Positive Yield of Autologous Plasma Skin Testing among Thai Patients with Urticaria and Angioedema due to Non-steroidal Anti-inflammatory Drugs

Kanokvalai Kulthanan, M.D.*, Sumruay Pinkaew, M.Sc.*, Leena Chularojanamontri, M.D.*, Araya Manapajon, M.D.*, Kanchalit Thanomkitti, M.D.*, Kumpol Aiempanakit, M.D.*, Rasthawathana Desomchoke, M.D.*, Kowit Jongjarearnprasert, M.Pharm.**

**Department of Dermatology, **Adverse Drug Reaction Center, Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.*

ABSTRACT

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are over-the-counter drugs which are widely used. In Thailand, cutaneous reactions to nonsteroidal anti-inflammatory drugs were frequently angioedema and urticaria. However, there are many limitations of the diagnostic investigations, so the diagnosis is still based on history and clinical manifestation. In 2007, there was a study in Italy, which reported that an autologous plasma skin test (APST) could detect autoreactive state in patients with multiple intolerances to NSAIDs.

Objective: We aimed to investigate whether APST is positive in single and multiple NSAID reactors in the Thai population or not.

Methods: The patients with recent history of urticaria and/or angioedema following the administration of NSAIDs were prospectively recruited. Individuals were classified into two groups (single or multiple NSAID reactors) based on history, clinical manifestation and/or laboratory investigation and then APST was done after at least a month free of symptoms.

Results: Of all sixty-eight patients, thirteen (19.1%) were men and fifty-five (80.9%) were women. The mean age was 42.7 ± 15.0 years (range 17-77 years). In our study, single NSAID reactors (69.1%) were more common than multiple NSAID reactors (30.9%). Multiple NSAID reactors tended to have a personal and family history of atopy (p = 0.030 and 0.012, respectively) than single reactors. APST was positive 19.0% and 10.6% in multiple and single NSAID reactors, respectively. However, there was no statistically significant relationship between positive APST and multiple NSAID reactivity (p = 0.442).

Conclusion: This study showed no statistically significant association between APST positivity and multiple NSAID reactors in Thai patients. However, our study revealed significantly higher proportions of personal and family history of atopic diathesis in multiple NSAID reactors.

Keywords: Urticaria, angioedema, autologous plasma skin testing, multiple NSAID reactor, single NSAID reactor

Siriraj Med J 2014;66:11-14
E-journal: http://www.sirirajmedj.com

INTRODUCTION

Angioedema and urticaria are the most frequent cutaneous reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) in Thailand.[1] According to the proposed classification system of allergic and pseudoallergic reactions to NSAIDs,[2,3] patients with NSAID-induced urticaria can be classified into single and multiple drug reactors. Single drug reactors are normal subjects who have reactions to only one specific NSAID. The reaction is now considered as possibly IgE-mediated,[3-5] whereas multiple drug reactors can be either normal or have underlying chronic urticaria and react to chemically unrelated substances which are most likely based on the inhibition of cyclooxygenase (COX)-1 enzyme.[3-5] Because the challenge tests are potentially harmful, the diagnosis of NSAIDs intolerance is based mainly on history and clinical manifestations.[5,6] Since immune mechanisms are not the only causes in the pathogenesis of NSAID intolerance, the determination of IgE antibodies are not

Correspondence to: Sumruay Pinkaew
E-mail: sumruay.pin@mahidol.ac.th
Received 30 April 2013
Revised 19 June 2013
Accepted 1 July 2013

always through diagnostic procedures. Other tests, such as basophil histamine release by platelet-activating factor,[5,7] determination of platelet hydrogen peroxide metabolism[8] and sulfidoleukotriene level determination[5,6] have limitations and have not been routinely used for diagnostic confirmation.

To distinguish between single and multiple NSAID reactors is valuable for patients and health care practitioners. Practically, when a patient develops urticaria or angioedema from taking one NSAID, a skin prick test (SPT) may be used to confirm single NSAID intolerance. When SPT is not available, another non selective COX inhibitor should be prescribed. If there are no signs or symptoms of urticaria or angioedema, the patient can continue taking the later prescribed drug. However, if these reactions reoccur, the drug should be changed to COX-2 inhibitors.[9,10]

It has been reported that autoreactivity is associated with multiple NSAID intolerance.[3,11] According to Asero et al., autologous serum skin test (ASST) and autologous plasma skin test (APST) can detect the autoreactive state in patients with multiple NSAIDs intolerances.[3,11] Because of the excellent negative predictive value and positive predictive value of these tests, APST might have a role in multiple NSAID reactors detection in patients who are prone to react to chemically unrelated anti-inflammatory drugs.[3] Therefore, the purpose of this study was to investigate whether APST is positive in single and multiple NSAID reactors in the Thai population or not, which may represent Asian population as a whole.

