

A Review of Ibuprofen and Acetaminophen Use in Febrile Children and the Occurrence of Asthma-Related Symptoms

Dipak Kanabar, FRCPH¹; Stephen Dale, MBChB²; and Mariyam Rawat, MBA²

¹Evelina Children's Hospital, London, United Kingdom; and ²Reckitt Benckiser Group Plc, Slough, United Kingdom

ABSTRACT

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, pediatric, 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 sub-analyses 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, ibupro-

fen 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.

Conclusions: 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. (*Clin Ther.* 2007;29:2716–2723) Copyright © 2007 Excerpta Medica, Inc.

Key words: asthma, aspirin, acetaminophen, ibuprofen, morbidity, paracetamol, pediatric, treatment algorithm.

INTRODUCTION

In some patients, ingestion of aspirin (acetylsalicylic acid) can result in aspirin-induced asthma (AIA)—an airway mucosa inflammatory disease—that can culminate in episodes of asthma and attacks of rhinitis.¹ AIA has been recognized as a distinct clinical syndrome for decades; it was first described by Widall² in 1922, after aspirin first became available. In

Accepted for publication August 27, 2007.

doi:10.1016/j.clinthera.2007.12.021

0149-2918/\$32.00

Printed in the USA. Reproduction in whole or part is not permitted. Copyright © 2007 Excerpta Medica, Inc.

~10% of cases, the asthma attacks are severe and might be life threatening.^{3–6} For these reasons, the use of aspirin in the asthmatic population, both adult and pediatric, is largely discouraged because of its association with AIA. The underlying pathophysiologic basis of AIA has been proposed to be the inhibitory effect of aspirin on the cyclooxygenase (COX) pathway of arachidonic acid metabolism. By inhibiting the COX pathway, aspirin alters the balance between lipooxygenase and COX activity in favor of lipooxygenase activity. This indirectly causes an increase in the production of leukotrienes and subsequent bronchoconstriction.⁷ Furthermore, inhibition of the COX pathway results in a decline in the production of the anti-inflammatory prostaglandin E₂ (PGE₂).⁷

Symptoms of AIA usually start after the age of 10 years and peak around the third decade of life.⁷ The reported prevalence of AIA in adults varies widely, affecting between 4% and 44% of the population.⁸ Differences in the reported rates of AIA are dependent on the populations studied, methods used, definitions of outcomes, and criteria for defining sensitivity reactions. In an unselected population of children with or without history of AIA, and with or without increased levels of AIA markers subject to oral provocation, the prevalence of AIA has been reported to be 5%.⁸

Owing to the high level of cross-sensitivity to aspirin, caution over the use of aspirin in the asthmatic population has been extrapolated to other NSAIDs that inhibit both COX-1 and COX-2. The cross-sensitivity of aspirin is a pharmacologically determined reaction. However, it has been well established that all patients are cross-sensitive to NSAIDs^{9,10} and that the exacerbation of asthma might occur in patients following the use of any drug that inhibits COX. The earliest clinical study on the subject, conducted in 1976 by Szczeklik et al,¹¹ found that NSAIDs induced bronchoconstriction, as evidenced by a decrease in peak expiratory flow. Another study,⁸ which assessed the prevalence of AIA, found that cross-sensitivity to doses of over-the-counter NSAIDs was present in most patients with AIA—98%, 100%, and 93% of those receiving ibuprofen, naproxen, or diclofenac, respectively.

Studies have suggested that acetaminophen (paracetamol) might also contribute to the exacerbation of asthma or asthma-related adverse events (AEs). In an oral provocation challenge study¹² designed to assess the prevalence of cross-sensitivity to high-dose acetaminophen (1000–1500 mg), 34% of aspirin-sensitive

patients were also sensitive to acetaminophen in a dose-dependent manner. A systematic review⁸ reported that the prevalence of cross-sensitivity to acetaminophen was 7% in adults with AIA. In a cross-sectional analysis¹³ using the Third National Health and Nutrition Examination Survey (a representative sample of the US population), acetaminophen use but not ibuprofen or aspirin use, was associated with an increased prevalence of asthma in adults.

