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Clinical Features of Immediate Hypersensitivity to Isopropylantipyrine

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Hypersensitivities induced by isopropylantipyrine (IPA), a pyrazolone derivative within the wider family of non-steroidal anti-inflammatory drugs (NSAIDs), are rarely reported. We characterized the clinical features of 12 patients with IPA-induced hypersensitivity. Twelve patients with immediate hypersensitivity to IPA were enrolled and classified into two groups: group I, consisting of eight patients (66.7%) with selective hypersensitivity; and group II, consisting of four patients (33.3%) showing cross-intolerance to other NSAIDs. Skin prick and intradermal and oral provocation tests with IPA were performed. To confirm selective hypersensitivity, an aspirin oral provocation test was also conducted. The most common manifestations were cutaneous reactions (91.7%), followed by anaphylaxis (66.7%), respiratory (41.7%), ocular (16.7%), and gastrointestinal reactions (16.7%). The median age and the median age at onset were 34.5 (range, 23-55) years and 28.0 (range, 7-47) years, respectively. In both groups I and II, all patients showed negative responses to skin prick testing, whereas only two patients in group I were positive in response to intradermal IPA tests. The response time after drug exposure was shorter in group I than in group II. Here, we report on two types of IPA hypersensitivity: selective and cross-intolerant NSAID hypersensitivity. An immediate IgE-mediated reaction may be involved in patients with selective hypersensitivity, whereas a cyclooxygenase-1-related inhibition mechanism may be a responsible mechanism for the patients with cross-intolerance to multiple NSAIDs.

Key Words: Drug hypersensitivity; immediate hypersensitivity; isopropylantipyrine; pyrazolone

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a common cause of hypersensitivity, which may manifest more broadly as a cross-intolerance to multiple NSAIDs, or a more specific intolerance to a single drug or group of derivatives, such as the pyrazolone derivatives, including antipyrine (phenazone), 4-aminopyrine (aminophenazone), metamizol (also known as sulpyrine or dipyrone), or 4-isopropylpyrine (isopropylantipyrine or propyphenazone).[1,2] Mechanistically, the former is thought to be related to cyclooxygenase-1 (COX-1) inhibition, whereas the latter seems to depend on an allergic, IgE-mediated mechanism involving specific antibodies to the given drug or group of derivatives. In support of this, pyrazolone-specific IgE has been reported in serum.[1,3]

In the United States and Europe, hypersensitivity to the pyrazolone derivative isopropylantipyrine (IPA) is rare in recent years, likely due to the relatively low consumption of this drug. In Korea, however, IPA is widely prescribed as an additional component of various other NSAIDs, which are administered in a single tablet with caffeine and dimethylaminoethanol bitartrate. There have been two reports of selective hypersensitivity to IPA in Korea.[4,5] Urticaria, angioedema, and/or anaphylaxis are the most common symptoms in patients with IPA hypersensitivity.[6] Diagnosis is based on the patient's history of clinical symptoms, an intradermal skin test if possible, and/or an oral provocation test.

Here, we report the clinical characteristics of immediate hypersensitivity to IPA and compared among patients with selective hypersensitivity to IPA and individuals with cross-intolerance to NSAIDs.

MATERIALS AND METHODS

We enrolled twelve patients who presented with immediate

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hypersensitivity reactions to IPA, and this sensitivity was confirmed through an IPA oral challenge test. Patients were classified into two groups depending on the presence of hypersensitivity to other NSAIDs. Group I included eight patients with selective hypersensitivity to IPA, and group II included four patients with cross intolerance to other NSAIDs, which was confirmed through an aspirin oral provocation test.

Skin tests with solutions of IPA dissolved in 50% alcohol were performed in two stages: 1) skin prick test (SPT); and 2) if SPT showed a negative result, intradermal test (IDT) were done. For SPT, 2 mg/mL IPA solution was used; if it showed a negative result after 15 minutes, a second SPT was performed using 20 mg/mL IPA. If second SPT showed a negative result, IDT with 2 mg/mL and 20 mg/mL solutions were performed. The result of SPT was presented as the wheal ratio to histamine which was used as positive control. If this ratio was higher than 1, it was considered as a positive result. For IDT, wheal reaction was larger than 3 mm in diameter with associated flare was considered a positive result.[4,6,7]

Serum specific IgE antibodies against *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* and total IgE were measured using the CAP system (Pharmacia-Upjohn, Uppsala, Sweden). Clinical parameters, such as gender, age, onset age, atopy, response time after exposure, time interval, underlying allergic disorder, and other NSAID allergies were recorded for each patient.

