

Hypersensitivity to non-steroidal anti-inflammatory drugs in childhood

Sánchez-Borges M, Capriles-Behrens E, Caballero-Fonseca F.
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Pediatr Allergy Immunol 2004; 15: 376–380. © 2004 Blackwell Munksgaard

Although largely investigated in adults, the issue of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) in childhood is unsettled due to lack of sufficient data. The purpose of this study is to examine the clinical syndromes of hypersensitivity to NSAIDs in children and adolescents. We performed a review of relevant papers on cutaneous and respiratory adverse reactions triggered by NSAIDs in pediatric patients, and a recount of our own experience in 43 well-characterized NSAID-sensitive children with cutaneous reactions who were submitted to controlled oral challenges with NSAIDs and the new inhibitors of the enzyme isoform cyclooxygenase-2 (COX-2). Although it has been suggested that allergic and pseudoallergic reactions to NSAIDs in children occur rarely, their prevalence remains largely unknown due to the scarcity of studies. About 23% of NSAID-sensitive patients seen in our institutions are young patients aged 8–18 yr who more frequently develop facial angioedema as their main clinical manifestation. Most patients are atopic and show reactions to more than one drug (cross-reactors). Drugs that inhibit COX-2 with higher specificity than classic NSAIDs are better tolerated in young NSAID-hypersensitive patients.

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Key words: angioedema; aspirin; aspirin-exacerbated respiratory disease; COX-1; COX-2; cyclooxygenases; non-steroidal anti-inflammatory drugs; urticaria

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Accepted 2 December 2003

Adverse reactions to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are commonly observed in clinical practice. Two major drug patterns, which are likely mediated by different pathogenic mechanisms, have been recognized: Some individuals will react to a single chemical group (and closely related compounds) through specific IgE antibodies directed to hapten (drug) bound to a carrier protein, as described for aspirin (1), acetaminophen (2), ketorolac (3), and pyrazolones (4). This allergic reaction is thought to be involved in the production of some cases of urticaria and angioedema (5) and in systemic anaphylaxis (6).

On the other hand, there exist a group of patients who will develop adverse pseudoallergic reactions to NSAIDs of diverse chemical composition, which have in common the ability to inhibit cyclooxygenase 1 (COX-1). These crossed reactions are clinically manifested as aspirin-intolerant asthma (7), cross-reacting urticaria,

and angioedema (5) or anaphylactoid reactions (6), and are mediated by COX-1 inhibition and shunting of the arachidonic acid metabolism toward the 5-lipoxygenase pathway resulting in increased cysteinyl leukotriene release.

In patients with aspirin-intolerant asthma [aspirin-exacerbated respiratory disease (AERD), Samter's syndrome or aspirin triad], the following observations support this cyclooxygenase theory: (i) excessive production of cysteinyl leukotrienes, both basal and after aspirin challenge (8); (ii) enhanced airway responsiveness to inhaled LTE₄ (9); (iii) increased numbers of nasal submucosal inflammatory cells expressing the CysLT₁ receptor (10); (iv) increased numbers of infiltrating leukocytes expressing LTC₄ synthase in airway mucosa (11); (v) clinical tolerance to selective inhibitors of cyclooxygenase 2 (COX-2) (12).

Adverse pseudoallergic reactions due to NSAIDs have been particularly observed in

certain population subgroups such as AERD in 9–20% of adult asthmatics, and in up to 33% of asthmatics with nasal polyposis and sinusitis (7); not many epidemiological data have been published for children (0–18 yr of age). Cutaneous reactions, typically urticaria and angioedema occur in about 4% of atopic children and in only 0.3% of the population at large (13).

NSAID sensitivity has been extensively studied in adults though relatively few papers have described it in young subjects, due in part to the obvious difficulties of the ethical and methodological nature to carry out provocation tests in this patient population. We would like to review published studies about adverse allergic and pseudoallergic reactions in pediatric patients, and report data from our institutions with regard to their clinical picture, provoking pharmaceutical products and tolerance to new selective analgesic and anti-inflammatory drugs.

Respiratory reactions to NSAIDs in children

There are few studies about respiratory NSAID hypersensitivity in pediatric patients. These reactions including asthma, rhinosinusitis, and nasal polyposis are seen more often in adults with AERD. In asthmatic children, respiratory reactions to NSAIDs have ranged between 0% and 28% in different studies (Table 1).

