

Amale HASSANI¹
Claude PONVERT²
Chantal KARILA²
Muriel LE BOURGEOIS²
Jacques DE BLIC²
Pierre SCHEINMANN²

¹ Pediatric Service: Military Hospital
Mohamed V, Rabat-Salé, Morocco
² Paris V University: Department of
Pediatrics, Pulmonology & Allergy Unit,
Sick Children's Hospital: 149 rue de Sèvres,
75015, Paris, France

Reprints: C. Ponvert
<claude.ponvert@nck.aphp.fr>

Hypersensitivity to cyclooxygenase inhibitory drugs in children: a study of 164 cases

Hypersensitivity to cyclooxygenase (COX) inhibitors is rare in children. We studied 164 children reporting 213 reactions to paracetamol, ibuprofen and/or acetylsalicylic acid (ASA). Most reactions were cutaneous, either isolated or associated with respiratory symptoms and/or anaphylaxis. Based on a convincing clinical history or positive responses in challenges with the drug(s), hypersensitivity to one or several drug(s) was diagnosed in 49.4% of the children (60, 76.5 and 23.2% of the children reporting reactions to ASA, ibuprofen and paracetamol respectively). Cross-reactivity between nonsteroidal anti-inflammatory drugs (NSAIDs) was frequent (69.1%), but only 10.6% of the NSAID-sensitive children reacted to paracetamol. In contrast, all paracetamol-sensitive children reacted to NSAIDs. Anaphylaxis, immediate and accelerated reactions, atopy, older age and chronic/recurrent urticaria were risk factors for hypersensitivity and/or cross-reactivity between ASA, ibuprofen and paracetamol. In conclusion, hypersensitivity to COX inhibitors was frequent, especially in children reporting severe and/or immediate and accelerated reactions, and in older and atopic children. Cross-reactivity was frequent, suggesting that most reactions resulted from a non allergic hypersensitivity linked to the pharmacological properties of the drugs. However, in a few children, the reactions may result from allergic hypersensitivity to selective (families of) drugs, with tolerance to other drugs.

Key words: acetylsalicylic acid, children, cyclooxygenase inhibitors, drug hypersensitivity, ibuprofen, non steroidal anti-inflammatory drugs, paracetamol

Article accepted on 2/4/2008

Three to 15% of hospitalized and outpatients report suspected hypersensitivity (HS) to drugs and biological substances [1, 2]. The most frequently suspected drugs are anti-infectious drugs (40-70%) and cyclooxygenase (COX) inhibitors (non-opioid analgesics, antipyretics and nonsteroidal anti-inflammatory drugs) ($\approx 20\%$) [1, 3]. According to the revised nomenclature for allergy [4], these reactions should be called hypersensitivity reactions, either allergic when they involve specific antibodies and/or T cells, or non allergic when specific immunological mechanisms are not involved or cannot be proven.

Although COX inhibitors are widely used in clinical practice, the prevalence of suspected HS to these drugs is low (0.3-1%) in the general population [5, 6]. Patients with chronic urticaria or asthma and atopic patients [5-8] are at higher risk for non allergic HS to COX inhibitors than other patients. Hypersensitivity to these drugs is probably less frequent in children than in adults. In the randomized prospective study of Lesko *et al.* [9], in 27,000 children younger than two years old, all the children tolerated prolonged treatments with paracetamol (acetaminophen) and ibuprofen. In the study of Martin-Munoz *et al.* [10], only

10% of the children with suspected drug HS reported reactions to COX inhibitors. In another study, HS to COX inhibitors was suspected in only 2% of 754 adverse reactions to drugs occurring in hospitalized children [11].

The most frequently reported reactions are cutaneous, especially urticaria and/or angioedema, rhinitis and/or asthma. Anaphylaxis and potentially severe toxicodermas are rare. In 260 children and adults with suspected HS to COX inhibitors, 61.5% of the patients reported urticaria and/or angioedema, and 24.2% rhinitis and/or asthma. Unidentified skin reactions were reported by 10.8% of the patients, and anaphylaxis accounted for only 3.5% of the reactions [12]. Thirty-five per cent of 17 children with suspected HS to COX inhibitors reported urticaria and/or angioedema (facial oedema especially), 35.3% pruritus and/or unidentified skin reactions, 23.5% asthma, and 5.9% anaphylaxis [11]. Finally, in another study, all the children with proven non allergic HS to COX inhibitors reported facial oedema, 38% generalized urticaria, and 42% respiratory symptoms [13]. In studies based on skin tests, *in vitro* tests and challenge tests, 13 to 50% of the patients with suspected HS to COX inhibitors were diagnosed as hypersensitive to these drugs [10, 12, 14, 15]. Hypersensitivity to COX inhibitors was