MATERIALS AND METHODS

Patients and study design

This study was approved by the ethics committee of Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University and was performed at Siriraj Hospital, a medical school and tertiary referral centre, Thailand.

Cutaneous adverse reactions from NSAIDs in patients were reported to an Adverse Drug Reaction (ADR) center by attending physicians and dermatologists. Then, experienced ADR–center pharmacists and dermatologists reviewed patients' history, clinical manifestations and laboratory investigations about adverse events and assessed the causative agents. Drug imputability was classified into six levels according to WHO-UMC guidelines.[12] Patients over 18 years old who had recent history (within 3 months) of development of acute urticaria/ angioedema or both after taking one or more NSAIDs were included, but patients with anaphylaxis were excluded. Then, individuals were classified into single NSAID reactors and multiple NSAID reactors by history of COX-1 NSAIDs administration as mentioned above.

All patients, who were at least one month free of symptoms, were informed about the process of APST and asked to stop short-acting, long-acting antihistamines and any systemic corticosteroids (equivalent to 10 mg per day of prednisolone or more) at least 3, 7 or 28 days prior to the test, respectively.

Then, they were treated with intradermal test by using 0.05 mL of fresh autologous plasma anti-coagulated with sodium citrate (APST), normal saline (negative control) and histamine 10 mg/ml (positive control) at the same time.[13]

Fresh autologous plasma was prepared from 3 mL of venous blood, kept in a sterile vacutainer (VACUETTE® coagulation tubes, Greiner Bio-One International AG; Kremsmuenster, Austria, containing 3.2% of sodium citrate) at room temperature for 15 minutes, centrifuged for 3 minutes at 1250 g, and immediately used. The results were all noted at 30 minutes after the test was performed. Only an unequivocal wheal-and-flare reaction with a wheal which had larger diameter by at least 3 mm than the negative control was considered a positive result.[14]

Statistical analysis

Data were analyzed using SPSS version 17.0. Descriptive statistics, e.g. mean, median, minimum, maximum and percentages were calculated to describe demographic data. Proportions were compared using Pearson's Chi-square test or Fisher's exact test when appropriate. *p*-value of < 0.05 was considered to be significant.

RESULTS

Sixty-eight patients with history of acute urticaria and/or angioedema following the administration of NSAIDs were recruited. Thirteen (19.1%) were men, fifty-five (80.9%) were women. The mean age was 42.7 ± 15.0 years (range 17-77 years). Table 1 shows the demographic data and clinical data of the participants. Forty-seven patients (69.1%) were classified as single NSAID reactors. Twenty-one patients (30.9%) who had reported adverse reaction to more than one type of NSAIDs were classified as multiple NSAID reactors. There was a significantly higher proportion of personal and family history of atopy in multiple NSAID reactors compared to single NSAID reactors ($p = 0.030$ and 0.012, respectively). Thirty-six cases (52.9%) presented with angioedema, 22 cases (32.4%) had both angioedema and urticaria and 10 cases (14.7%) were patients with only acute urticaria. There was no statistically significant difference in clinical presentations between single and multiple NSAID reactors. Twenty-five of 68 cases (36.8%) also had histories of adverse reaction to other drugs (beta-lactams 20.6%, tetracyclines 2.9%, macrolides 2.9%. acetaminophen 2.9%, clindamycin 1.5%, pethidine 1.5%, domperidone 1.5%, others 10.3%). Table 2 demonstrates culprit drugs involved with urticaria and/or angioedema in patients diagnosed single or multiple NSAID intolerance.

APST was positive in 4 of 21 (19.0%) multiple NSAID reactors and 5 of 47 (10.6%) single NSAID reactors. However, there was no significant difference of positive APST between single and multiple NSAID reactors ($p = 0.442$).

TABLE 1. Demographic and clinical data of patients with a history of NSAIDs intolerance classified as single or multiple NSAID reactors.