Rachelefsky et al. observed 14 respiratory reactions in 50 asthmatic children, and identified female sex, sinusitis, and early beginning of asthma as risk factors (14). Schuhl and Pereyra observed mixed results when peak expiratory flow rates (PEFR) were measured before and after aspirin challenge in 32 children, with > 8% PEFR decrease in three patients and a mean increase of 13.9% in the group as a whole (15). It must be noticed that this is an unusual cutoff point since most investigators use a $\geq 15\%$ cutoff.

Fischer et al. studied 25 asthmatic children and found positive challenges only in four (16%), whereas provocation tests with acetaminophen were positive in two patients (8%) (16). Towns and Mellis studied the role of ASA in 29 children and observed six (21%) with respiratory reactions (17). Hussein used inhalation challenges with lysine acetylsalicylate in 75 patients and two of them (2.7%) experienced a 25% decrease of FEV1 (18). None of the 70 children challenged with diclofenac by Short et al. had respiratory adverse reactions (19). Two papers have described 20 additional cases of childhood AERD (20, 21), and risk factors such as extrinsic asthma, atopy, exercise-induced asthma, sinusitis, and urticaria have been pointed out. It must be noticed that only three of these studies used controlled oral challenges (14, 16, 17) (Table 1). Different results reported in these studies might be due to a combination of factors such as population under study, clinical picture, methods of evaluation, outcomes measured.

From the data summarized in Table 1, it can be concluded that adverse bronchial reactions to NSAIDs are present in a substantial proportion of asthmatic children. The clinical significance of this finding is uncertain since in daily practice we do not see aspirin (NSAID)-provoked asthma in children.

Cutaneous reactions to NSAIDs in children

Data for NSAID-induced cutaneous reactions in children are also scarce (Table 2). Settipane et al. reported that NSAID sensitivity prevalence in normal children is about 0.3%, similar to the rates found in adulthood (13). Ibero et al. studied 25 patients with a suspected history of food-triggered allergic symptoms by means of oral provocation with ASA, and observed a reaction rate of 7.8% (22). Botey et al. obtained a rate of

Table 1. Respiratory reactions to NSAIDs in asthmatic children

Author (year)	n	Age	Controlled challenges	Parameter tested	Positive (%)	Remarks	References
Rachelefsky et al. (1975)	50	6–18	DB	FEV1	↓14 (28)	Female sex, sinusitis, asthma before 2 yr of age	14
Schuhl and Pereyra (1979)	32	6–14	No	PEFR	↓3 (9.3)	–	15
Fischer et al. (1983)	25	8–18	DB	FEV1	↓ ASA 4 (16) ↓ Acetaminophen 2 (8)	–	16
Towns and Mellis (1984)	29	NA	SB	–	6 (21)	–	17
Botey et al. (1988)	4	–	No	–	–	Report of four cases, two atopic	20
Hussein (1989)	75	6–17	No	FEV1	↓2 (2.7)	Inhalation of lysine acetylsalicylate	18
Estrada Rodríguez et al. (1993)	16	2–14	No	–	–	Report of 16 cases; extrinsic asthma, EIA, sinusitis, urticaria	21
Short et al. (2000)	70	6–16	No	–	0 (0)	Diclofenac	19

PEFR, peak expiratory flow rate; EIA, exercise-induced asthma; ASA, aspirin; DB, double-blinded; SB, single-blinded.

Table 2. Cutaneous reactions to NSAIDs in allergic children

Author (year)	Method	n	%	Remarks	References
Ibero et al. (1982)	OPT ASA	25	7.81	History suggesting food allergy	22
Botey et al. (1984)	OPT ASA	1632	0.55	—	23
Botey et al. (1988)	OPT ASA	—	—	Report of six cases	27
De Almeida et al. (1997)	OPT ASA/acetaminophen	—	—	Report of one case sensitive to ASA and acetaminophen	28
Martín-Muñoz et al. (1999)	OPT ASA	239	4	History suggesting drug allergy	24
Capriles-Behrens et al. (2000)	Medical record	1007	4	Atopic, age dependency	25
Díaz-Jara et al. (2001)	Medical record	—	—	One patient with acute urticaria due to ibuprofen, tolerant to ASA and acetaminophen	29

OPT, oral provocation test; ASA, aspirin.