diagnosed more frequently in patients with anaphylactic and/or immediate reactions than in the other patients [15]. In a few patients, the reactions may result from immediate or non immediate allergic HS, with positive responses in *in vivo* and/or *in vitro* tests to a specific family and tolerance to other families of COX inhibitors [16-21]. However, most reactions result from a non-allergic HS, as suggested by a high degree (25-100%) of cross-reactivity between the various structurally unrelated families of NSAIDs, and 2-83% of cross-reactivity with drugs with a low COX-1 inhibitory activity, such as paracetamol, nimesulide and coxibs [13, 15, 22-25].

Only a few studies have been performed selectively in children with suspected or proven HS to COX inhibitors [10-13, 22-24]. We studied 164 children reporting suspected HS to commonly used COX inhibitors (paracetamol, ibuprofen and acetylsalicylic acid). The aims of this study performed in the pediatric pulmonology and allergy service of the Sick Children's Hospital (Paris, France) were to determine the clinical characteristics and risk factors for HS to these drugs in children.

Patients and methods

Patients

We studied 164 children (102 M + 62 F), mean age 7.2 ± 4.2 years (range: 7 mths-17.3 yrs), reporting 213 reactions to COX inhibitors between 1993 and 2004. The demographic characteristics of the children are indicated in *table 1*.

The initially suspected drugs were acetylsalicylic acid (ASA, n = 106), ibuprofen (n = 64), and paracetamol (n = 43). Forty-nine (29.8%) children reported several reactions to a single or several drugs. A previous known exposure to the suspected drug(s) was reported in only 23 (14%) of the children. Other drugs or biological substances

(antibiotics, vaccines, etc.) were also suspected to be a possible cause of the reaction in 79 cases.

The reactions (*table 2*) were classified according to their nature, severity and chronology. The reactions occurring less than 1h, between 1 and 48 h, and more than 48 h after the beginning of the treatment were classified as immediate, accelerated and delayed, respectively [26]. Most children reported immediate and accelerated reactions, and most reactions were cutaneous, either isolated (n = 129, 61%) or associated with respiratory symptoms (n = 33, 15.6%) and shock (n = 24, 11.4%). Isolated respiratory symptoms (rhinitis, cough, asthma) and conjunctivitis were exceedingly rare. Children reporting several reactions were classified on the basis of their more severe and/or rapid reaction.

Diagnosis

Diagnosis was based on a convincing clinical history (recurrent and/or anaphylactic or immediate or accelerated reactions to isolated administrations of COX inhibitors) or on positive response to oral challenge (OC) with the suspected drug(s). OC tests were performed in the hospital under strict supervision, during 24 h (immediate reactions) or 48-72 h (non-immediate reactions), after informed consent of the parents. Children received a first dose of 1 or 10 mg of the drug, based on the severity of the reaction. The dose was increased gradually, with a 20 mn interval between each dose, until the appropriate cumulative dose per day for age and weight was reached. The second and third days, the children received half the therapeutic dose at 9 A.M. and 12, and were supervised for a possible reaction until 17-18 h. OC were performed at least with another one COX inhibitor in children with a convincing clinical history of HS or a positive OC to a single drug (i.e. paracetamol in children reacting to ibuprofen and/or ASA, or ASA and/or ibuprofen in children reacting to paracetamol), except for the children with a known tolerance to these drugs since

Table 1. Demographic characteristics of 164 children with suspected hypersensitivity to COX inhibitors

Number and sex	164 (102 M, 62 F)
Age	Mean = 7.2 yrs (range: 7 mths-17.3 yrs)
Time between the (last) reaction and work-up	Mean = 8 mths (range: 4-20 mths)
Familial history of atopy	85 (52%)
Personal atopy	102 (62%)
Previous known exposure to the suspected drug	23 (14%)
Suspected allergic reactions to other drugs	60 (37%)

Table 2. Clinical characteristics of 213 suspected allergic reactions to COX inhibitors reported by 164 children

