubMedID: 19935543
Database: Medline

48. Assessment of febrile seizures in children.
Authors: Fetveit, Arne
Source: European journal of pediatrics; Jan 2008; vol. 167 (no. 1); p. 17-27
Publication Date: Jan 2008
Publication Type(s): Journal Article Review
PubMedID: 17768636
Database: Medline
Available at European journal of pediatrics from SpringerLink - Medicine
Available at European journal of pediatrics from EBSCO (Biomedical Reference Collection - Comprehensive)
Available at European journal of pediatrics from ProQuest (Hospital Premium Collection) - NHS Version
Available at European journal of pediatrics from EBSCO (MEDLINE Complete)
Febrile seizures are the most common form of childhood seizures, affecting 2-5% of all children and usually appearing between 3 months and 5 years of age. Despite its predominantly benign nature, a febrile seizure (FS) is a terrifying experience for most parents. The condition is perhaps one of the most prevalent causes of admittance to pediatric emergency wards worldwide. FS, defined as either simple or complex, may be provoked by any febrile bacterial or (more usually) viral illness. No specific level of fever is required to diagnose FS. It is essential to exclude underlying meningitis in all children with FS, either clinically or, if any doubt remains, by lumbar puncture. There is no evidence, however, to support routine lumbar puncture in all children admitted with simple FS, especially when typical clinical signs of meningitis are lacking. The risk of epilepsy following FS is 1-6%. The association, however small, between FS and epilepsy may demonstrate a genetic link between FS and epilepsy rather than a cause and effect relationship. The effectiveness of prophylactic treatment with medication remains controversial. There is no evidence of the effectiveness of antipyretics in preventing future FS. Prophylactic use of paracetamol, ibuprofen or a combination of both in FS, is thus a questionable practice. There is reason to believe that children who have experienced a simple FS are over-investigated and over-treated. This review aims to provide physicians with adequate knowledge to make rational assessments of children with febrile seizures.

49. Treatment of pediatric fever: Are acetaminophen and ibuprofen equivalent?
Authors Allan, G Michael; Ivers, Noah; Shevchuk, Yvonne
Source Canadian family physician Medecin de famille canadien; Aug 2010; vol. 56 (no. 8); p. 773
Publication Date Aug 2010
Publication Type(s) Journal Article
PubMedID 20705883
Database Medline
Available at Canadian family physician Medecin de famille canadien from EBSCO (MEDLINE Complete)

Authors Brown, Jonathon M; Udorphorn, Yuthana; Suz, Pilar; Vavilala, Monica S
Source Child’s nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery; Apr 2008; vol. 24 (no. 4); p. 477-483
Publication Date Apr 2008
Publication Type(s) Journal Article
PubMedID 17917733
Database Medline
Available at Child’s nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery from SpringerLink - Medicine
Available at Child’s nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery from EBSCO (MEDLINE Complete)

Abstract OBJECTIVEThe purpose of this study was to describe the treatment of noninfectious fever in children with severe traumatic brain injury (TBI). MATERIALS AND METHODS We conducted a retrospective study to compare type of and response to antipyretic treatment strategies in children less than or equal to 17 years and Glasgow Coma Scale (GCS) score less than 9. RESULTS The average admission GCS score was 4. Forty children (35 boys, 5 girls), age 7.8 +/- 5.2 years, had noninfectious fever. Seventy percent (28 of 40) received acetaminophen only, and 30% (12 of 40) received acetaminophen plus either ibuprofen or physical cooling. Time to next febrile episode was longer in patients receiving combination therapy than those receiving monotherapy (p = 0.03). Fever refractory to treatment dose or strategy occurred in more than 40% of the patients. CONCLUSIONS Early combination antipyretic therapy may be needed to effectively maintain normothermia in children with severe TBI.

51. . . . And which works better on fever--acetaminophen, ibuprofen, or both?
Source Child health alert; Oct 2008; vol. 26 ; p. 1-2
Publication Date Oct 2008
Publication Type(s) Journal Article
PubMedID 19006804
Database Medline
Available at Child health alert from EBSCO (MEDLINE Complete)

Authors Saleh, Ezzeldin; Swamy, Geeta K; Moody, M Anthony; Walter, Emmanuel B
Source Clinical pediatrics; May 2017; vol. 56 (no. 5); p. 435-442
Publication Date May 2017
Publication Type(s) Journal Article
PubMedID 27798399
53. Non-prescription medicines for pain and fever--a comparison of recommendations and counseling from staff in pharmacy and general sales stores.

Authors: Bardage, Carola; Westerlund, Tommy; Barzi, Sahra; Bernsten, Cecilia

Source: Health policy (Amsterdam, Netherlands); Apr 2013; vol. 110 (no. 1); p. 76-83

Abstract: OBJECTIVE: The purpose of this study is to map and analyze the content and quality of the encounter when customers buy non-prescription medicines for pain and fever. METHODS: 297 pharmacies and 801 general sales stores (GSS) in Sweden were selected. A “Mystery shopper” exercise was conducted. Three scenarios were used and a total of 366 units were selected for each scenario. There were in total 625 observers: 208 in the child with fever scenario, 225 in the Reliv scenario, and 192 in the painkiller during pregnancy scenario. DATA COLLECTION: 21st September to 20th November 2011. RESULTS: In two out of three visits to GSS, the staff proposed a medicine for a heavily pregnant woman. The staff suggested in 9% of the visits a medicine that is inappropriate in late pregnancy. The corresponding percentage in pharmacies was 1%. Both pharmacies and GSS proposed, in 6% a medicine that is inappropriate for babies to a feverish child. Only 16% of the pharmacists and 14% of the staff in GSS asked for the age of the child. General sales staff recommended in 10% ibuprofen and in 4% an acetylsalicylic acid product when an acetaminophen preparation was requested. The corresponding percentage in the pharmacy were 4% ibuprofen, 2% diclofenac, and 1% an acetylsalicylic acid product. CONCLUSION: The staff in GSS and pharmacies do not pay sufficient attention to the heterogeneity of the child. Both pharmacies and GSS proposed a medicine for a heavily pregnant woman. The staff suggested in 9% of the visits a medicine that is inappropriate in late pregnancy. The corresponding percentage in pharmacies was 1%. Both pharmacies and GSS proposed, in 6% a medicine that is inappropriate for babies to a feverish child. Only 16% of the pharmacists and 14% of the staff in GSS asked for the age of the child. General sales staff recommended in 10% ibuprofen and in 4% an acetylsalicylic acid product when an acetaminophen preparation was requested. The corresponding percentage in the pharmacy were 4% ibuprofen, 2% diclofenac, and 1% an acetylsalicylic acid product.