Although it is recognized in adults, the prevalence of NSAID- or acetaminophen-triggered asthma in children is thought to be less frequent and is less well defined because it might be difficult to recognize. In a randomized, double-blind, placebo-controlled, crossover bronchoprovocation challenge study^{14,15} in 100 children aged 6 to 18 years with mild-to-moderate asthma, the prevalence of ibuprofen-sensitive asthma was 2%.

Both ibuprofen and acetaminophen are commonly used in the management of fever in children. One study¹⁶ found that respiratory-related adverse drug reactions in children aged 4 months to 22 years were greater with ibuprofen compared with acetaminophen. However, in febrile children, ibuprofen has been suggested to be as effective and well tolerated as acetaminophen.¹⁷ In febrile children with a history of asthma, ibuprofen was as well tolerated as acetaminophen.¹⁸

Because acetaminophen is associated with the exacerbation of asthma or asthma-related AEs in adults,^{8,13} the possibility of it having similar effects in children needs to be clarified. It also remains to be determined whether ibuprofen exacerbates the symptoms of asthma in affected children. As aspirin is not recommended in children because of Reye's syndrome, and the symptoms of AIA can be nonspecific, it might be difficult to identify children likely to have cross-sensitivity to other NSAIDs or to acetaminophen. An algorithm has been developed to allow health care professionals to make informed decisions in the administration of NSAIDs to adults at risk for AIA.¹⁹ However, this algorithm cannot be used for the pediatric population because the classic symptoms and markers of AIA displayed by adults are not expressed by children. Therefore, the identification and management of children receiving ibuprofen or acetaminophen should be a critical process.

This article provides a review of the literature to assess whether ibuprofen exacerbates the symptoms of asthma or asthma-related AEs in febrile children

as well as how it compares with acetaminophen. The article also proposes an algorithm developed specifically for use in the pediatric population, based on the available evidence.

METHODS

The objective of the search was to identify studies that assessed the safety and tolerability of ibuprofen or acetaminophen in febrile children, with specific reference to asthma and asthma-related AEs. Twelve electronic databases—MEDLINE, EMBASE, Cochrane Database, DARE, British Nursing Index, CBIB, Derwent Drug File, International Pharmaceutical Abstracts, Pharm-Line, CINAHL, PASCAL, and SCZZ-SciSearch—were searched from their year of inception to June 2007, to identify publications on the use of ibuprofen and acetaminophen in the asthmatic pediatric population. The search criteria contained the following key terms: *asthma*, *child*, *pediatric*, *pediatrics*, *ibuprofen*, *Nurofen*, *Brufen*, *Motrin*, *Advil*, *propionic acid*, *paracetamol*, and *acetaminophen*. Various combinations of the search terms were used to maximize the results. Publications were included if they fulfilled the following criteria: English language; clinical study design, epidemiologic studies, systematic reviews, and narrative reviews; children aged ≤ 16 years; oral routes of administration; and all doses administered were either ibuprofen or paracetamol/acetaminophen. Publications were excluded if they contained the following criteria: animal data; in vitro studies; adult studies; or trials that included aspirin (as it is no longer recommended for children aged < 16 years). Only randomized controlled trials (RCTs) were considered for the development of the algorithm.

RESULTS

Of a total of 472 articles, 3 articles were considered directly relevant for the analysis. A summary of the study design and key outcomes for each is included in the analysis and is provided in the **table**. Two of these articles were based on subanalyses of the RCT, the Boston University Fever Study (BUFS), which specifically evaluated asthma morbidity in children receiving ibuprofen or acetaminophen.²⁰ The BUFS, which included $> 84,000$ children throughout the United States, assessed the risk for rare but serious AEs in children following the short-term use of ibuprofen or acetaminophen. The main outcome measures included hospitalization for gastrointestinal

bleeding, acute renal failure, and anaphylaxis, but not respiratory events—consequently, the BUFS was not included in this analysis. However, the BUFS included a number of subanalyses.