RESULTS

Of the 12 enrolled patients, 10 (83.3%) were female and eight (66.7%) were atopic. Their median age was 34.5 (range, 23-55) years. Group II showed cross-intolerance to aspirin and other NSAIDs, such as ketoprofen and acetaminophen, as well as IPA hypersensitivity (Table 1). The most common clinical manifestations were urticaria and/or angioedema (91.7%), followed by anaphylaxis (66.7%), respiratory reactions (41.7%), ocular reactions (16.7%), and gastrointestinal reactions (16.7%; Tables 1 and 2). The median age at onset and the median time to develop symptoms after exposure to the drug were 28.0 (range, 7-47) years and 0.8 (range, 0.1-3) hours, respectively. Eleven (91.7%) of the patients had a past history of allergic diseases other than drug allergy; common comorbidities included allergic rhinitis (75.0%), bronchial asthma (41.7%), urticaria (25.0%), food allergy (16.7%), and eosinophilic bronchitis (8.3%). Among the patients evaluated *in vivo*, two patients from group I showed a positive IPA intradermal test result, whereas no patient from

Table 2. Comparison of clinical parameters between group I and II

	Group I (n=8)	Group II (n=4)	*P* value†
Female (%)	6 (75.0)	4 (100)	0.515
Age*	29.5 [23-55]	36.0 [34-46]	0.395
Onset age*	28.0 [7-47]	34.0 [24-40]	0.170
Response time after exposure* (hr)	0.5 [0.1-1.0]	1.8 [1.0-3.0]	0.009‡
Atopy	5 (62.5)	3 (75.0)	>0.99
Cutaneous manifestation only (U, A)	3 (37.5)	1 (25.0)	>0.99
Anaphylaxis	5 (62.5)	3 (75.0)	>0.99
Total IgE (KU/L) *	102.0 [8-1125]	106.0 [31-149]	0.895

Data were presented as n (%) or *Median [min-max].
†*P* value is measured by *Mann-Whitney analysis or Fisher's Exact test, ‡*P*<0.05.

Table 1. Clinical characteristics of study subjects

Patient	Sex (M/F)	Age	Atopy	Allergic disease	Manifestation	Response time (hr)	Onset age (yr)
Group I							
1	F	31	+	AR, AC	A	1	28
2	M	23	+	AR, BA	U, A, R, ANA	0.6	7
3	F	55	+	AR, BA, AU, FA	U, A	0.5	47
4	F	39	-	NAR	U, A	0.5	29
5	F	48	-	NAR, AD, AC, CU	U, A, R, ANA	0.1	28
6	F	26	-	FA	U, ANA	0.5	19
7	M	28	+		U, R, ANA	0.5	28
8	F	23	+	AR, EB	U, A, GI, ANA	1	21
Group II							
9	F	46	+	AR, BA	A	2	40
10	F	35	+	CU	U, A, R, ANA	1	34
11	F	34	-	NAR, NBA	R, GI, ANA	3	24
12	F	37	+	AR, BA	U, A, R, ANA	1.5	34

+: The subjects with atopic tendency, -: The subjects without atopic tendency.
AR, allergic rhinitis; AC, allergic conjunctivitis; A, angioedema; BA, bronchial asthma; U, urticaria; R, dyspnea; ANA, anaphylaxis; AU, acute urticaria; FA, food allergy; NAR, non-allergic rhinitis; AD, atopic dermatitis; CU, chronic urticaria; EB, eosinophilic bronchitis; GI, abdominal discomfort; NBA, non-allergic asthma.

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group II was positive in the IPA intradermal test.

When the clinical parameters of groups I and II were compared, response time after exposure was significantly shorter in group I than in group II (0.6 vs. 1.9 hours, P=0.008), whereas the remaining parameters were not significantly different (Table 2).