54. Management of children’s fever by parents and caregivers: Practical measurement of functional health literacy.

Authors: Emmerton, Lynne; Chaw, Xin Yao; Kelly, Fiona; Kairuz, Therese; Marriott, Jennifer; Wheeler, Amanda; Moles, Rebekah

Source: Journal of child health care : for professionals working with children in the hospital and community; Dec 2014; vol. 18 (no. 4); p. 302-313

Abstract: Functional health literacy is founded on general and numerical literacy and practical skills and is required for the appropriate and effective management of health symptoms in children. This study aimed to assess the health literacy skills of parents and caregivers of preschool-aged children, using a progressive scenario describing a child with fever and presenting tasks relating to selection of a medicine and hypothetical dosing of their child. Participants (n = 417) from 33 childcare- and health-related sites in Sydney, Brisbane, Melbourne and Auckland completed the study. Participants’ responses were largely appropriate regarding actions in response to worsening symptoms, selection of an appropriate product (from a limited range), whereby 84.5% of responses were for a single-ingredient paracetamol product and use of the package directions to state the frequency of dosing (93.1% of frequencies appropriate for paracetamol and 66.7% for ibuprofen). However, in only 50.8% of cases was an appropriate weight-based dose calculated, and doses were not measured to within 10% of the stated dose in 16.7% of cases. Future studies should focus on skill development via educational campaigns for parents and caregivers.


Authors: Chiappini, Elena; Venturini, Elisabetta; Remaschi, Giulia; Principi, Nicola; Longhi, Riccardo; Tovo, Pier-Angelo; Becherucci, Paolo; Bonsignori, Francesca; Esposito, Susanna; Festini, Filippo; Galli, Luisa; Lucchesi, Bice; Mugelli, Alessandro; Marseglia, Gian Luigi; de Martino, Maurizio; Italian Pediatric Society Panel for the Management of Fever in Children
### OBJECTIVE
To review new scientific evidence to update the Italian guidelines for managing fever in children as drafted by the panel of the Italian Pediatric Society.

### STUDY DESIGN
Relevant publications in English and Italian were identified through search of MEDLINE and the Cochrane Database of Systematic Reviews from May 2012 to November 2015.

### RESULTS
Previous recommendations are substantially reaffirmed. Antipyretics should be administered with the purpose to control the child’s discomfort. Antipyretics should be administered orally; rectal administration is discouraged except in the setting of vomiting. Combined use of paracetamol and ibuprofen is discouraged, considering risk and benefit. Antipyretics are not recommended preemptively to reduce the incidence of fever and local reactions in children undergoing vaccination, or in attempt to prevent febrile convulsions in children. Ibuprofen and paracetamol are not contraindicated in children who are febrile with asthma, with the exception of known cases of paracetamol- or nonsteroidal anti-inflammatory drug-induced asthma.

### CONCLUSIONS
Recent medical literature leads to reaffirmation of previous recommendations for use of antipyretics in children who are febrile.

### 56. Balancing the risks and benefits of the use of over-the-counter pain medications in children.

**Authors**
Bárzaga Arencibia, Zeina; Choonara, Imti

**Source**
Drug safety; Dec 2012; vol. 35 (no. 12); p. 1119-1125

**Publication Date**
Dec 2012

**PubMedID**
23078168

**Database**
Medline

**Abstract**
Paracetamol (acetaminophen) and ibuprofen are the most frequently purchased over-the-counter (OTC) medicines for children. Parents purchase these medicines for the treatment of fever and pain. In some countries other NSAIDs such as aspirin (acetylsalicylic acid) and dipyrone are available. We aimed to perform a narrative review of the efficacy and toxicity of OTC analgesic medicines for children in order to give guidance to health professionals and parents regarding the treatment of pain in a child. Neither aspirin nor dipyrone are recommended for OTC use because of the association with Reye's syndrome for the former and the risk of agranulocytosis for the latter. Both paracetamol and ibuprofen are effective for the treatment of mild pain in children. Adverse effects with both medicines are infrequent. Ibuprofen is an NSAID and therefore there is a greater risk of gastrointestinal adverse effects and hypersensitivity. Aspirin and dipyrone should be avoided. Paracetamol is the drug of first choice for mild pain in children because of its favourable safety profile. For the treatment of significant musculoskeletal pain, ibuprofen is the drug of first choice.

### 57. Alternating acetaminophen with ibuprofen for fever: is this a problem?

**Authors**
Miller, Alvin A

**Source**
Pediatric annals; Jul 2007; vol. 36 (no. 7); p. 384

**Publication Date**
Jul 2007

**PubMedID**
17691622

**Database**
Medline

**Abstract**

### 58. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study.

**Authors**
Magnus, Maria C; Karlstad, Øystein; Håberg, Siri E; Nafstad, Per; Davey Smith, George; Nystad, Wenche

**Source**
International journal of epidemiology; Apr 2016; vol. 45 (no. 2); p. 512-522

**Publication Date**
Apr 2016

**PubMedID**
26861476

**Database**
Medline

**Available at**

- International journal of epidemiology from HighWire - Free Full Text
- International journal of epidemiology from EBSO (MEDLINE Complete)
Abstract

BACKGROUND Paracetamol exposure has been positively associated with asthma development. The relative importance of prenatal vs infant exposure and confounding by indication remains elusive. We examined the association of prenatal and infant (first 6 months) paracetamol exposure with asthma development while addressing confounding by indication.

METHODS We used information from the Norwegian Mother and Child Cohort Study, including 53169 children for evaluation of current asthma at 3 years, 25394 for current asthma at 7 years and 45607 for dispensed asthma medications at 7 years in the Norwegian Prescription Database. We calculated adjusted relative risks (adj. RR) and 95% confidence intervals (CI) using log-binomial regression.

RESULTS There were independent modest associations between asthma at 3 years with prenatal paracetamol exposure (adj. RR 1.13; 95% CI: 1.02-1.25) and use of paracetamol during infancy (adj. RR 1.29; 95% CI: 1.16-1.45). The results were consistent for asthma at 7 years. The associations with prenatal paracetamol exposure were seen for different indications (pain, respiratory tract infections/influenza and fever). Maternal pain during pregnancy was the only indication that showed an association both with and without paracetamol use. Maternal paracetamol use outside pregnancy and paternal paracetamol use were not associated with asthma development. In a secondary analysis, prenatal ibuprofen exposure was positively associated with asthma at 3 years but not asthma at 7 years.

CONCLUSION This study provides evidence that prenatal and infant paracetamol exposure have independent associations with asthma development. Our findings suggest that the associations could not be fully explained by confounding by indication.