A BUFS subanalysis²¹ of 1879 children with asthma and a febrile illness assessed whether short-term use of ibuprofen increased asthma morbidity. Children aged 6 months to 12 years were randomized to receive either ibuprofen 5 mg/kg ($n = 636$), ibuprofen 10 mg/kg ($n = 611$), or acetaminophen 12 mg/kg ($n = 632$) for 4 weeks. Children with known sensitivity to aspirin, NSAIDs, or acetaminophen were excluded from the study. During follow-up, the rate of outpatient visits for asthma was 3.4% (335 per 10,000 courses of treatment). After adjusting for age, sex, and race, compared with acetaminophen, the relative risk (RR) of hospitalization with asthma for children assigned to receive ibuprofen was 0.63.²¹ Compared with acetaminophen, the RR of an outpatient visit for asthma for those receiving ibuprofen was 0.56. After excluding children taking any anti-inflammatory medication before the study drug, the RR of an outpatient visit for asthma was 0.54. There were no significant differences in the risk for outpatient visits between children assigned either the 5- or 10-mg/kg doses of ibuprofen.

Another BUFS subanalysis²² that included 27,065 febrile children aged ≤ 2 years assessed the prevalence of serious adverse clinical events (acute gastrointestinal bleeding, acute renal failure, anaphylaxis, Reye's syndrome, asthma, bronchiolitis, and vomiting/gastritis) following treatment with ibuprofen 5 mg/kg ($n = 9159$), ibuprofen 10 mg/kg ($n = 8779$) or acetaminophen 12 mg/kg ($n = 9127$) for 4 weeks. To avoid misdiagnosis, asthma and bronchiolitis were combined in the study. The RR of hospitalization in the acetaminophen group ($n = 9127$) was 1.0 compared with an RR of 0.9 in the ibuprofen groups ($n = 17,938$). The study found that antipyretic assignment was not associated with a risk for asthma/bronchiolitis-related hospitalization. Data from this study indicated that serious adverse clinical events requiring hospitalization among febrile children treated with acetaminophen or ibuprofen were low and did not vary significantly with choice of antipyretic.²²

The third article, a double-blind, parallel-group, multidose study by McIntyre and Hull,¹⁷ compared the efficacy and tolerability of PO ibuprofen 20 mg/kg QD ($n = 76$) or acetaminophen 50 mg/kg QD ($n = 74$)

Table. Summary of study design and key outcomes in studies assessing the safety and tolerability of ibuprofen and acetaminophen in febrile children.

Study	Design	Patients	Treatment Groups	Outcomes
Lesko et al, 2002 ²¹	4-Week, randomized, double-blind, acetaminophen-controlled study	Children aged between 6 months and 12 years with asthma and fever (n = 1879)	PO ibuprofen 5 mg/kg (n = 636) vs PO ibuprofen 10 mg/kg (n = 611) vs PO acetaminophen 12 mg/kg (n = 632)	Morbidity from asthma defined as a report of hospitalization or outpatient visits for asthma. RR of hospitalization with asthma in the ibuprofen group 0.63 (95% CI, 0.25–1.6) compared with acetaminophen. RR of outpatient visits for asthma in the ibuprofen group 0.56 (95% CI, 0.37–0.93) compared with acetaminophen.
Lesko and Mitchell, 1999 ²²	4-Week, randomized, double-blind, acetaminophen-controlled study	Children aged between 6 months and 2 years with fever (n = 27,065)	PO ibuprofen 5 mg/kg (n = 9159) vs PO ibuprofen 10 mg/kg (n = 8779) vs PO acetaminophen 12 mg/kg (n = 9127)	Morbidity from asthma defined as a report of hospitalization for asthma/bronchiolitis RR of hospitalization with asthma/bronchiolitis in the ibuprofen group 0.9 (95% CI, 0.5–1.4) compared with acetaminophen.
McIntyre and Hull, 1996 ¹⁷	Double-blind, parallel-group, multidose study (up to 3 days)	Children aged between 2 months and 12 years with fever (n = 150)	PO ibuprofen 20 mg/kg · 24 hours (n = 76) vs PO acetaminophen 50 mg/kg · 24 hours (n = 74) at 6-hourly intervals for ≤12 doses (3 days)	No reports of asthma attacks in the treatment groups. Two patients in the acetaminophen group experienced mild wheezing (1 with no history of wheezing and 1 with a history of wheezing).

