

Diagnosis of Ibuprofen allergy through oral challenge

To the Editor,

Ibuprofen is the most commonly used non-steroidal anti-inflammatory drug (NSAID) and is the only NSAID approved for use in infants less than three months of age.¹ It is available over-the-counter for the treatment of fever, inflammation and pain, and is often prescribed to treat inflammatory conditions. Over the past decade, there has been a reported shift towards Ibuprofen consumption as an over-the-counter drug, with 70% of ibuprofen being purchased without prescription in 2015, as well as an overall increase in consumption.¹ However, there has been a paralleled increase in reports of severe adverse reactions to NSAID, such as anaphylaxis, with Ibuprofen being the most common trigger of all NSAIDs.^{1,2} Despite the obvious need, there is little research on the diagnosis and management of patients and in particular children with reported Ibuprofen reactions. We aimed to evaluate diagnosis and management of NSAID allergy in children (defined as children that are 18 years old or younger).

This cohort study, with both retrospective and prospective recruitment, took place between January 2017 and July 2019 at the Montreal Children's Hospital. All children presenting to the Montreal Children's Hospital for suspected NSAID allergy were included in this study. After obtaining parental consent, a standardized questionnaire was filled out in order to collect data on demographics, clinical characteristics and management of the suspected Ibuprofen reaction. Table 1 displays the results of these questionnaires. The treating allergist then assessed the patient and decided if they were eligible to undergo a drug provocation test (DPT) (10% and 90% of the oral dose) to the culprit NSAID. As per guidelines set by the American Academy of Allergy, Asthma and Immunology (AAAAI), controlled oral provocation with the suspected allergen was used as it is considered to be the most conclusive way to confirm a diagnosis.³ Children were observed for one hour after receiving their last dose. Parents of children who did not react were asked to contact our research team by email in case a non-immediate reaction developed. In addition, patients were contacted after 1 year to determine if subsequent use of NSAID was well tolerated. For patients that were not recruited at the time of presentation to the clinic, data were collected retrospectively through chart review. Diagnosing a positive reaction required objective symptoms such as angioedema, macular/popular rash or wheezing as previously described.⁴ Diagnosis of a delayed reaction required objective symptoms manifesting over an hour later, or the presence of arthritis. This study was approved by the McGill University Ethics Committee and followed EQUATOR reporting.

All statistical analyses were done using R version 3.5.0. (R Core Team [2013]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

Percentages with 95% confidence intervals (CI, binomial or multinomial for variables with more than two categories), were used to assess patient demographics, symptoms, severity and provocation test outcomes. Univariate and multivariate logistic regression models were compared to estimate factors associated with positive DPT to NSAIDs.

Between January 2017 and July 2019, 971 drug challenges were conducted at our center. Of these, 44 were challenges to Ibuprofen. The median age was six years old (IQR = 11.75), and approximately half (48%) were male. All had taken Ibuprofen due to fever. The majority of the reactions (70%) occurred within one hour after using the medication and nineteen children (43%) reported it had been their first exposure to Ibuprofen. The most common symptom was angioedema (54%). Nearly a third (27%) of children had symptoms consistent with anaphylaxis, which we define as an allergic reaction involving at least two organ systems. All cases of anaphylaxis received epinephrine and all cases of reaction were to Ibuprofen.

All children underwent an DPT. Of these, ten patients (22.73% [95%CI, 11.99%, 38.22%]) had a positive test. Seven of all the positive tests were immediate reactions and symptoms were consistent with anaphylaxis in five (50%). All children were challenged to Ibuprofen. Among the 30 patients with negative DPT eligible for follow-up, fifteen (50%) patients responded. Of the contacted patients, nine (60%) reported subsequent Ibuprofen use of which two patients (22.22% [95%CI, 3.95%, 59.81%]) reacted and had symptoms consistent with anaphylaxis (skin and respiratory symptoms).

A positive DPT was found to be more likely among older patients (adjusted Odds Ratio (aOR) 1.03 [95% CI 1, 1.1]) while adjusting for sex, asthma, first time use, accelerated reaction time, number of treatments given, and for family history of atopy. Our study has some potential limitations. Our sample size is relatively small, and many patients were lost to follow up.