59. Association between an excess risk of acute kidney injury and concomitant use of ibuprofen and acetaminophen in children, retrospective analysis of a spontaneous reporting system.

Authors Yue, Zhihua; Jiang, Pengli; Sun, He; Wu, Jing

Source European journal of clinical pharmacology; Apr 2014; vol. 70 (no. 4); p. 479-482

Abstract

PURPOSE Ibuprofen and acetaminophen are frequently alternated or simultaneously used to treat fever or pain in children, while the evidence for the safety of such a combination is lacking. In this study, we analyzed the association of acute kidney injury (AKI) with ibuprofen, acetaminophen, and the combination of both drugs in children (0-12 years) by using the FDA Adverse Event Reporting System (AERS) database between January 2004 and June 2012.

METHODS Adverse event reports in children aged 0 to ≤12 years were included in the study. Cases were defined as reports of AKI according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology, non-cases as all other reports. Exposure categories were divided into three index groups: two groups where ibuprofen or acetaminophen were used in absence of one another and another group where both drugs were used concomitantly. There was also a reference group, in which neither ibuprofen nor acetaminophen were used. These index groups were compared with the reference group using reporting odds ratios (RORs). RESULTS In total, 47,803 reports were included in the study. After adjusting for year of reporting, age, and sex, the ROR for an AKI in children who used only ibuprofen or acetaminophen compared with children who used neither ibuprofen nor acetaminophen was 2.14 (95% CI: 1.59-2.88) and 1.53 (95% CI: 1.18-1.97), respectively, while the adjusted ROR was 4.01 (95% CI: 2.96-5.43) when both drugs were concomitantly used.

CONCLUSION The results illustrate that the concomitant use of ibuprofen and acetaminophen in children might be associated with increased risk of AKI.

60. Paracetamol is no more likely to exacerbate asthma in children than ibuprofen, shows study.

Authors Mayor, Susan

Source BMJ (Clinical research ed.); Aug 2016; vol. 354 ; p. i4558

61. Febrile seizures.

Authors Mewasingh, Leena D

Source BMJ clinical evidence; Nov 2010; vol. 2010

Database Medline

Available at BMJ (Clinical research ed.) from BMJ Journals - NHS
INTRODUCTION Simple febrile seizures are generalised in onset, last <15 minutes, and do not occur more than once in 24 hours. Complex febrile seizures are longer lasting, have focal symptoms, and can recur within 24 hours. This review only deals with simple febrile seizures. About 2% to 5% of children in the USA and Western Europe, and 6% to 9% of infants and children in Japan will have experienced at least one febrile seizure by the age of 5 years. Simple febrile seizures may slightly increase the risk of developing epilepsy, but have no known adverse effects on behaviour, scholastic performance, or neurocognition.

METHODS AND OUTCOMES
We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments given during episodes of fever in children with one or more previous simple febrile seizures? What are the effects of long-term (daily, for >1 month) anticonvulsant treatment in children with a history of simple febrile seizures? What are the effects of treatments on reducing the risk of subsequent epilepsy in children with a history of simple febrile seizures? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

RESULTS We found 18 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions.

CONCLUSIONS In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticonvulsants (intermittent or continuous) and antipyretic treatments (physical antipyretic measures, paracetamol, ibuprofen).


Authors Serwint, Janet R
Source Pediatrics in review; Oct 2007; vol. 28 (no. 10); p. 395
Publication Date Oct 2007
Publication Type(s) Journal Article
PubMedID 17908663
Database Medline


Authors Brandlistuen, Ragnhild Eek; Ystrom, Eivind; Nulman, Irena; Koren, Gideon; Nordeng, Hedvig
Source International journal of epidemiology; Dec 2013; vol. 42 (no. 6); p. 1702-1713
Publication Date Dec 2013
Publication Type(s) Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article
PubMedID 24163279
Database Medline

Abstract BACKGROUND Paracetamol is used extensively during pregnancy, but studies regarding the potential neurodevelopmental sequela of foetal paracetamol exposure are lacking. Method Between 1999 and 2008 all pregnant Norwegian women were eligible for recruitment into the prospective Norwegian Mother and Child Cohort Study. The mothers were asked to report on their use of paracetamol at gestational weeks 17 and 30 and at 6 months postpartum. We used data on 48 631 children whose mothers returned the 3-year follow-up questionnaire by May 2011. Within this sample were 2919 same-sex sibling pairs who were used to adjust for familial and genetic factors. We modelled psychomotor development (communication, fine and gross motor development), externalizing and internalizing behaviour problems, and temperament (emotionality, activity, sociability and shyness) based on prenatal paracetamol exposure using generalized linear regression, adjusting for a number of factors, including febrile illness, infections and co-medication use during pregnancy.

RESULTS The sibling-control analysis revealed that children exposed to prenatal paracetamol for more than 28 days had poorer gross motor development (β 0.24, 95% confidence interval (CI) 0.12-0.51), communication (β 0.20, 95% CI 0.01-0.39), externalizing behaviour (β 0.28, 95% CI 0.15-0.42), internalizing behaviour (β 0.14, 95% CI 0.01-0.28), and higher activity levels (β 0.24, 95% CI 0.11-0.38). Children exposed prenatally to short-term use of paracetamol (1-27 days) also had poorer gross motor outcomes (β 0.10, 95% CI 0.02-0.19), but the effects were smaller than with long-term use. Ibuprofen exposure was not associated with neurodevelopmental outcomes.

CONCLUSION Children exposed to long-term use of paracetamol during pregnancy had substantially adverse developmental outcomes at 3 years of age.

64. Febrile seizures.

Authors Mewasingh, Leena D
Source BMJ clinical evidence; May 2008; vol. 2008
Publication Date May 2008
Publication Type(s) Journal Article Review
PubMedID 19450310
Database Medline
INTRODUCTION

Simple febrile seizures are generalised in onset, last less than 15 minutes, and do not occur more than once in 24 hours. Complex seizures are longer lasting, have focal symptoms, and can recur within 24 hours. This review only deals with simple febrile seizures. About 2-5% of children in the USA and Western Europe, and 6-9% of infants and children in Japan, will have experienced at least one febrile seizure by the age of 5 years. Simple febrile seizures may slightly increase the risk of developing epilepsy, but have no known adverse effects on behaviour, scholastic performance, or neurocognition.

METHODS AND OUTCOMES

We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments given during episodes of fever in children with one or more previous simple febrile seizures? What are the effects of treatments on reducing the risk of subsequent epilepsy in children with a history of simple febrile seizures? What are the effects of long-term (daily, for more than 1 month) anticonvulsant treatment in children with a history of simple febrile seizures? We searched: Medline, Embase, The Cochrane Library and other important databases up to August 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

RESULTS

We found 19 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions.