0.55% (nine patients with positive oral challenge) in a population of 1632 children attending an allergy outpatient clinic (23).

Martín-Muñoz et al. studied the role of ASA in 239 children with history suggesting drug allergy and observed a reaction rate of 4% (24), similar to the rate obtained by Capriles-Behrens et al. from the retrospective review of medical charts in 1007 atopic children (25). In such studies, other findings were: (i) NSAID hypersensitivity in childhood is often manifested as facial angioedema; (ii) this clinical picture increases progressively in frequency with age (Fig. 1), and correlates with the progression of atopic diseases ('Allergic March'), especially allergic rhinitis; (iii) atopic children are particularly at risk for cutaneous pseudoallergic reactions to NSAIDs (23, 26).

Three additional studies reported a total of eight cases of urticaria and/or angioedema due to aspirin, acetaminophen, or ibuprofen in children (27–29).

During the last few years we have studied the clinical picture of young and adult patients

attending our institutions because of cutaneous and respiratory symptoms occurring after the administration of NSAIDs. In those previously published papers (12, 30, 31), out of 186 consecutive patients with NSAID hypersensitivity confirmed by single-blind oral challenge, 43 (23.1%) are children or adolescents (mean age 14.0 ± 2.8 yr, range 8–18 yr). Twenty-four (55.8%) are males. Clinical history of atopic disease was present in 40 patients (93.0%), 20 with rhinitis (46.5%), 17 with rhinitis and asthma (39.5%), and three (6.9%) with asthma alone. Immediate-type hypersensitivity skin (prick) tests with inhalant allergens were positive in 36 out of 38 patients (94.7%).

History and oral provocation tests carried out as previously described (5) showed that 37 patients (86.0%) were cross-reactors and six (13.9%) were single reactors. The clinical pattern was cutaneous (urticaria, angioedema, rash) in 31 patients (72.0%) and mixed (cutaneous and respiratory) in 12 (27.9%).

Drugs implicated in the reactions observed in this group of patients were: aspirin in 31, ibuprofen in 23, dipyrone in 21, acetaminophen in 14, diclofenac in eight, nimesulide in three, piroxicam in two, ketoprofen in one, and naproxen in one.

Tolerance to preferential and specific COX-2 inhibitors in NSAID-sensitive children

In adults intolerant to aspirin and other NSAIDs with respiratory and cutaneous reactions, it has been demonstrated that the new selective drugs that inhibit cyclooxygenase-2 are better tolerated than the classic NSAIDs that inhibit both COX-1 and COX-2 enzyme isoforms (12). We have performed controlled oral challenges with five different COX-2 inhibitors in the 43 NSAID-hypersensitive children described above (Table 2). Cumulative drug doses were: nimesulide 100 mg, meloxicam 15 mg, rofecoxib 50 mg, celecoxib 200 mg, and valdecoxib 40 mg.

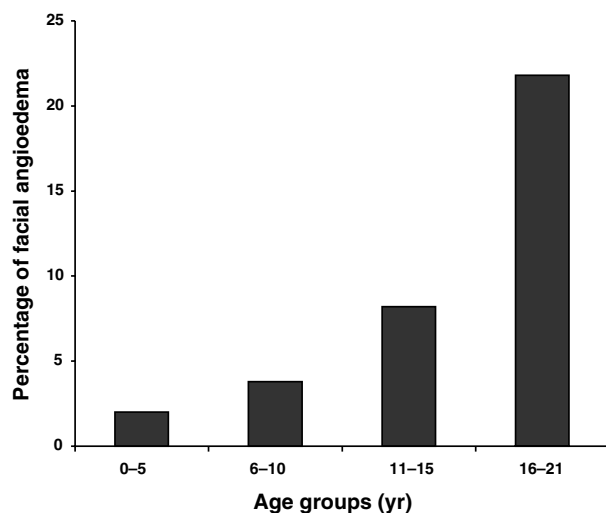


Fig. 1. Age dependence of facial angioedema induced by NSAIDs in atopic children (see ref. 25).