RR = relative risk.

at 6-hour intervals in febrile children aged between 2 months and 12 years. In the study, 33 of the 150 children (22%) had a history of wheezing and/or asthma—21 in the ibuprofen group and 12 in the acetaminophen group. At the time of admission to the study,

the primary diagnosis of 15 children was asthma/wheezing—11 in the ibuprofen group and 4 in the acetaminophen group. Two children in the acetaminophen group experienced mild wheezing—1 child with and 1 child without a history of wheezing. No severe

asthma exacerbations were reported in either treatment group. The findings suggested that ibuprofen was as effective and well tolerated as acetaminophen in the treatment of fever in young children.

DISCUSSION

Although there are many studies that have investigated the safety and tolerability of ibuprofen or acetaminophen use in children, few have specifically examined the association of ibuprofen or acetaminophen and the occurrence of asthma or asthma-related AEs in children. Three relevant articles were identified in this analysis, indicating a paucity of data in this area of research. The results from all 3 articles indicated that the use of ibuprofen in the pediatric population does not exacerbate asthma morbidity.^{17,21,22}

The trial by Lesko and Mitchell²⁰ specifically included children with asthma who were receiving treatment for the condition. Results from the first BUFS²¹ subanalysis indicated that children who received ibuprofen had lower rates of hospitalization and significantly lower rates of outpatient visits for asthma compared with children assigned to receive acetaminophen. In the other subanalysis of the BUFS,²² no association between treatment assignment and risk for hospitalization for asthma/bronchiolitis was detected. Despite this outcome, caution was advised on the use of ibuprofen in children predisposed to asthma, and this caution has been factored into the algorithm created in the present study. Furthermore, because children with known sensitivity to aspirin or NSAIDs were excluded from the study, the results cannot be extended to this group.

Overall, the findings of the BUFS subanalyses^{21,22} do not support the theory that ibuprofen is more likely than acetaminophen to increase the risk for acute bronchospasm in children with asthma and no history of AIA. However, there is growing evidence suggesting that acetaminophen use in children is associated with an increased risk for developing asthma and related atopic disease. Newson et al²³ reported that for each 1-g increase in per capita sales of acetaminophen in children aged 13 to 14 years, there was a significant increase in the prevalence of asthma symptoms, eczema, and allergic rhinoconjunctivitis. It also has been found that frequent use of acetaminophen during late pregnancy is not only associated with an increased risk for wheezing during early infancy in the offspring but also an increased risk for asthma,

wheezing, and other atopic diseases in school-aged children.^{24,25}

The trial by McIntyre and Hull¹⁷ was designed to reflect common practice; therefore, patients with asthma were not excluded. In the trial, 14% of the children administered ibuprofen had a primary diagnosis of wheezing and 28% had a history of asthma and/or wheezing. However, ibuprofen was not associated with an exacerbation of asthma in these children.¹⁷ In contrast, 2 children who received acetaminophen experienced wheezing—one with and another without a history of wheezing.