CONCLUSIONS

In this systematic review we present information relating to the effectiveness and safety of the following interventions: anticonvulsants (intermittent or continuous), and antipyretic treatments (physical antipyretic measures, paracetamol, ibuprofen).


Authors
Demir, Figen; Sekreter, Ozgur

Source
Italian journal of pediatrics; Sep 2012; vol. 38 ; p. 40

Publication Date
Sep 2012

Publication Type(s)
Journal Article

PubMedID
22950655

Database
Available at Italian journal of pediatrics from BioMed Central
Available at Italian journal of pediatrics from SpringerLink - Medicine
Available at Italian journal of pediatrics from Europe PubMed Central - Open Access
Available at Italian journal of pediatrics from ProQuest (Hospital Premium Collection) - NHS Version

Abstract

BACKGROUND

Fever is an extremely common sign in paediatric patients and the most common cause for a child to be taken to the doctor. The literature indicates that physicians and parents have too many misconceptions and conflicting results about fever management. In this study we aim to identify knowledge, attitudes and misconceptions of primary care physicians regarding fever in children.

METHODS

This cross-sectional study was conducted in April-May 2010 involving primary care physicians (n=80). The physicians were surveyed using a self-administered questionnaire. Descriptive statistics were used.

RESULTS

In our study only 10% of the physicians knew that a body temperature of above 37.2 °C according to an auxiliary measurement is defined as fever. Only 26.2% of the physicians took into consideration signs and symptoms other than fever to prescribe antipyretics. 85% of the physicians prescribed antipyretics to control fever or prevent complications of fever especially febrile seizures. Most of the physicians (76.3%) in this study reported that the height of fever may be used as an indicator for severe bacterial infection. A great majority of physicians (91.3%) stated that they advised parents to alternate the use of ibuprofen and paracetamol.

CONCLUSION

There were misconceptions about the management and complications of fever. There is a perceived need to improve the recognition, assessment, and management of fever with regards to underlying illnesses in children.


Authors
Lava, Sebastiano A G; Simonetti, Giacomo D; Ramelli, Gian Paolo; Tschumi, Sibylle; Bianchetti, Mario G

Source
Clinical therapeutics; Jan 2012; vol. 34 (no. 1); p. 250-256

Publication Date
Jan 2012

Publication Type(s)
Journal Article

PubMedID
22218087

Database
Available at Clinical therapeutics from ProQuest (Hospital Premium Collection) - NHS Version
Abstract

BACKGROUND: Symptomatic management is often all that is recommended in children with fever. To date, only 2 nationwide surveys of pediatricians regarding their attitudes toward fever have been published. OBJECTIVE: The aim of this study was to describe the management of children with fever by pediatricians in Switzerland. METHODS: For this survey, an initial close-ended questionnaire was tested and subsequently corrected. Between June 2010 and March 2011, an invitation was sent via electronic mail containing a link to the final version of the questionnaire. The survey was not commercially sponsored. RESULTS: The questionnaire was sent to 900 pediatricians, of whom 322 (36%) responded. A total of 96% of respondents identified ≥38.5°C as the rectal temperature threshold for fever treatment, and 64% indicated that they prescribe antipyretics for the treatment of general discomfort. A total of 95% of respondents indicated that they prescribe paracetamol (acetaminophen) as the first choice of antipyretic drug, and 91% indicated that they often prescribe ibuprofen as well. An alternating regimen of 2 drugs and physical antipyresis were indicated as common practice by 77% and 65% of pediatricians, respectively. Homeopathic remedies are rarely prescribed (<10% of respondents). The most commonly prescribed routes of administration in children aged 18 months, 5 years, and 10 years were rectal (78%), oral (87%), and oral (99%), respectively. Ninety-two percent of respondents indicated that they believe that an exaggerated fear of fever is common among parents, but 81% stated that they do not lower the temperature threshold for initiating pharmacologic treatment exclusively to calm parents. Most respondents (95%) indicated a belief that it is possible to educate families about the fear of fever. CONCLUSIONS: Based on the findings from the present survey, antipyretics are often prescribed to treat the general discomfort that accompanies fever. Nonetheless, a gap exists between available evidence and clinical practice. Guidelines should take this fact into account.

67. Tramadol infusion for the pain management in sickle cell disease: a case report.

Authors: Erhan, Elvan; Inal, Mehmet T; Aydinok, Yesim; Balkan, Can; Yegul, Ibrahim
Source: Paediatric anaesthesia; Jan 2007; vol. 17 (no. 1); p. 84-86

We present the analgesic management of a 4-year-old child who suffered from severe abdominal and leg pain during his first vaso-occlusive crisis with sickle cell disease, diagnosed as beta/S disease when he was 1 year old. His mother and father were carriers of beta-thalassemia and hemoglobin S, respectively. He had an upper respiratory tract infection in which a vaso-occlusive crisis was precipitated. On admission to hospital, fever, severe abdominal and leg pain were noted. Hemoglobin was 4 g x dl(-1) with accompanying prominent reticulocytosis and acute spleen enlargement. These findings indicated a sequestration crisis as well as vaso-occlusive disease. He was transfused with packed red cells. Paracetamol (40-60 mg x kg(-1) x day(-1)) and ibuprofen (20 mg x kg(-1) x day(-1)) were administered to relieve pain. The child experienced moderate to severe pain (Oucher score 60-80) despite nonopioid analgesics, so a tramadol infusion (0.25 mg x kg(-1) x h(-1)) was started. During the tramadol infusion no morphine was required, the intensity of pain gradually decreased (Oucher score 20) and the child was able to move his legs. At the end of 3 days splenomegaly regressed, no fever and pain were observed and the infusion was stopped. In conclusion, tramadol infusion i.v. (0.25 mg x kg(-1) x h(-1)) combined with nonopioids was effective to relieve moderate to severe pain due to vaso-occlusive crisis and can be recommended before using morphine in a pediatric sickle cell crisis.

68. Ibuprofen increases soft tissue infections in children.

Authors: Ospina, Carlos A Calderon; Salcedo, Alejandra
Source: BMJ (Clinical research ed.); Sep 2008; vol. 337; p. a1767

69. Fever without a localizing source.

Authors: Trainor, Jennifer L; Stamos, Julie Kim
Source: Pediatric annals; Jan 2011; vol. 40 (no. 1); p. 21-25
70. Adherence among Italian paediatricians to the Italian guidelines for the management of fever in children: a cross sectional survey.