Type and chronology of the reactions	Immediate (≤ 2 h)	Accelerated (≤ 48 h)	Delayed (> 48 h)	Total: n (%)
Isolated urticaria and/or angioedema	45	69	15	129 (61%)
Cutaneous + respiratory symptoms	16	7	10	33 (15.6%)
Anaphylactic shock ($\pm$ skin and/or respiratory symptoms)	18	6	0	24 (11.4%)
Isolated rash	6	7	3	16 (7.5%)
Isolated respiratory symptoms (rhinitis, cough, asthma)	0	10	0	10 (4.3%)
Isolated conjunctivitis	0	1	0	1 (0.5%)
Total	85 (40.1%)	100 (46.7%)	28 (13.2%)	213 (100%)

their suspected allergic reaction. One hundred and thirty-nine OC were performed (ASA: 83, ibuprofen: 44, and paracetamol: 12). Challenges were classified as positive if an objective adverse reaction (*e.g.* urticaria and/or angioedema, conjunctivitis, rhinitis and/or asthma) occurred during or within 24 to 48 hours of the end of the challenge. Diagnosis of HS to other drugs or biological substances was based on positive immediate, semi-late or late responses in skin tests (betalactams, vaccines) and challenge with the suspected drugs or biological substances, as previously reported [27, 28]. Familial and personal atopy was determined by means of anamnesis (known history of atopic dermatitis, food allergy, allergic rhinitis/rhinoconjunctivitis and asthma) and/or prick-tests with common aeroallergens and/or foods, and serum specific IgE determinations.

Statistical analysis

The differences for quantitative data were assessed by the Student's *t* test, and the differences for qualitative data were assessed by the *Chi*² test or by the Fisher's test when the number of cases was low. A *p* value < 0.05 was considered significant.

Results

The mean time between the (last) suspected allergic reaction and the allergological work-up was 8 mths (range: 4-20 mths). Two children reporting accelerated urticaria and/or angioedema to ASA and/or ibuprofen were initially diagnosed tolerant to COX inhibitors based on negative responses in a one-day OC. However, these children reported relapses during subsequent treatments with the initially suspected drugs and were diagnosed intolerant to COX inhibitors based on positive responses in a 2-day OC performed in the hospital. Thus, HS to one or several COX inhibitors was diagnosed in 81 children (49.4%, 55 M + 26 F), based on a convincing clinical history (*n* = 36/81, 44.4%) or positive responses in OC tests (*n* = 45/81, 55.6%).

ASA hypersensitivity was diagnosed in 64 of the 106 (60%) children with suspected HS to this drug, based on a convincing clinical history (*n* = 42/64, 65.6%) or on a positive response in OC (*n* = 22, 34.4%). Ibuprofen HS was diagnosed in 49 (76.5%) of the 64 children reporting reactions to this drug, based on clinical history (*n* = 40/49, 81.6%) or OC (*n* = 9, 18.4%). Paracetamol HS was diagnosed in 10 of the 43 children (23.2%) with suspected HS to this drug, based on clinical history (*n* = 8/10, 80%) or OC (*n* = 2, 20%). In OC, the mean reactogenic dose was 9 mg/kg (range: 0.9-21.8) with ASA, 9.7 mg/kg (range: 1.7-18.2) with ibuprofen, and 19.4 mg/kg (range: 3.4-37.5) with paracetamol. The mean time between the beginning of the OC and the reaction was 190 mn (range: 15 mn-24 h) with ASA, 60 mn (range: 20 mn-2 h) with ibuprofen, and 35 mn (range: 15 mn-2 h) with paracetamol.

Among the 64 children with ASA hypersensitivity, 39 (61%) cross-reacted with ibuprofen (5 based on response in OC, and 34 on clinical history) and 8 (12.5%) with paracetamol (1 in OC, and 7 based on clinical history). Thirty-nine of the 49 children with ibuprofen HS (79.6%) cross-reacted with ASA (20 in OC, and 19 based on clinical history) and 4 (8%) with paracetamol (1 in OC, and 3 based

on clinical history). Thus, cross-reactivity between ASA and ibuprofen was frequent (78/113 = 69.1% *vs.* 35/113 = 30.9% of children with selective reactions to ASA or ibuprofen, *p* < 0.0001). In contrast, only 12/113 (10.6%) of the children with ASA and/or ibuprofen hypersensitivity were intolerant to paracetamol, but all the children with paracetamol HS (10/10 = 100%) were intolerant to ASA and/or ibuprofen (3 based on response in OC, and 7 on clinical history, *p* < 0.001).