In adults, a positive, dose-dependent association between acetaminophen use and an increased prevalence in asthma and chronic obstructive pulmonary disease was demonstrated in a cross-sectional analysis using the Third National Health and Nutrition Examination Survey.¹³ In contrast, the investigators found that regular use of ibuprofen was associated with improved lung function.¹³ Ibuprofen has also been found to preserve pulmonary function more effectively compared with placebo in children with cystic fibrosis and mild lung disease.²⁶ It is possible to attribute the apparent protective role of ibuprofen to its ability to inhibit other modulators of inflammation, such as nuclear factor kappa, differentiating it from aspirin in relation to its anti-inflammatory mechanism.^{22,27,28}

A number of possible mechanisms for the relationship between acetaminophen, asthma, and decreased lung function have been presented. First is the link between oxidative stress and the risk for asthma and impaired lung function. Acetaminophen has been found to decrease the concentration of glutathione, an antioxidant, in the lungs; decreased levels of glutathione can result in the vulnerability of the asthmatic patient to oxidative stress.²⁹ Reactive oxygen species can trigger leukotriene release and bronchospasm, which can precipitate an adverse respiratory episode in sensitive asthmatic patients. A second, less familiar mechanism is related to the lack of inhibition of COX-2 by acetaminophen. The subsequent synthesis of PGE₂ promotes immunologic activity with a T-helper cell type 2 response, which establishes an allergic tendency in the immune response to various stimuli.²⁹ It has been suggested that the decrease in intracellular glutathione levels associated with frequent use of acetaminophen might be a risk factor for asthma morbidity.³⁰

In their literature review, Kauffman and Lieh-Lai²⁷ assert that the therapeutic benefit of ibuprofen as an

antipyretic and analgesic outweighs any putative risk for acute bronchospasm in children with asthma. However, they advise caution in children who have experienced wheezing in response to aspirin or NSAIDs. Other investigators have concurred with this view that unless there is a history of AIA, ibuprofen treatment should at least be considered in the short term, as it is as well tolerated as acetaminophen

in this population and is not likely to exacerbate asthma.^{31,32}

The algorithm, based on the findings of the 3 articles and the conclusions of the expert reviews, is presented in the **figure**. We believe this algorithm might serve as a guide to assist health care professionals in making informed decisions about ibuprofen use in the asthmatic pediatric population.