**Authors**
Chiappini, Elena; D’Elios, Sofia; Mazzantini, Rachele; Becherucci, Paolo; Pierattelli, Monica; Galli, Luisa; de Martino, Maurizio

**Source**
BMC pediatrics; Dec 2013; vol. 13; p. 210

**Publication Date**
Dec 2013

**Publication Type(s)**
Journal Article

**PubMedID**
24350822

**Database**
Medline

**Abstract**
BACKGROUND Italian guidelines for the management of fever in children (IFG) have been published in 2009 and thereafter disseminated in all country. A survey was conducted before their publication and three years later to investigate their impact on knowledge and behaviors of paediatricians.

METHODS A questionnaire was administered to convenient samples of paediatricians in 2009 and in 2012, eliciting information about fever definition, methods of temperature measurement, and antipyretic use. Differences in responses between 2009 and 2012 and between paediatricians who were or were not aware of the IFG were evaluated.

RESULTS The responses rates were 74% (480/648) in 2009 and 69% (300/434) in 2012. In 2012 168/300 (56%) of participants were aware of the IFG. The proportion of paediatricians who correctly would never suggest the use of physical methods increased from 18.7% to 36.4% (P < 0.001). In 2009 11% of paediatricians declared that the use of antipyretic drugs depends on patient discomfort and did not use a temperature cut off. In 2012 this percentage reached 45.3% (P < 0.001). Alternate use of antipyretics decreased from 27.0% to 11.3% (P < 0.001). Use of rectal administration of antipyretics in absence of vomiting decreased from 43.8% in 2009 to 25.3% in 2012 (P < 0.001). In general, improvements were more striking in paediatricians who were aware of the IFG than in those who were not aware of them.

CONCLUSIONS Behaviours of Italian paediatricians improved over time. However, some wrong attitudes need to be further discouraged, including use of physical methods and misuse of rectal administration. Further strategy to disseminate the IFG could be needed.

71. Acetaminophen and Ibuprofen overdosage.

**Authors**
Argentieri, Jennifer; Morrone, Kerry; Pollack, Yehudit

**Source**
Pediatrics in review; Apr 2012; vol. 33 (no. 4); p. 188-189

**PubmedID**
22474118

**Database**
Medline

72. Necrotising fasciitis, dermal infections and NSAIDs: caution.

**Source**
Prescrire international; Feb 2007; vol. 16 (no. 87); p. 17

**PubmedID**
17323524

**Database**
Medline

**Abstract**
An analysis of the French national pharmacovigilance database suggests that NSAIDs increase the risk of necrotising fasciitis and dermal infection. Patients with infections and/or fever should use paracetamol instead.

73. Is combining or alternating antipyretic therapy more beneficial than monotherapy for febrile children?

**Authors**
Nabulsi, Mona

**Source**
BMJ (Clinical research ed.); Oct 2009; vol. 339; p. b3540

**PubmedID**
19797346

**Database**
Medline

**Abstract**
An analysis of the French national pharmacovigilance database suggests that NSAIDs increase the risk of necrotising fasciitis and dermal infection. Patients with infections and/or fever should use paracetamol instead.

74. Does acetaminophen in comparison to ibuprofen effectively reduce fevers in children younger than 18 years of age?

**Authors**
Arpa, Marie

**Source**
Pediatric nursing; 2010; vol. 36 (no. 4); p. 219-220

**PubmedID**
18742804

**Database**
Medline
75. Antipyretic treatment for feverish young children in primary care.

Authors: Harnden, Anthony
Source: BMJ (Clinical research ed.); Sep 2008; vol. 337; p. a1409
Publication Type(s): Editorial Comment
PubMedID: 18765451
Database: Medline
Available at: BMJ (Clinical research ed.) from BMJ Journals - NHS

76. AAP reports on the use of antipyretics for fever in children.

Authors: Hoover, Lindsey
Source: American family physician; Mar 2012; vol. 85 (no. 5); p. 518-519
Publication Type(s): Journal Article
PubMedID: 22534232
Database: Medline
Available at: American family physician from EBSCO (MEDLINE Complete)

77. Dipyrone and acetaminophen: correct dosing by parents?

Authors: Alves, João Guilherme Bezerra; Cardoso Neto, Fortunato José; Almeida, Camila Dornelas Câmara; Almeida, Natalia Dornelas Câmara
Source: Sao Paulo medical journal = Revista paulista de medicina; Jan 2007; vol. 125 (no. 1); p. 57-59
Publication Date: Jan 2007
Publication Type(s): Journal Article
PubMedID: 17505687
Database: Medline
Abstract: CONTEXT AND OBJECTIVESeveral studies in developed countries have documented that a significant percentage of children are given inappropriate doses of acetaminophen and ibuprofen. The objective of this paper was to investigate parents’ accuracy in giving dipyrone and acetaminophen to their children, in a poor region.DESIGN AND SETTINGCross-sectional study at the pediatric emergency department of Instituto Materno-Infantil Prof. Fernando Figueira, a teaching hospital in Pernambuco.METHODSThe inclusion criteria were age between 3 and 36 months, main complaint of fever and at least one dose of dipyrone or acetaminophen given to the child during the 24 hours preceding their arrival at the emergency department. The mothers were asked for demographic information and about the antipyretic doses given, which were compared with the recommended dosage.RESULTSAmong the 200 patients studied, 117 received dipyrone and 83 received acetaminophen. Overall, 75% received an incorrect dose of antipyretic. Of the patients who received dipyrone, 105 (89.7%) were given an incorrect dose; 16 (15.2%) received too little dipyrone, and 89 (84.8%) received too much. Of the patients who received acetaminophen, 45 (54.2%) were given an incorrect dose; 38 (84.4%) received too little acetaminophen, and 7 (15.6%) received too much. There were no differences in maternal and child characteristics between the groups receiving correct and incorrect doses of medication, except for the type of medication (dipyrone versus acetaminophen).CONCLUSIONSMost of the children treated were given inappropriate doses, mainly dipyrone overdosing and acetaminophen underdosing.

78. Acetaminophen use and asthma in children.

Authors: Sakulchit, Teeranai; Goldman, Ran D
Source: Canadian family physician Medecin de famille canadien; Mar 2017; vol. 63 (no. 3); p. 211-213
Publication Date: Mar 2017
Publication Type(s): Journal Article Review
PubMedID: 28292797
Database: Medline
Available at: Canadian family physician Medecin de famille canadien from EBSCO (MEDLINE Complete)
Abstract

A child with a history of asthma came to my clinic with acute fever. I have heard that acetaminophen might be associated with exacerbation of asthma. Is it safe if I recommend acetaminophen for this child? Answer Most studies suggest an association between acetaminophen use in children and development of asthma later in childhood. However, several confounding factors in study design might contribute to this positive correlation, and without a prospective controlled trial, confirming this finding is challenging. If children have a known history of asthma, it is likely safe to administer a single dose of acetaminophen without concern of precipitating adverse respiratory symptoms. Regular use of acetaminophen to relieve fever or pain does not seem to exacerbate asthma in children more than ibuprofen does.