Potential risk factors for HS to COX inhibitors were anaphylaxis (83.3% *vs.* 40.4% for other reactions, *p* = 0.002) and immediate and accelerated reactions (55.4% *vs.* 32.1% for delayed reactions, *p* = 0.02), personal atopy (75.3% *vs.* 49.3% in the tolerant children, *p* < 0.001), and older age (mean age = 8.2 ± 4.1 *vs.* 6.2 ± 4.0 yrs in the tolerant children, *p* = 0.003). Chronic/recurrent urticaria was reported in 11/81 (13.6%) children intolerant to COX inhibitors, ASA and/or ibuprofen especially, and 4/83 (4.8%) children tolerant to these drugs. However, the difference was not statistically significant (*p* = 0.061). Sex was not a risk factor. Cross-reactivity between COX inhibitors was more frequent in children with anaphylaxis than in the other children (50% *vs.* 20%, *p* < 0.02).

Finally, 12 (14.4%) of the 83 children diagnosed tolerant to COX inhibitors were differentially diagnosed as having allergic or non allergic HS to antibiotics (*n* = 7), DTP vaccine (*n* = 1) and miscellaneous drugs (*n* = 4).

Discussion

To our knowledge, we report the largest study performed in children with suspected HS to commonly used COX inhibitors. Most reactions were cutaneous (urticaria and/or angioedema especially), either isolated or associated with respiratory symptoms and/or anaphylaxis. Diagnosis was based on a convincing clinical history or on positive responses in OC tests. Immediate-reading skin tests and *in vitro* tests (specific IgE determination, histamine and leukotriene release tests, basophil activation test) were not performed because these tests are not standardized and because their diagnostic and predictive values are controversial [10, 16-18, 21, 29, 30]. Theoretically, several children may have been misdiagnosed as having paracetamol, ibuprofen or ASA hypersensitivity by means of clinical history only. However, according to the international guidelines, challenge tests are contra-indicated in patients with a suggestive clinical history and/or in whom the challenge may induce a severe reaction. Alternatively, challenge with other COX inhibitors are indicated to evaluate the tolerance of the COX inhibitor-sensitive patients to these alternative drugs [31, 32]. Moreover, numerous children diagnosed as having HS to a single suspected drug, based on clinical history, also reacted to one or several other COX inhibitors, based on their clinical history or on challenge tests. These results strongly suggest that the children were also sensitive to the initially suspected drug.

In this study, HS to paracetamol, ibuprofen and ASA was frequent (49.4%) in a selected population of children with suspected HS to these drugs, consistent with the results of other studies showing that 13 to 50% of patients with suspected HS to COX inhibitors have allergic or non allergic HS to these drugs [10, 12, 13, 15]. We confirm and extend the results of Kvedariene *et al.* [15], showing that

severe and/or immediate and accelerated reactions are risk factors for HS to COX inhibitors. In their study, 9 of 13 (69.2%) patients with paracetamol HS reported immediate, and 5 (38.5%) anaphylactic reactions. In our study, atopy was also diagnosed as a significant risk factor for HS to COX inhibitors, consistent with the results of other studies [7, 8, 13, 24]. In the study of Sanchez-Borges *et al.* [24], in 50 adults and children with HS to COX inhibitors, 41 patients (82%) had a personal history of atopy versus 7 (14.5%) of the control subjects. This relation between atopy and non allergic HS to COX inhibitors may result from a non specific hyperreactivity of preactivated basophils, mast cells and eosinophils, as reported in patients intolerant to ionic and hyperosmolar radiocontrast media [33]. Although the difference was not statistically significant, chronic/recurrent urticaria was also more frequent in the children intolerant to COX inhibitors than in the children tolerant to these drugs, consistent with the results of previous studies performed in adult patients [5-7]. Finally, mean age was significantly higher in the sensitive children than in the children tolerant to COX inhibitors, in agreement with the results of other studies [34].