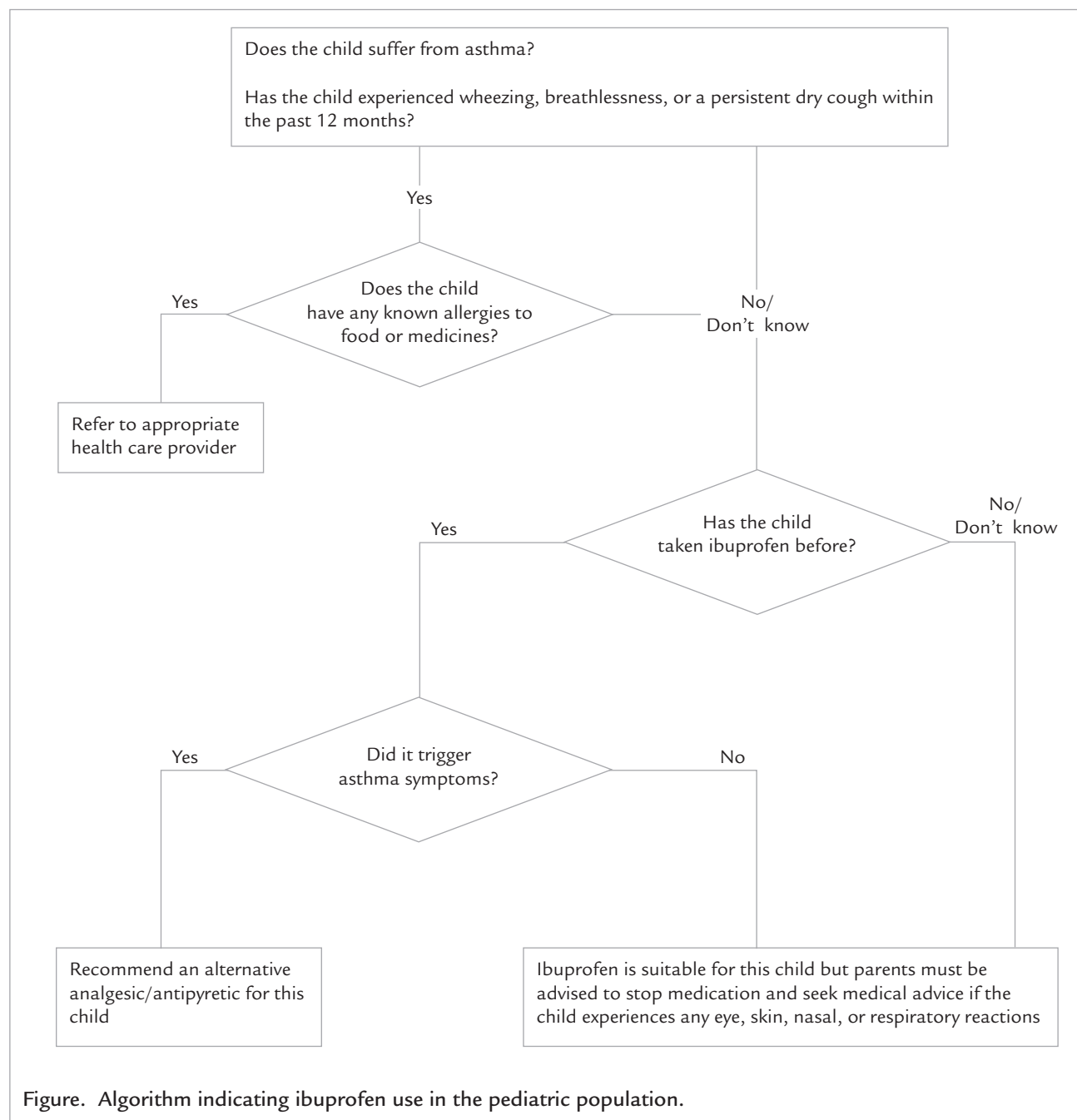


Figure. Algorithm indicating ibuprofen use in the pediatric population.

While the majority of data collated regarding the relationship between acetaminophen use and asthma are from association studies, the use of acetaminophen in the asthmatic population and by women during early pregnancy should be considered. Current evidence^{24,25} indicates a possible risk associated with acetaminophen use and asthma in children. Additional prospective studies are required to investigate any further association between acetaminophen use and the increased risk for asthma in children. Further studies are also required to evaluate the effects of chronic ibuprofen use in both asthmatic and nonasthmatic pediatric populations. These studies are of great importance, given the increasing prevalence of asthma in children and the over-the-counter availability of both drugs.

CONCLUSIONS

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.

ACKNOWLEDGMENTS

The authors would like to acknowledge Vandana Sahajpal, PhD (Sudler & Hennessey, London, United Kingdom) for medical writing and Amy Pedrick (Sudler & Hennessey) for editorial assistance.

This study was funded by Reckitt Benckiser Group Plc. Dr Dipak Kanabar is an independent advisor to Reckitt Benckiser Group Plc and has received speaker fees.