Characteristics	Single NSAID reactors (n=47)	Multiple NSAID reactors (n=21)	*p*-value
Mean age ± SD (years)	42.6±15.5	43.0±14.3	0.92
Sex (Male : Female)	8:39	5:16	0.52
Clinical presentation; No. (%)			
Urticaria	8 (17.0)	2 (9.5)	
Angioedema	25 (53.2)	11 (52.4)	0.65
Urticaria and angioedema	14 (29.8)	8 (38.1)	
Personal history of atopy; No. (%)	25 (53.2)	17 (81.0)	0.03
Family history of atopy; No. (%)	14 (29.8)	13 (61.9)	0.01
History of food allergy; No. (%)	17 (36.2)	8 (38.1)	0.88
History of other drugs reaction; No. (%)	15 (31.9)	10 (47.6)	0.22
Median onset (hours)	1	2	0.40
(min, max)	(5 min, 7 days)	(10 min, 9 days)	
Median remission (days)	1	2	0.18
(min, max)	(1 hour, 60 days)	(1 hour, 7 days)	
Treatment; No. (%)			
None	13 (27.7)	4 (19.0)	
Antihistamine only	18 (40.0)	10 (47.6)	
Corticosteriods only	2 (4.4)	0 (0.0)	0.71
Corticosteroids & antihistamine	12 (26.7)	7 (33.3)	
Positive APST; No. (%)	5 (10.6)	4 (19.0)	0.442

APST = autologous plasma skin test

DISCUSSION

Both immunological and nonimmunological reactions from NSAIDs are responsible for 25% of reported adverse drug events.[5] IgE-mediated reaction is considered to be involved in the mechanism of single NSAID-induced reactions. A previous publication proposed that underlying atopic diathesis, food allergy and drug allergy are usually present in single NSAID reactors, but not in multiple reactors.[5] Our study showed significantly higher proportions of positive personal and family history of atopy in multiple NSAID reactors. On the other hand, there were no significant differences in underlying food allergy and drug allergy between both groups. However, we found both single and multiple NSAID intolerances had more prevalence of atopy (51.1%), especially allergic rhinitis (76.2%), compared to the normal Thai population (26%).[15]

TABLE 2. Culprit drugs involved with urticaria and/or angioedema in patients diagnosed with single or multiple NSAID intolerance.

	Single NSAID reactors (n=47) No. (%)	Multiple NSAID reactors (n=21) No. (%)	Total (n=68) No. (%)
Ibuprofen	26 (55.3)	5 (23.8)	31 (45.6)
Diclofenac	6 (12.8)	5 (23.8)	11 (16.2)
Naproxen	6 (12.8)	3 (14.3)	9 (13.2)
Aspirin	1 (2.1)	4 (19.0)	5 (7.4)
Celecoxib	2 (4.3)	2 (9.5)	4 (5.9)
Loxoprofen	0 (0)	2 (9.5)	2 (2.9)
Etoricoxib	2 (4.3)	0 (0)	2 (2.9)
Floctafenine	1 (2.1)	0 (0)	1 (1.5)
Indomethacin	1 (2.1)	0 (0)	1 (1.5)
Meloxicam	1 (2.1)	0 (0)	1 (1.5)
Mefenamic acid	1 (2.1)	0 (0)	1 (1.5)

*One patient may have adverse reaction to more than one medication

Besides COX-1 inhibition, autoreactivity as demonstrated by the positive results of ASST and/or APST has been proposed to be involved in multiple drug allergy syndrome[16] and multiple NSAID intolerance.[11] Asero et al., reported the positive relation between multiple NSAID reactors and positivity of APST.[3] From their study, APST demonstrated positive results in all multiple reactors (100%) while the single reactors yielded only 3 out of 14 (21%), and the positive predictive value and negative predictive value of APST for multiple NSAID reactors were 86 and 100%, respectively. Even though our study revealed a higher proportion of positive APST in multiple NSAID reactors than single reactors (19.0% and 10.6%, respectively), there was no statistically significant association between APST positivity and multiple NSAID reactors. Even though we selected 19 patients who just recently experienced NSAID intolerance (only 1 month before) to consider, this also gave the same result.