The anti-inflammatory properties of non opioid analgesics, antipyretics and NSAIDs are related to their inhibitory activity on the cyclo-oxygenase enzymes COX-1 and COX-2. Classical NSAIDs, such as ASA and ibuprofen, are strong inhibitors of the COX-1 and weak inhibitors of the COX-2. In contrast, paracetamol, nimesulide and coxibs have low COX-1 and high COX-2 inhibitory activities [35, 36]. Most patients with NSAID hypersensitivity cross-react with other COX inhibitors, including drugs with a weak COX-1 inhibitory activity [13, 15, 22-25]. Cross-reactivity is dependent on the COX-1 inhibitory activity and the dose of the drugs. In patients with NSAID intolerance, drugs with a low COX-1 inhibitory activity may be tolerated when given at low doses, but may induce a reaction when given at higher doses [25]. In our study, two children tolerated the low doses of NSAIDs given in a one-day OC, but were intolerant to a higher cumulative dose administered in a 2-day challenge. We also showed a high degree of cross-reactivity between ASA and ibuprofen, and a 100% degree of cross-reactivity with NSAIDs in the children with paracetamol HS. Finally, only 14% of the children with suspected HS to paracetamol, ibuprofen and/or ASA had been previously treated with the suspected drug. Thus, most children had not been previously « sensitized », and their reactions could not result from allergic HS. Thus, our results strongly suggest that, in children as in adults, most HS reactions to COX inhibitors result from a non allergic HS linked to the COX-1 inhibitory activity of these drugs. However, in a few children, HS reactions may result from allergic HS to selective (families of) drugs, without cross-reactivity with structurally unrelated COX inhibitors, as previously reported [16-21].

Conclusion

We show that HS to commonly used COX inhibitors is frequent in children with suspected HS to these drugs. In most cases, the reactions are cutaneous (urticaria and/or angioedema especially), either isolated or associated with respiratory symptoms and/or anaphylaxis. We also show that the risk of HS to these drugs is significantly increased

in children reporting severe and/or immediate and accelerated reactions, in children reporting reactions to NSAIDs (ASA, ibuprofen), and in older and atopic children than in other children. Finally, our results show a high degree of cross-reactivity between the various families of COX inhibitors, and suggest that, in children as in adults, most HS reactions to COX inhibitors result from a non allergic HS linked to the COX-1 inhibitory activity of these drugs. In those children, « selective » COX-2 inhibitors, such as coxibs and nimesulide, could be interesting alternative drugs. Unfortunately, at the moment, these anti-inflammatory drugs are contra-indicated in children under the age of 12 years in most European countries. ■

Acknowledgements. Financial support: none. Conflict of interest: none.

References

1. Haddi E, Charpin M, Tafforeau M, Kulling G, Lanteaume A, Kleisbauer JP, *et al.* Atopy and systemic reactions to drugs. *Allergy* 1990; 45: 236-9.
2. Rebelo Gomes E, Demoly P. Epidemiology of drug hypersensitivity reactions. *Curr Opin Allergy Clin Immunol* 2005; 5: 309-16.
3. Hunziker T, Kunzi EP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive drug monitoring (CHDM): adverse skin reactions, a 20-year study. *Allergy* 1997; 52: 388-93.
4. Johansson SGO, Hourihane JO B, Bousquet J, Brujnzeel-Koomen C, Dreborg S, Haastela T, *et al.* A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001; 56: 813-24.
5. 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.
6. Settipane RA. Aspirin and allergic diseases: a review. *Am J Med* 1983; 74: 102-9.
7. Bochenek G, Nizankowska E, Szczeklik A. Testing for aspirin hypersensitivity. *Allergy* 2002; 57: 562-5.
8. Kalyoncu AF, Karakaya G, Sahin AA, Baris YI. Occurrence of allergic conditions in asthmatics with analgesic intolerance. *Allergy* 1999; 54: 428-35.
9. Lesko SM, Mitchell AA. The safety of acetaminophen and ibuprofen among children younger than two years old. *Pediatrics* 1999; 104: e39-e44.
10. Martin-Munoz F, Moreno-Ancillo A, Dominguez-Noce C, Diaz-Pena JM, Garcia Ara C, Boyano T, *et al.* Evaluation of drug-related hypersensitivity reactions in children. *Invest Allergol Clin Immunol* 1999; 9: 172-7.
11. Titchen T, Cranswick N, Beggs S. Adverse reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a pediatric hospital. *Br J Clin Pharmacol* 2005; 59: 718-23.
12. Schubert B, Grosse Perdekamp MT, Pfeuffer P, Raith P, Bröcker EB, Trautmann A. Nonsteroidal anti-inflammatory drug hypersensitivity: fable or reality? *Eur J Dermatol* 2005; 15: 164-7.
13. Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A, *et al.* Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal anti-inflammatory drugs among young, asian, atopic children. *Pediatrics* 2005; 116: e675-e680.
14. Asero R. Oral aspirin challenges in patients with a history of intolerance to single nonsteroidal anti-inflammatory drugs. *Clin Exp Allergy* 2005; 35: 713-6.
15. Kvedariene V, Bencherioua AM, Messaad D, Godard P, Bousquet J, Demoly P. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial. *Clin Exp Allergy* 2002; 32: 1366-9.
16. Gala G, Blanco R, Quirce S, Perez-Camo I, Alvarez-Fernandez JA, Diez-Gomez ML. Diclofenac-induced urticaria with aspirin tolerance. *Allergy* 1998; 53: 623-4.
17. Gamboa PM, Sanz ML, Caballero MR, Antépara I, Urrutia I, Jauregui I, *et al.* Use of CD63 expression as a marker of in vitro basophil activation and leukotriene determination in metamizol-allergic patients. *Allergy* 2003; 58: 312-7.