To our knowledge, this is the largest pediatric cohort assessing NSAID allergy through DPT. Nearly 77% of cases with suspected NSAID were able to tolerate the culprit drug in challenge and 80% of those will be able to tolerate a subsequent dose in the future. This confirms the reliability of DPT as a method of Ibuprofen allergy diagnosis.

Our results are consistent with previously published reports that have reported similar rates of true NSAID allergy.^{5,6} Our study differs by looking at a pediatric population, and reactions specifically to Ibuprofen. This indicates that nearly one third of children presenting

TABLE 1 Characteristics of Patients with suspected Ibuprofen Allergy

Variable N = 44	Number of patients (%)	95% CI
Age at Ibuprofen reaction (Median, (IQR))	5.85 (3, 11.75)	
Age at Ibuprofen reaction (Mean, standard deviation)	6.90 , 4.71	
Sex (% males)	47.73%	(26.76%, 60.48%)
Culprit NSAID		
Ibuprofen	100%	
How long ago did the reaction occur		
Less than 3 mo ago	9 (20.45%)	
3-6 mo ago	7 (15.91%)	
6-12 mo ago	10 (22.72%)	
More than 12 mo ago	18 (40.91%)	
Symptoms		
Pruritis	14 (31.82%)	
Urticaria	16 (36.36%)	
Flushing	8 (18.18%)	
Rhino conjunctivitis	6 (13.64%)	
Angioedema	24 (54.55%)	
Breathing difficulties	22.73%	
Macular/papular rash	9 (20.45%)	
Erythema multiforme	3 (6.82%)	
Anaphylaxis ^a	12 (27.27%)	
How long did the reaction last		
1-3 d	37 (84.10%)	
4-7 d	5 (11.36%)	
More than 7 d	0	
Unknown	2 (4.55%)	
How long were they using the medication		
1-3 d	41 (93.18%)	
4-7 d	1 (2.27%)	
More than 7 d	0	
Unknown	2 (4.55%)	
The reaction after exposure occurred in how long after last dose		
Less than 5 m	11 (25%)	
Less than 1 h	20 (45.45%)	
Less than 8 h	6 (13.64%)	
More than 8 h	4 (9.1%)	
Unknown	3 (6.82%)	
Was it the first exposure to NSAID		
Yes	19 (43.18%)	(29.55%, 58.58%)
No	24 (54.54%)	(40.91%, 69.94%)
Where did it occur		

(Continues)

TABLE 1 (Continued)

Variable N = 44	Number of patients (%)	95% CI
At home	40 (90.91%)	
Daycare	1 (2.27%)	
Other ^b	3 (6.82%)	
Seen in the emergency room	17 (38.64%)	
Epinephrine IM	5 (29.42%)	
Antihistamines	6 (35.29%)	
SABA	1 (5.88%)	
Corticosteroids	2 (11.76%)	
Observed	5 (29.42%)	
Other ^c	2 (11.76%)	
How many did the challenge test?	44 (100%)	
Symptoms of challenge reaction (n = 10)		
Pruritis	40%	(13.69%, 72.63%)
Urticaria	20%	(3.54%, 55.78%)
Flushing	0%	(0%, 34.45 %)
Rhino conjunctivitis	30%	(8.1%, 64.63%)
Angioedema	70%	(35.56%, 91.91%)
Breathing difficulties	30%	(8.1%, 64.63%)
Macular/papular rash	0%	(0%, 34.45%)
Erythema multiforme	0%	(0%, 34.45 %)
Anaphylaxis ^a	50%	(23.65%, 76.34%)
Results of the challenge		
Positive (n = 10)	22.73%	(11.99%, 38.22%)
Patient had immediate reaction (n = 7)	70%	(35.37%, 91.91%)
Patient had delayed reaction (n = 3)	30%	(8.09%, 64.63%)
Negative challenge (n = 34)	77.27%	(61.77%, 88.01%)
Reaction consistent with anaphylaxis	50%	(18.76%, 81.24%)
Follow up (n = 15)	55.55%	(33.15%, 66.85%)
Subsequent use (n = 9)	60%	(32.89%, 82.54%)
Subsequent reaction (n = 2)	22.22%	(3.94%, 59.81%)
The child is known to have		
Asthma	11 (25%)	
Eczema	8 (18.18%)	
Other known allergies	14 (31.81%)	
Symptoms of challenge reaction		
Pruritis	23.53%	(11.38%, 41.57%)