79. Pediatric rash and joint pain: a case review.
Authors Dixson, Mindi
Source Journal of emergency nursing: JEN : official publication of the Emergency Department Nurses Association; Nov 2010; vol. 36 (no. 6); p. 591-593
Publication Date Nov 2010
Publication Type(s) Case Reports Journal Article
PubMedID 21078480
Database Medline
Available at Journal of emergency nursing: JEN : official publication of the Emergency Department Nurses Association from Edge Hill Aintree LIRC (lib302411) Local Print Collection [location] : Edge Hill Aintree LIRC.

80. Antipyretic therapy for influenza infection--benefit or harm?
Authors Eyers, Sally; Jefferies, Sarah; Shirtcliffe, Philippa; Perrin, Kyle; Beasley, Richard
Source The New Zealand medical journal; Jul 2011; vol. 124 (no. 1338); p. 126-128
Publication Date Jul 2011
Publication Type(s) Research Support, Non-u.s. Gov't Letter
PubMedID 21946975
Database Medline

Authors Jones, Virginia M
Source Journal of pain & palliative care pharmacotherapy; 2011; vol. 25 (no. 4); p. 340-349
Publication Date 2011
Publication Type(s) Journal Article Review
PubMedID 21936636
Database Medline
Available at Journal of pain & palliative care pharmacotherapy from EBSCO (MEDLINE Complete)
Abstract
Acetaminophen injection is an antipyretic and analgesic agent recently marketed in the United States as Ofirmev. Five published trials directly compare acetaminophen injection to drugs available in the United States. For management of pain in adults, acetaminophen injection was at least as effective as morphine injection in renal colic, oral ibuprofen after cesarean delivery, and oral acetaminophen after coronary artery bypass surgery. In children (3 to 16 years old), single-dose acetaminophen injection was similar to meperidine intramuscular (i.m.) for pain after tonsillectomy; readiness for discharge from the recovery room was shorter with acetaminophen injection (median 15 minutes) compared with meperidine i.m. (median 25 minutes), P = .005. In children (2 to 5 years old) postoperative adenotonsillectomy or adenoidectomy, the time to rescue analgesia was superior with high-dose acetaminophen rectal suppository (median 10 hours) compared with acetaminophen injection (median 7 hours), P = .01. One published trial demonstrated acetaminophen injection is noninferior to propacetamol injection for fever related to infection in pediatric patients. Dosing adjustments are not required when switching between oral and injectable acetaminophen formulations in adult and adolescent patients. Acetaminophen injection represents another agent for multimodal pain management.

82. Influenza like Illness (ILI): prescribing behaviour of 83 sentry doctors in Lazio region in the period 2001-2002. Is it adherent to Italian ILI guidelines?
Authors Orzella, L; Perria, C; Jefferson, T; Pasquarella, A; D'Amato, M; Faraone, M; Volpe, E; Guasticchi, G
Source Annali di igiene : medicina preventiva e di comunità; 2007; vol. 19 (no. 1); p. 19-26
Publication Date 2007
Publication Type(s) Journal Article
PubMedID 17405509
Database Medline
Abstract

To describe different doctors' attitudes in drug prescribing in case of influenza-Like-Illness during 2001-2002 influenza season in Lazio region, with regard to consumption and expenditure and its adherence to Italian Guidelines on ILI Management. Prospective study aimed to assess doctors' behaviour in prescribing in respect with the following events: (a) ILI and subsequent controls after diagnosis, (b) complications, (c) adverse events to influenza vaccine. 7,629 subjects, have been identified and only 17% presents one or more comorbidities. There are totally 7,766 cases of ILI: 23% are complicated and out of the remaining 77%, only 14% presents comorbidities. Almost all elderly people have been vaccinated. Antibiotics were prescribed to complicated cases (82%) with comorbidities (55%); 1,075 patients (12%) had second or third contact with doctors in a period longer than 7 days and about 65% of them received antibiotics in case of acute bronchitis; children received mainly ibuprofen and paracetamol for fever control; acetylsalicylic acid in children group has been delivered only in 1% of cases. Overall, doctors’ attitude in prescribing is generally coherent with Italian Guidelines on ILI even though a high variability still persists.

83. Ketoprofen pharmacokinetics, efficacy, and tolerability in pediatric patients.

Authors Kokki, Hannu
Source Paediatric drugs; Oct 2010; vol. 12 (no. 5); p. 313-329
Publication Date Oct 2010
Publication Type(s) Journal Article Review
PubMedID 20799760
Database Medline
Available at Paediatric drugs from SpringerLink - Medicine
Available at Paediatric drugs from EBSCO (Biomedical Reference Collection - Comprehensive)
Available at Paediatric drugs from ProQuest (Hospital Premium Collection) - NHS Version
Available at Paediatric drugs from EBSCO (MEDLINE Complete)

Abstract

The NSAID ketoprofen is used widely in the management of inflammatory and musculoskeletal conditions, pain, and fever in children and adults. Pharmacokinetic studies show that drug exposure after a single intravenous dose is similar in children and adults (after dose normalization), and thus similar mg/kg bodyweight dosing may be used in children and adults. Ketoprofen crosses the blood-brain barrier and therefore has the potential to cause central analgesic effects. Ketoprofen has been investigated in children for the treatment of pain and fever, peri- and postoperative pain, and inflammatory pain conditions. The results of four clinical trials in febrile conditions with the oral syrup formulation indicate that ketoprofen is as effective as acetaminophen (paracetamol) and ibuprofen, allowing children to rapidly return to daily activities with improvements in sleep quality and appetite. Studies of ketoprofen in the management of postoperative pain indicate that ketoprofen is a highly effective analgesic when administered perioperatively for a variety of surgical types, by a variety of routes, and whether given preoperatively or postoperatively. For adenoidectomy, intravenous ketoprofen provided superior postoperative analgesic efficacy compared with placebo. Analgesic efficacy was similar with intravenous, intramuscular, or rectal routes of administration, but oral administration just before surgery was inferior to intravenous administration in this setting. In patients undergoing a tonsillectomy, intravenous ketoprofen was superior to intravenous tramadol in terms of the need for postoperative rescue analgesia, but did not remove the need for rescue opioid therapy in these patients. Intravenous ketoprofen had superior postoperative analgesic efficacy to placebo when given as an adjuvant to epidural sufentanil analgesia after major surgery. Oral ketoprofen has shown efficacy in the treatment of juvenile rheumatoid arthritis. Ketoprofen is generally well tolerated in pediatric patients. Most of the adverse events reported are mild and transient, and are similar to those observed with other NSAIDs. Long-term tolerability has not yet been fully established in children, but data from three studies in >900 children indicate that oral ketoprofen is well tolerated when administered for up to 3 weeks after surgery. In conclusion, ketoprofen is effective and well tolerated in children for the control of post-surgical pain and for the control of pain and fever in inflammatory conditions.

84. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents.

Authors Eccleston, Christopher; Cooper, Tess E; Fisher, Emma; Anderson, Brian; Wilkinson, Nick Mr
Source The Cochrane database of systematic reviews; Aug 2017; vol. 8 ; p. CD012537
Publication Date Aug 2017
Publication Type(s) Research Support, Non-u.s. Gov't Journal Article Review
PubMedID 28770976
Database Medline
Available at The Cochrane database of systematic reviews from Cochrane Collaboration (Wiley)
BACKGROUND

Pain is a common feature of childhood and adolescence around the world, and for many young people, that pain is chronic. The World Health Organization guidelines for pharmacological treatments for children's persisting pain acknowledge that pain in children is a major public health concern of high significance in most parts of the world. While in the past pain was largely dismissed and was frequently left untreated, views on children's pain have changed over time, and relief of pain is now seen as important. We designed a suite of seven reviews on chronic non-cancer pain and cancer pain (looking at antidepressants, antiepileptic drugs, non-steroidal anti-inflammatory drugs, opioids, and paracetamol) in order to review the evidence for children's pain utilising pharmacological interventions. As the leading cause of morbidity in the world today, chronic disease (and its associated pain) is a major health concern. Chronic pain (that is pain lasting three months or longer) can arise in the paediatric population in a variety of pathophysiological classifications (nociceptive, neuropathic, or idiopathic) from genetic conditions, nerve damage pain, chronic musculoskeletal pain, and chronic abdominal pain, as well as for other unknown reasons. Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat pain, reduce fever, and for their anti-inflammatory properties. They are commonly used within paediatric pain management. Non-steroidal anti-inflammatory drugs are currently licensed for use in Western countries, however they are not approved for infants under three months old. The main adverse effects include renal impairment and gastrointestinal issues. Common side effects in children include diarrhoea, headache, nausea, constipation, rash, dizziness, and abdominal pain.

OBJECTIVES

To assess the analgesic efficacy and adverse events of NSAIDs used to treat chronic non-cancer pain in children and adolescents aged between birth and 17 years, in any setting. SEARCH METHODS

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE via Ovid, and Embase via Ovid from inception to 6 September 2016. We also searched the reference lists of retrieved studies and reviews, as well as online clinical trial registries. SELECTION CRITERIA

Randomised controlled trials, with or without blinding, of any dose and any route, treating chronic non-cancer pain in children and adolescents, comparing any NSAID with placebo or an active comparator. DATA COLLECTION AND ANALYSIS

Two review authors independently assessed studies for eligibility. We planned to use dichotomous data to calculate risk ratio and number needed to treat for one additional event, using standard methods. We assessed GRADE and created three 'Summary of findings' tables.

MAIN RESULTS

We included seven studies with a total of 1074 participants (aged 2 to 18 years) with chronic juvenile polyarthritis or chronic juvenile rheumatoid arthritis. All seven studies compared an NSAID with an active comparator. None of the studies were placebo controlled. No two studies investigated the same type of NSAID compared with another. We were unable to perform a meta-analysis. Risk of bias varied. For randomisation and allocation concealment, one study was low risk and six studies were unclear risk. For blinding of participants and personnel, three studies were low risk and four studies were unclear to high risk. For blinding of outcome assessors, all studies were unclear risk. For attrition, four studies were low risk and three studies were unclear risk. For selective reporting, four studies were low risk, two studies were unclear risk, and one study was high risk. For size, three studies were unclear risk and four studies were high risk. For other potential sources of bias, seven studies were low risk. Primary outcomes Three studies reported participant-reported pain relief of 30% or greater, showing no statistically significant difference in pain scores between meloxicam and naproxen, celecoxib and naproxen, or rofecoxib and naproxen (P > 0.05) (low-quality evidence). One study reported pain relief of 50% or greater, showing no statistically significant difference in pain scores between low-dose meloxicam (0.125 mg/kg) and high-dose meloxicam (0.25 mg/kg) when compared to naproxen 10 mg/kg (P > 0.05) (low-quality evidence). One study reported Patient Global Impression of Change, showing 'very much improved' in 85% of ibuprofen and 90% of aspirin participants (low-quality evidence). Secondary outcomes All seven studies reported adverse events. Participants reporting an adverse event (one or more per person) by drug were: aspirin 85/202; fenofenap 28/49; ibuprofen 40/45; indomethacin 9/30; ketoprofen 9/30; meloxicam 18/47; naproxen 44/202; and rofecoxib 47/209 (very low-quality evidence). All seven studies reported withdrawals due to adverse events. Participants withdrawn due to an adverse event by drug were: aspirin 16/120; celecoxib 10/159; fenofenap 0/49; ibuprofen 0/45; indomethacin 0/30; ketoprofen 0/30; meloxicam 10/147; naproxen 17/285; and rofecoxib 3/209 (very low-quality evidence). All seven studies reported serious adverse events. Participants experiencing a serious adverse event by drug were: aspirin 13/120; celecoxib 5/159; fenofenap 0/79; ketoprofen 0/30; ibuprofen 4/45; indomethacin 0/30; meloxicam 11/147; naproxen 10/285; and rofecoxib 0/209 (very low-quality evidence). There were few or no data for our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning as defined by validated scales; and quality of life as defined by validated scales (very low-quality evidence). We rated the overall quality of the evidence (GRADE rating) for our primary and secondary outcomes as very low because there were limited data from studies and no opportunity for a meta-analysis. AUTHORS' CONCLUSIONS

We identified only a small number of studies, with insufficient data for analysis. As we could undertake no meta-analysis, we are unable to comment about efficacy or harm from the use of NSAIDs to treat chronic non-cancer pain in children and adolescents. Similarly, we cannot comment on our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality; acceptability of treatment; physical functioning; and quality of life. We know from adult randomised controlled trials that some NSAIDs, such as ibuprofen, naproxen, and aspirin, can be effective in certain chronic pain conditions.
85. The association of acetaminophen and asthma prevalence and severity.