According to a previous pharmacogenetic study of aspirin intolerance, the various drug responses and risk of developing drug intolerance were found associated with polymorphisms in drug-related enzymes and receptors.[17] Therefore, the discordance between our study

and another publication which was conducted in Italy might be explained by this pharmacogenomics condition. However, there were some limitations in our study. We found predominant cases of single NSAID reactors unlike previous reports.[18,19] This may be caused by most of the diagnosis being dependent on history directly taken from the patient, not medical record documentation. Moreover, SPT was not performed routinely to confirm the diagnosis of single NSAID reactors because it had a potential risk of anaphylaxis.[5]

In conclusion, there was no significant association between APST positivity and multiple NSAID reactors in Thai patients which may represent the general Asian population. However, our study revealed significantly higher proportions of personal and family history of atopic diathesis in multiple NSAID reactors. To distinguish single and multiple NSAID reactors is practically significant because other culprit drugs may be prescribed in single drug reactors safely. Therefore, further study about single and multiple NSAID reactors with a larger sample size, or other diagnostic tools, in Thailand is recommended.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Chulalak Komoltri of the Epidemiology Unit, Faculty of Medicine Siriraj Hospital, Mahidol University for assistance in statistical analysis.

REFERENCES

1. Kasemsarn P, Kulthanan K, Tuchinda P, Dhana N, Jongjarearnprasert K. Cutaneous reactions to non-steroidal anti-inflammatory drugs. J Drugs Dermatol. 2011 Oct;10(10):1160-7.
2. Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. Ann Allergy Asthma Immunol. 2001 Sep;87(3):177-80.
3. Asero R. Predictive value of autologous plasma skin test for multiple nonsteroidal anti-inflammatory drug intolerance. Int Arch Allergy Immunol. 2007;144(3):226-30.
4. Sanchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. NSAID-induced urticaria and angioedema: a reappraisal of its clinical management. Am J Clin Dermatol. 2002;3(9):599-607.
5. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011 Jul;66(7):818-29.
6. May A, Weber A, Gall H, Kaufmann R, Zollner TM. Means of increasing sensitivity of an in vitro diagnostic test for aspirin intolerance. Clin Exp Allergy. 1999 Oct;29(10):1402-11.
7. Okuda Y, Hattori H, Takashima T, Miyatake A, Yamatodani A, Tsuyuguchi I, et al. Basophil histamine release by platelet-activating factor in aspirin-sensitive subjects with asthma. J Allergy Clin Immunol. 1990 Oct; 86(4 Pt 1):548-53.
8. Pearson DJ, Suarez-Mendez VJ. Abnormal platelet hydrogen peroxide metabolism in aspirin hypersensitivity. Clin Exp Allergy. 1990 Mar;20(2): 157-63.
9. Sanchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). Med Clin North Am. 2010 Jul;94(4): 853-64, xiii.
10. Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Cortellini G, Nizankowska-Mogilnicka E, et al. Clinical management of patients with a history of urticaria/angioedema induced by multiple NSAIDs: an expert panel review. Int Arch Allergy Immunol. 2013;160(2):126-33.
11. Asero R, Tedeschi A, Lorini M. Autoreactivity is highly prevalent in patients with multiple intolerances to NSAIDs. Ann Allergy Asthma Immunol. 2002 May;88(5):468-72.
12. WHO-UMC. Causality Assessment of Suspected Adverse Reactions2012: Available from: http://www.who-umc.org/Graphics/24734.pdf.
13. Asero R, Tedeschi A, Riboldi P, Cugno M. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. J Allergy Clin Immunol. 2006 May;117(5):1113-7.
14. Godse KV. Autologous serum skin test v/s autologous plasma skin test. Indian J Dermatol Venereol Leprol. 2008 Sep-Oct;74(5):496-7.
15. Vichyanond P, Sunthornchart S, Singhirannusorn V, Ruangrat S, Kaewsomboon S, Visitsunthorn N. Prevalence of asthma, allergic rhinitis and eczema among university students in Bangkok. Respir Med. 2002 Jan;96 (1):34-8.
16. Asero R, Tedeschi A, Lorini M, Caldironi G, Barocci F. Sera from patients with multiple drug allergy syndrome contain circulating histamine-releasing factors. Int Arch Allergy Immunol. 2003 Jul;131(3):195-200.
17. Agundez JA, Martinez C, Perez-Sala D, Carballo M, Torres MJ, Garcia-Martin E. Pharmacogenomics in aspirin intolerance. Curr Drug Metab. 2009 Nov;10(9):998-1008.
18. Dona I, Blanca-Lopez N, Cornejo-Garcia JA, Torres MJ, Laguna JJ, Fernandez J, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011 Jan;41(1):86-95.
19. Viola M, Quaratino D, Gaeta F, Caringi M, Valluzzi R, Caruso C, et al. Celecoxib tolerability in patients with hypersensitivity (mainly cutaneous reactions) to nonsteroidal anti-inflammatory drugs. Int Arch Allergy Immunol. 2005 Jun;137(2):145-50.