(Continues)

TABLE 1 (Continued)

Urticaria	29.41%	(15.71%, 47.67%)
Flushing	14.71%	(5.54%, 31.83%)
Rhino conjunctivitis	14.71%	(5.54%, 31.83%)
Angioedema	61.76%	(43.62, 77.31%)
Breathing difficulties	26.47%	(13.51%, 44.65%)
Macular/papular rash	23.53%	(11.38%, 41.57%)
Erythema multiforme	8.82%	(2.30%, 24.81%)
Anaphylaxis ^a	29.41%	(15.71%, 47.67%)

Hypotension and/or involvement of two organ systems.

Hockey practice.

Tylenol.

with a reported ibuprofen allergy will have a true allergy, and should avoid the culprit drug in the future. However, the tests sensitivity seems to be limited as one patient with a negative test had a subsequent reaction upon re exposure.

Given that skin tests are non-specific and have poor predictive values, especially due to the lack of standardization for doses and procedure, it is crucial to have large scale studies assessing the properties of provocation tests in establishing NSAID allergy.⁷ Large scale studies establishing the accuracy and safety of NSAID provocation tests in children are required in order to develop appropriate management strategies of individuals with suspected NSAID allergy. Provocation tests must be performed in a safe environment under medical supervision, to minimize associated risks.^{4,8}

A risk factor found to be associated with a positive DPT to Ibuprofen was older age, which remained significant when controlling for gender, asthma and first time use, accelerated reaction time, number of treatments given and those with a family history of atopy. This could be due to the fact that, in small children viral infections can often present with symptoms resembling a drug allergy.⁹ Studies looking at the epidemiology of anaphylaxis state that older age is associated with more severe anaphylaxis, with the incidence of fatal anaphylaxis rising with increasing age.¹⁰ This may be due to sensitization to chemical compounds, or the culprit drug itself, overtime. An exposure to a chemically similar drug could also potentially sensitize the body overtime, which could increase the severity of reaction on eventual exposure. Other studies looking at hypersensitivity to all NSAIDs in children and adults commonly found older age, accelerated reaction time, anaphylaxis and parental allergy were associated with a positive DPT.⁵

Sincerely,

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REFERENCES

- de Martino M, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal. *Drugs*. 2017;77(12):1295-1311.
- Alves C, Romeira AM, Abreu C, Carreiro-Martins P, Gomes E, Leiria-Pinto P. Nonsteroidal anti-inflammatory drug hypersensitivity in children. *Allergol Immunopathol*. 2017;45(1):40-47.
- Solensky R, Khan DA, Bernstein IL, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. In press 2010;105(4):259-273.
- Mill C, Primeau MN, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr*. 2016;170(6):e160033.
- Cavkaytar O, Arik Yilmaz E, Karaatmaca B, et al. Different phenotypes of non-steroidal anti-inflammatory drug hypersensitivity during childhood. *Int Arch Allergy Immunol*. 2015;167(3):211-221.
- Nissen CV, Bindslev-Jensen C, Mortz CG. Hypersensitivity to non-steroidal antiinflammatory drugs (NSAIDs): classification of a

- Danish patient cohort according to EAACI/ENDA guidelines. *Clin Transl Allergy*. 2015;5:10.
7. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. *J Allergy Clin Immunol Pract*. 2015;136(2):245-251.
 8. Renaudin JM, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin DA. Severe druginduced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy*. 2013;68(7):929-937.
 9. Imbalzano E, Casciaro M, Quartuccio S, et al. Association between urticaria and virus infections: A systematic review. *Allergy Asthma Proc*. 2016;37(1):18-22.
 10. Yu JE, Lin RY. The epidemiology of anaphylaxis. *Clin Rev Allergy Immunol*. 2018;54(3):366-374.