**Authors** McBride, John T

**Source** Pediatrics; Dec 2011; vol. 128 (no. 6); p. 1181-1185

**Publication Date** Dec 2011

**Publication Type(s)** Journal Article

**PubMedID** 22065272

**Database** Medline

**Available at** Pediatrics from HighWire - Free Full Text

**Abstract**

The epidemiologic association between acetaminophen use and asthma prevalence and severity in children and adults is well established. A variety of observations suggest that acetaminophen use has contributed to the recent increase in asthma prevalence in children: (1) the strength of the association; (2) the consistency of the association across age, geography, and culture; (3) the dose-response relationship; (4) the timing of increased acetaminophen use and the asthma epidemic; (5) the relationship between per-capita sales of acetaminophen and asthma prevalence across countries; (6) the results of a double-blind trial of ibuprofen and acetaminophen for treatment of fever in asthmatic children; and (7) the biologically plausible mechanism of glutathione depletion in airway mucosa. Until future studies document the safety of this drug, children with asthma or at risk for asthma should avoid the use of acetaminophen.


**Authors** Chiappini, Elena; Principi, Nicola; Mansi, Nicola; Serra, Agostino; De Masì, Salvatore; Camaioni, Angelo; Esposito, Susanna; Felisati, Giovanni; Galli, Luisa; Landi, Massimo; Speciale, Anna Maria; Bonsignori, Francesca; Marchisio, Paola; de Martino, Maurizio; Italian Panel on the Management of Pharyngitis in Children

**Source** Clinical therapeutics; Jun 2012; vol. 34 (no. 6); p. 1442

**Publication Date** Jun 2012

**Publication Type(s)** Research Support, Non-u.s. Gov't Journal Article

**PubMedID** 22691611

**Database** Medline

**Available at** Clinical therapeutics from ProQuest (Hospital Premium Collection) - NHS Version

**Abstract**

**BACKGROUND**

Discrepancies in the management of pharyngitis in children have been reported in Europe and the United States, and recommendations concerning the use of clinical scores, rapid antigen diagnostic tests (RADTs) or throat cultures, and the indications for antibiotic treatment largely differ.

**OBJECTIVE**

This article summarizes the Italian guidelines on the management of pharyngitis in children issued by the National Institute of Health.

**METHOD**

A multidisciplinary panel of experts (the Guidelines Development Group) developed and used a set of key questions to conduct a systematic review of the literature. Relevant publications in English were identified through a systematic review of MEDLINE and the Cochrane Database of Systematic Reviews from their inception through April 30, 2011. Final recommendations were scaled according to the Italian National Guidelines Program grading.

**RESULTS**

Eighteen clinical questions were defined, and 44 recommendations were issued. None of the available scoring systems is sufficiently accurate to identify group A β-hemolytic streptococci (GABHS) pharyngitis in settings with low prevalence for rheumatic disease. RADT should be performed by trained personnel in every child with a history and signs/symptoms suggestive of GABHS pharyngitis. RADT is not recommended in children with a McIsaac score of 0 or 1 with ≥2 signs/symptoms suggestive of viral infection. Backup culture in children with negative RADT result is not recommended. Culture test with antibiotic susceptibility assay should be performed exclusively for epidemiologic purposes. Streptococcal antibody titers are of no value in diagnosing acute pharyngitis. Antibiotic therapy is recommended in microbiologically documented GABHS pharyngitis. Because penicillin V is not available in Italy, amoxicillin (50 mg/kg/d in 2-3 doses orally) for 10 days is the first choice of treatment. In noncompliant cases, benzathine penicillin may be administered. Although not routinely recommended due to the high cost and wide spectrum of activity, a 5-day course with a second-generation cephalosporin may be used in noncompliant cases. Macrolides should be limited to children with demonstrated type I hypersensitivity to penicillin. Ibuprofen or paracetamol is recommended for relief of pain or fever associated with discomfort. Because the carrier state is not associated with increased risk of suppurative complications and risk of GABHS transmission to contacts is minimal, the carrier state should never be investigated and treated.

**Recommendations for the management of suppurative complications are given.**

**CONCLUSIONS**

This guideline provides a comprehensive, evidence based, tool for the diagnosis and therapy of acute pharyngitis in children.
<table>
<thead>
<tr>
<th>#</th>
<th>Database</th>
<th>Search term</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medline</td>
<td>exp IBUPROFEN/</td>
<td>7752</td>
</tr>
<tr>
<td>2</td>
<td>Medline</td>
<td>(ibuprofen).ti,ab</td>
<td>11444</td>
</tr>
<tr>
<td>3</td>
<td>Medline</td>
<td>(nurofen).ti,ab</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>Medline</td>
<td>(brufen).ti,ab</td>
<td>86</td>
</tr>
<tr>
<td>5</td>
<td>Medline</td>
<td>(1 OR 2 OR 3 OR 4)</td>
<td>12845</td>
</tr>
<tr>
<td>6</td>
<td>Medline</td>
<td>exp ACETAMINOPHEN/</td>
<td>16111</td>
</tr>
<tr>
<td>7</td>
<td>Medline</td>
<td>(paracetamol).ti,ab</td>
<td>9909</td>
</tr>
<tr>
<td>8</td>
<td>Medline</td>
<td>(calpol).ti,ab</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Medline</td>
<td>(6 OR 7 OR 8)</td>
<td>20150</td>
</tr>
<tr>
<td>10</td>
<td>Medline</td>
<td>(5 AND 9)</td>
<td>1438</td>
</tr>
<tr>
<td>11</td>
<td>Medline</td>
<td>exp FEVER/</td>
<td>39436</td>
</tr>
<tr>
<td>12</td>
<td>Medline</td>
<td>(fever).ti,ab</td>
<td>144368</td>
</tr>
<tr>
<td>13</td>
<td>Medline</td>
<td>(pyrexia).ti,ab</td>
<td>3972</td>
</tr>
<tr>
<td>14</td>
<td>Medline</td>
<td>(febrile).ti,ab</td>
<td>31797</td>
</tr>
<tr>
<td>15</td>
<td>Medline</td>
<td>(11 OR 12 OR 13 OR 14)</td>
<td>184995</td>
</tr>
<tr>
<td>16</td>
<td>Medline</td>
<td>(10 AND 15)</td>
<td>253</td>
</tr>
<tr>
<td>17</td>
<td>Medline</td>
<td>(10 AND 15) [DT 2007-2017] [Human age groups Infant,newborn OR Infant OR Child,preschool OR Child] [Languages English]</td>
<td>86</td>
</tr>
</tbody>
</table>