18. Grob M, Pichler WJ, Wüthrich B. Anaphylaxis to celecoxib. *Allergy* 2002; 57: 264-5.
19. Mendizabal S, Diez-Gomez ML. Paracetamol sensitivity without aspirin intolerance. *Allergy* 1998; 53: 457-8.
20. Romano A, Pietrantonio F. Delayed hypersensitivity to flurbiprofen. *J Intern Med* 1997; 241: 81-3.
21. Zhu DX, Zhao L, Mo L, Li HL. Identification and characterization of IgE reactivities to aspirin and related compounds. *J Invest Allergol Clin Immunol* 1997; 160-8.
22. Boussetta K, Ponvert C, Karila C, Le Bourgeois M, de Blic J, Scheinmann P. Hypersensitivity reactions to paracetamol in children. *Allergy* 2005; 60: 1174-7.
23. Kidon M, Kang LW, Chin CW, Hoon LS, Goh A, Poh Lin JT, et al. Hypersensitivity to paracetamol in NSAID-sensitive Asian children. *Int Arch Allergy Immunol* 2007; 144: 51-6.
24. Sanchez-Borges M, Capriles-Behrens E, Caballero-Fonseca F. Hypersensitivity to nonsteroidal anti-inflammatory drugs in childhood. *Pediatr Allergy Immunol* 2004; 15: 376-80.
25. Setticone RA, Stevenson DD. Cross-reactivity with acetaminophen in aspirin-sensitive subjects with asthma. *J Allergy Clin Immunol* 1989; 84: 26-33.
26. Levine BB. Immunological mechanisms of penicillin allergy: a haptenic model system for the study of allergic diseases in man. *N Engl J Med* 1966; 275: 1115-25.
27. Ponvert C, de Blic J, Le Clainche L, Paupe J, Scheinmann P. Allergy to betalactam antibiotics in child. *Pediatrics* 1999; 104: e45-e54.
28. Ponvert C, Karila C, Bakondé VB, de Blic J, Le Bourgeois M, Scheinmann P. Allergy to multivalent vaccines in children: a study of 30 cases using immediate, semi-late and late responses in skin tests, specific antibody determinations, and challenge with monovalent and bivalent vaccines. *Rev Fr Allergol Immunol Clin* 2001; 41: 701-11.
29. Lebel B, Messaad D, Kvedariene K, Rougier M, Bousquet J, Demoly P. Cysteinyl-leukotriene release test (CAST) in the diagnosis of immediate drug reactions. *Allergy* 2001; 56: 688-92.
30. Sanz ML, Gamboa P, de Weck AL. A new combined test with flow cytometric basophil activation and determination of sulfidoleukotrienes is useful for in vitro diagnosis of hypersensitivity to aspirin and other nonsteroidal anti-inflammatory drugs. *Int Arch Allergy Immunol* 2005; 136: 58-72.
31. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierzyńska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007; 62: 1111-8.
32. Ispano M, Fontana A, Scibilia J, Ortolani C. Oral challenge with alternative nonsteroidal anti-inflammatory drugs and paracetamol in patients intolerant to these agents. *Drugs* 1993; 46: 253-6.
33. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and non-ionic contrast media: a report from the Japanese Committee on the safety of contrast media. *Radiology* 1990; 175: 621-8.
34. Adkinson NF. Drug allergy. In: Adkinson Jr. NF, Yunginger JW, Busse WW, et al., eds. *Middleton's allergy: principles and practice*, 6th edn. Philadelphia, USA: Mosby, 2003: 1679-94.
35. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998; 104: 413-21.
36. Kato M, Nishida S, Kitasato H, Sakata N, Kawai S. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of nonsteroidal anti-inflammatory drugs: investigation using human peripheral monocytes. *J Pharm Pharmacol* 2001; 53: 1679-85.