Table 3. Cutaneous reaction rates to COX-2 inhibitors in NSAID-sensitive children

Drug	Number challenged	Patients with positive challenges	%	p value*
Non-selective, NSAIDs	46	46	100.0	—
Nimesulide	21	3	14.2	0.0001
Meloxicam	11	3	27.2	0.0001
Rofecoxib	21	0	0	0.0001
Celecoxib	9	1	11.1	0.0001
Valdecoxib	13	1	7.6	0.0001

*Comparison of reaction rates to non-selective NSAIDs and to COX-2 inhibitors, chi-square test.

Results of such provocation tests are presented in Table 3 where it can be seen that eight patients reacted to COX-2 inhibitors with urticaria and/or angioedema. The lowest reaction rates were seen with the drugs that show higher specificity for COX-2, rofecoxib and valdecoxib. These results are similar to data from adult patients, and in our view the better tolerance to these coxibs for all age groups may be based in their higher COX-2 selectivity observed *in vitro* (32, 33).

Concluding remarks

There is a scarcity of data regarding NSAID hypersensitivity in young populations in spite of a progressive increase in NSAID consumption all over the world for pain or fever, among other uses. Although there is insufficient data concerning NSAID hypersensitivity in childhood, some conclusions may be drawn at this time. First, since atopic diseases are on the increase worldwide and atopic and asthmatic children appear to be one of the risk subgroups for cutaneous or respiratory reactions to NSAIDs, more studies are required in order to provide better care for children with this clinical condition. The emergence of new NSAIDs (COX-2 inhibitors) make it imperative that data for children and young adults be collected prospectively.

Retrospective epidemiological data and reports from the literature suggest that hypersensitivity cutaneous reactions occur more frequently in certain areas of the world in atopic populations and the drugs responsible have a country use bias.

References

1. BLANCA M, PEREZ E, GARCIA JJ, et al. Angioedema and IgE antibodies to aspirin: a case report. *Ann Allergy* 1989; 62: 295–8.
2. GRANT JA, WEILER JM. Report of a rare immediate reaction after ingestion of acetaminophen. *Ann Allergy Asthma Immunol* 2001; 87: 227–9.
3. SCALA E, GIANI M, PIRROTTA L, et al. Selective severe anaphylactic reaction due to ketorolac tromethamine without non steroidal anti-inflammatory drug intolerance. *J Allergy Clin Immunol* 2001; 107: 557.
4. KOWALSKI ML, BIENKIEWICZ B, WOSZCZEK G. Diagnosis of pyrazolone drug sensitivity: clinical history versus skin testing and *in vitro* testing. *Allergy Asthma Proc* 1999; 20: 347–52.
5. SÁNCHEZ-BORGES M, CAPRILES-HULETT A, CABALLERO-FONSECA F. Cutaneous reactions to aspirin and non-steroidal anti-inflammatory drugs. *Clin Rev Allergy Immunol* 2003; 24: 125–35.
6. BERKES EA. Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. *Clin Rev Allergy Immunol* 2003; 24: 137–48.
7. FAHRENHOLZ JM. Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol* 2003; 24: 113–24.
8. CHRISTIE PE, TAGARI P, FORD-HUTCHINSON AW. Urinary leukotriene E₄ concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. *Am Rev Respir Dis* 1991; 143: 1025–9.
9. ARM JP, O'HICKEY SP, SPUR BW, LEE TH. Airway responsiveness to histamine and leukotriene E₄ in subjects with aspirin-induced asthma. *Am Rev Respir Dis* 1989; 140: 148–53.
10. SOUSA AR, PRIKH A, SCADDING G. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* 2002; 347: 1493–9.
11. COWBURN AS, SLADEK K, SOJA J. Overexpression of leukotriene C₄ synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998; 101: 834–46.
12. SÁNCHEZ-BORGES M, CAPRILES-HULETT A, CABALLERO-FONSECA F. How safe are COX-2 inhibitors in NSAID-sensitive subjects with cutaneous reactions? *Allergy Clin Immunol Int* 2003; 15: 110–13.
13. SETTIPANE RA, CONSTANTINE HP, SETTIPANE GA. Aspirin intolerance and recurrent urticaria in normal adults and children. Epidemiology and review. *Allergy* 1980; 35: 149–54.
14. RACHELEFSKY GS, COULSON A, SIEGEL SC, STIEHM ER. Aspirin intolerance in chronic childhood asthma: detected by oral challenge. *Pediatrics* 1975; 56: 443–8.
15. SCHUHL JF, PEREYRA JG. Oral acetylsalicylic acid (aspirin) challenge in asthmatic children. *Clin Allergy* 1979; 9: 83–8.
16. FISCHER TJ, GUILFOILE TD, KESARWALA HH, et al. Adverse pulmonary responses to aspirin and acetaminophen in chronic childhood asthma. *Pediatrics* 1983; 71: 313–18.
17. TOWNS SJ, MELLIS CM. Role of acetyl salicylic acid and sodium metabisulphite in chronic childhood asthma. *Pediatrics* 1984; 63: 631–7.
18. HUSSEIN A. The incidence of analgesics intolerance in asthmatic children detected by history and inhalation challenge with lysine acetylsalicylate. *Klin Padiatr* 1989; 201: 1–5.
19. SHORT JA, BARR CA, PALMER CD, GODDARD JM, STACK CG, PRIMHAK RA. Use of diclofenac in children with asthma. *Anaesthesia* 2000; 55: 334–7.