DISCUSSION

In Korea, the prevalence of adverse reactions to IPA was reported at 4%, based on an adverse drug reaction database in an university hospital, which was higher than those of diclofenac, ibuprofen, and dexibuprofen except aspirin (2.5, 1.9, 1.2%, and 5.7 respectively).[8] In Europe, the aspirin hypersensitivity affects at 0.5 to 1.9% of general population and 10 to 20% of adult asthmatics, however, that of IPA has not been reported recently.[9,10] This may be due to disparities in the patterns of consumption and exposure rates over time and from country to country.[11] A change in NSAID consumption, characterized by an increased consumption of propionic acid derivatives and decreased consumption of pyrazolone derivatives, has occurred in Europe,[7] but IPA is still prescribed in Korea. Pyrazolone derivatives, including IPA, are one of the most common causes of selective hypersensitivity, comprising 60% of IPA hypersensitivity patients.[12,13] Patients with a genetic predisposition due to the HLA-DQ7 and -DR11 haplotypes may develop a specific IgE response to this drug.[2] HLA Class II alleles are expressed as highly polymorphic molecules on the cell surface, and play a crucial role in antigen presentation to CD4+ T cells and in regulating the IgE-mediated immune response. Positive associations between HLA antigens and specific IgE responses may reflect more efficient presentation of a particular antigen to T helper cells, thus promoting T cell switching to Th2 lymphocytes and a specific IgE response.[2] Based on these findings, IPA may be a cause of selective hypersensitivity in Korea.

This study described that middle-aged females with selective hypersensitivity were the predominant demographic group, which is comparable to the result of other study.[13] A previous study showed that anaphylaxis was more frequent in the selective hypersensitivity group;[7] however, anaphylaxis occurred in 66.7% of such individuals in this study and no differences in clinical manifestations were observed between groups I and II. A recent review reported two types of NSAID-induced hypersensitivity reactions: single NSAID-induced reactions associated with an IgE-mediated response, and multiple NSAID-induced reactions associated with COX-1 inhibition.[10] In this study, two group I patients showed a positive IDT response to IPA. Symptom onset time after IPA exposure was earlier in group I patients (0.5 vs 1.8 hours). Most immediate onset reactions of dug hypersensitivity if they are mediated by IgE mediated response occur within 1 hour, however, NSAID hypersensitivity reactions commonly occur after 1 hour as they are mediated by COX-1 inhibition, not IgE mediated response. Although we could not demonstrate the presence of serum specific IgE to IPA in this study, we may suggest that an IgE mediate reaction as pathogenic mechanism of group I, while COX-1 inhibition is the major mechanism of group II as suggested in the previous report.[3]

The oral provocation test remains the gold standard for confirmative diagnosis of IPA hypersensitivity.[14] The aspirin oral provocation test is useful for confirming that a patient belongs to the selective or cross-intolerant group.[7] Both a skin test and serum specific IgE measurement are necessary *in vivo* and *in vitro* tests, respectively, for selective hypersensitivity. Two studies reported positive responses to the skin test and high serum specific IgE to pyrazolone in patients with pyrazolone hypersensitivity;[1,3] however, this has not been confirmed in more recent reports. Skin prick test sensitivity (15%-50%) was insufficient to predict sensitization or risk of systemic response.[15] The basophil activation test has been proven adequate; however its sensitivity was 50% in cases with selective hypersensitivity to pyrazolone, and only 15% in patients cross-intolerant to NSAIDs.[16] These findings suggest that an IgE-mediated mechanism may be involved in selective IPA hypersensitivity, although we could not confirm the presence of serum specific IgE antibody using *in vitro* tests. Therefore, patients experiencing one or more reactions to the same drug, and in whom tolerance to a strong COX-1 inhibitor is unknown, should undergo an oral provocation test with a strong COX-1 inhibitor (*e.g.*, aspirin).[13] The confirming diagnosis can prevent patients from avoiding all kinds of NSAID.

In conclusion, we report two types of IPA hypersensitivity: selective sensitivity and cross-intolerance. An IgE-mediated immediate reaction may be involved in patients with selective hypersensitivity, whereas COX-1 inhibition may be a responsible mechanism for the patients with cross-intolerant hypersensitivity to multiple NSAIDs.

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