REFERENCES

1. Szczeklik A, Stevenson DD. Aspirin-induced asthma: Advances in pathogenesis and management. *J Allergy Clin Immunol.* 1999;104:5–13.
2. Widal MF, Abrami P, Lenmoyez J. Anaphylaxie et idiosyncrasie. *Presse Med.* 1922;30:189–192.
3. Ayres JG, Fleming DM, Whittington RM. Asthma death due to ibuprofen. *Lancet.* 1987;1:1082.
4. Bosso JV, Creighton D, Stevenson DD. Flurbiprofen (Ansaid) cross-sensitivity in an aspirin-sensitive asthmatic patient. *Chest.* 1992;101:856–858.
5. Chen AH, Bennett CR. Ketorolac-induced bronchospasm in an aspirin-intolerant patient. *Anesth Prog.* 1994;41:102–107.
6. Zikowski D, Hord AH, Haddox JD, Glascock J. Ketorolac-induced bronchospasm. *Anesth Analg.* 1993;76:417–419.
7. Babu KS, Salvi SS. Aspirin and asthma. *Chest.* 2000; 118:1470–1476.
8. Jenkins C, Costello J, Hodge L. Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ.* 2004;328:434.
9. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol.* 1977;60:276–284.
10. Stevenson DD. Diagnosis, prevention, and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol.* 1984;74:617–622.
11. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G, Zmuda A. Aspirin-induced asthma. Hypersensitivity to fenoprofen and ibuprofen in relation to their inhibitory action on prostaglandin generation by different microsomal enzymic preparations. *J Allergy Clin Immunol.* 1976;58:10–18.
12. Settipane RA, Schrank PJ, Simon RA, et al. Prevalence of cross-sensitivity with acetaminophen in aspirin-sensitive asthmatic subjects. *J Allergy Clin Immunol.* 1995;96:480–485.
13. McKeever TM, Lewis SA, Smit HA, et al. The association of acetaminophen, aspirin, and ibuprofen with respiratory disease and lung function. *Am J Respir Crit Care Med.* 2005;171:966–971.
14. Debley JS, Carter ER, Gibson RL, et al. The prevalence of ibuprofen-sensitive asthma in children: A randomized controlled bronchoprovocation challenge study. *J Pediatr.* 2005;147:233–238.
15. Duplantier JE. The prevalence of ibuprofen-sensitive asthma in children: A randomized controlled bronchoprovocation challenge study. *Pediatrics.* 2006;118:S34.
16. Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. *Br J Clin Pharmacol.* 2005;59:718–723.
17. McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Arch Dis Child.* 1996; 74:164–167.
18. Kadar A, Hildebrandt T, Powell C. How safe is ibuprofen in febrile asthmatic children? *Arch Dis Child.* 2004;89: 885–886.
19. Shaw H, Steans A, Lott D, Jackson B. Asthma and analgesics—A treatment algorithm. British Thoracic Society Winter Meeting; December 5–7, 2001; London, United Kingdom. Abstract P99.
20. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. *JAMA.* 1995;273:929–933.
21. Lesko SM, Louik C, Vezina RM, Mitchell AA. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics.* 2002;109:e20.
22. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics.* 1999;104:e39.

23. Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: An ecological analysis. *Eur Respir J*. 2000;16:817-823.
24. Shaheen SO, Newson RB, Sherriff A, et al, for the ALSPAC Study Team. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax*. 2002;57:958-963.
25. Shaheen SO, Newson RB, Henderson AJ, et al, for the ALSPAC Study Team. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy*. 2005;35:18-25.
26. Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med*. 1995;332:848-854.
27. Kauffman RE, Lieh-Lai M. Ibuprofen and increased morbidity in children with asthma: Fact or fiction [published correction appears in *Paediatr Drugs*. 2005;7:65]? *Paediatr Drugs*. 2004;6:267-272.
28. Glibetic M, Samlalsingh-Parker J, Raykova V, et al. Group B streptococci and inducible nitric oxide synthase: Modulation by nuclear factor kappa B and ibuprofen. *Semin Perinatol*. 2001;25:65-69.
29. Eneli I, Sadri K, Camargo C Jr, Barr RG. Acetaminophen and the risk of asthma: The epidemiologic and pathophysiologic evidence. *Chest*. 2005;127:604-612.
30. Dimova S, Hoet PH, Dinsdale D, Nemery B. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol*. 2005;37:1727-1737.
31. Body R, Potier K. Non-steroidal anti-inflammatory drugs and exacerbations of asthma in children. *Emerg Med J*. 2004;21:713-714.
32. Kader A, Hildebrandt T, Powell C. How safe is ibuprofen in febrile asthmatic children? *Arch Dis Child*. 2004;89:885-886.

Address correspondence to: Dipak Kanabar, FRCPH, Consultant Paediatrician, Evelina Children's Hospital, London SE1 7EH, UK. E-mail: dipak.kanabar@gstt.nhs.uk