20. BOTEY J, NAVARRO C, MARIN A, ESEVERRI JL. Aspirin-induced asthma in children. *Allergol Immunopathol* 1988; 16: 145–9.
21. ESTRADA RODRIGUEZ JL, FLORIDO LOPEZ JF, BELCHI HERNANDEZ J, et al. Asthma in children and ASA intolerance. *J Invest Allergol Clin Immunol* 1993; 3: 315–20.
22. IBERO M, ESEVERRI JL, BARROSO C, BOTEY J. Dyes, preservatives and salicylates in the induction of food intolerance and/or hypersensitivity in children. *Allergol Immunopathol* 1982; 10: 263–8.
23. BOTEY J, IBERO M, MALET A, MARIN A, ESEVERRI JL. Aspirin-induced recurrent urticaria and recurrent angioedema in non-atopic children. *Ann Allergy* 1984; 53: 265–7.
24. MARTIN-MUÑOZ F, MORENO-ANCILLO A, DOMINGUEZ-NOCHE C, et al. Evaluation of drug-related hypersensitivity reactions in children. *J Invest Allergol Clin Immunol* 1999; 9: 172–7.
25. CAPRILES-BEHRENS E, CAPLIN J, SÁNCHEZ-BORGES M. NSAID facial angioedema in a selected pediatric atopic population. *J Invest Allergol Clin Immunol* 2000; 10: 277–9.
26. SÁNCHEZ-BORGES M, CAPRILES-HULETT A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000; 84: 101–6.
27. BOTEY J, NAVARRO C, AULESA C, MARIN A, ESEVERRI JL. Acetyl salicylic acid-induced urticaria and/or angioedema in atopic children. *Allergol Immunopathol* 1988; 16: 43–7.
28. DE ALMEIDA MA, GASPAR AD, CARVALHO FS, NOGUEIRA JM, PINTO JE. Adverse reactions to acetaminophen, ASA, and NSAIDs in children: what alternatives? *Allergy Asthma Proc* 1997; 18: 313–18.
29. DIAZ-JARA M, PÉREZ-MONTERO A, GRACIA-BARA MT, CABRERIZO S, ZAPATERO L, MARTINEZ-MOLERO MI. Allergic reactions due to ibuprofen in children. *Pediatr Dermatol* 2001; 18: 66–7.
30. SÁNCHEZ-BORGES M, CAPRILES-HULETT A, CABALLERO-FONSECA F. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001; 87: 201–4.
31. SÁNCHEZ-BORGES M, CAPRILES-HULETT A, CABALLERO-FONSECA F. Valdecoxib is a safe alternative drug for NSAID-sensitive patients with cutaneous reactions. *J Allergy Clin Immunol* 2003; 111: S171 (Abstract).
32. OUELLET M, RIENDEAU D, PERCIVAL MD. A high level of cyclooxygenase-2 inhibitor selectivity is associated with a reduced interference of platelet cyclooxygenase-1 inactivation by aspirin. *Proc Natl Acad Sci USA* 2001; 98: 14583–8.
33. WALKER MC, KURURBAIL RG, KIEFER JR, et al. A three-step kinetic mechanism for selective inhibition of cyclo-oxygenase-2 by diarylheterocyclic inhibitors. *Biochem J* 2001; 357: 709–18.