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Cross-reactivity to Acetaminophen and Celecoxib According to the Type of Nonsteroidal Anti-inflammatory Drug Hypersensitivity

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Purpose: Identification of tolerable alternative analgesics is crucial for management in nonsteroidal anti-inflammatory drug (NSAID)-sensitive patients. We investigated cross-reactivity of acetaminophen and celecoxib according to the type of aspirin/NSAID hypersensitivity and aimed to determine the risk factors for cross-intolerance. **Methods:** We retrospectively reviewed the medical records of patients intolerant to aspirin and NSAIDs who had undergone an acetaminophen and/or celecoxib oral provocation test. Aspirin/NSAID hypersensitivity was classified into 4 types according to a recently proposed classification: aspirin-exacerbated respiratory disease (AERD), aspirin-exacerbated chronic urticaria (AECU), aspirin-induced acute urticaria/angioedema (AIAU), and NSAID-induced blended reaction (NIRD). **Results:** A total of 180 patients with hypersensitivity to aspirin and NSAIDs were enrolled; 149 acetaminophen provocation test results and 145 celecoxib provocation test results were analyzed. The overall cross-reaction rates to acetaminophen and celecoxib were 24.8% and 10.3%, respectively. There was a significant difference in the cross-reactivity to acetaminophen according to the type of NSAID hypersensitivity. Cross-reactivity to acetaminophen was highest in the AECU group (43.9%), followed by the AERD (33.3%), NIBR (16.7%), and AIAU (12.5%) groups. Underlying chronic urticaria was more prevalent in patients with cross-intolerance to both acetaminophen (P=0.001) and celecoxib (P=0.033). Intolerance to acetaminophen was associated with intolerance to celecoxib (P<0.001). **Conclusions:** Acetaminophen and celecoxib may induce adverse reactions in a non-negligible portion of aspirin/NSAID-sensitive patients. Physicians should be aware of the possible cross-reactions of these alternative drugs and consider an oral challenge test to confirm their tolerability.

Key Words: Acetaminophen; celecoxib; cross reactions; hypersensitivity; intolerance; anti-inflammatory agents; non-steroidal

INTRODUCTION

Aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely prescribed drugs, and hypersensitivity reactions to these agents are frequently of concern in clinical practice.[1,2] Such hypersensitivity reactions occur in approximately 0.6% to 2.5% of the general population, but patients with asthma and chronic urticaria are at higher risk of adverse reactions.[3] These hypersensitivity reactions are characterized by 2 different clinical syndromes: aspirin-induced asthma and aspirin-induced urticaria/angioedema.[3] Both reactions are elicited by nonallergic mechanisms via inhibition of cyclooxygenase (COX)-1 and subsequent alteration in eicosanoid biosynthesis, most prominently cysteinyl leukotriene overproduction.[1,3] Generally, patients with aspirin intolerance are also sensitive to all NSAIDs that preferentially inhibit COX-1.[4]

Acetaminophen, a weak COX inhibitor, and celecoxib, a selective COX-2 inhibitor, are known to be relatively safe therapeutic alternatives for patients with aspirin intolerance.[5,6] However, previous studies have reported that a portion of aspirin/NSAID-intolerant patients may also react to a high dose of acetaminophen or celecoxib.[5,6] The cross-reaction rates in the acetamino-

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phen challenge varied according to administered dose, challenge procedure, and patients' underlying condition, such as the type of aspirin hypersensitivity reaction and the presence and severity of asthma or chronic urticaria.[6] A high-dose acetaminophen challenge (>1,000 mg) was reported to provoke a hypersensitivity reaction in as much as one-third of aspirin-intolerant patients.[7] Early studies of selective COX-2 inhibitor challenges reported that most aspirin-intolerant patients can use them safely.[8-10] However, a recent report showed inconsistent results in that a substantial portion of patients with NSAID-induced urticaria/angioedema may also be sensitive to the selective COX-2 inhibitor etoricoxib, especially patients with acetaminophen cross-intolerance.[11]

Genetic susceptibility may be involved in the pathogenesis of aspirin and NSAID hypersensitivity,[12] but cross-reactivity among these medications has rarely been explored in the Asian population. Furthermore, risk factors for cross-reactivity and the characteristics of cross-reactions are not yet clearly understood. In the present study, we investigated cross-reactivity of acetaminophen and celecoxib according to the type of NSAID hypersensitivity in the Korean population and aimed to determine the risk factors associated with cross-intolerance.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed the medical records of 180 patients intolerant to aspirin and NSAIDs who had visited the allergy clinic in Seoul National University Hospital and Seoul National University Bundang Hospital. They had undergone an acetaminophen and/or celecoxib oral provocation test from November 2003 to November 2011. NSAID hypersensitivity was diagnosed by a positive oral aspirin provocation test result or convincing clinical history of aspirin and/or other NSAID-induced hypersensitivity reaction. Only patients with typical non-immunological aspirin hypersensitivity reactions, such as aspirin/NSAID-induced asthma, aspirin/NSAID-induced urticaria/angioedema, or aspirin/NSAID-induced anaphylaxis, were included in the study. Delayed-type cutaneous reactions or hypersensitivity reactions to single or limited NSAIDs that were possibly related to the immunological mechanism,[13] as well as miscellaneous adverse reactions to aspirin and NSAIDs, were excluded from the study. The study was approved by the institutional review board of each hospital.

Provocation test

Patients who were suspected to have aspirin/NSAID hypersensitivity underwent an aspirin provocation test in an open oral challenge manner. Patients with a convincing history of typical idiosyncratic reactions after administration of aspirin or NSAIDs were diagnosed with aspirin/NSAID hypersensitivity without a provocation test. An oral challenge was carried out under the supervision of an allergist skilled in performing provocation tests when the patients were in a stable clinical condition. Any medications that could influence the result of the provocation test were withdrawn before the oral challenge, including short-acting bronchodilators (8 hours), inhaled corticosteroids and long-acting bronchodilators (48 hours), antihistamines (3 days), and systemic corticosteroids and leukotriene antagonists (7 days).[14]

In our allergy clinic, an aspirin challenge was performed with the following 1-day protocol. The baseline forced expiratory volume in 1 second (FEV1) and blood pressure (BP) were measured before the start of the challenge. The aspirin oral challenge was performed with the following dose-escalating schedule: 25 mg for patients with a risk of anaphylaxis and acute bronchospasm, then 50, 100, 250, and 500 mg with a 1-hour interval between each dose. Patients were observed carefully, and FEV1 and BP were measured every 30 minutes after each consecutive dose. The observation was carried out until 2 to 4 hours after administration of the final dose. If there was no significant objective change in symptoms and signs, the result of the test was regarded as negative. The oral provocation test was regarded as positive when one or more of following symptoms and signs were observed[14]: 1) Bronchial reaction: bronchospasm, dyspnea, chest tightness, wheezing, and significant decrease in FEV1 (>20% of baseline FEV1); 2) Upper airway reaction: rhinorrhea and nasal congestion; 3) Cutaneous reaction: urticaria, erythema, and angioedema; 4) Cardiovascular: hypotension (systolic BP of less than 90 mmHg or greater than 30% decrease from the baseline); and 5) Others: abdominal cramping accompanied with other cutaneous, respiratory, cardiovascular symptoms. If the patient showed such significant changes in symptoms and signs, the challenge was stopped and medications such as antihistamines, systemic steroids, short-acting beta-2 agonist inhalation, and epinephrine injection were given to treat and relieve the symptoms.

To evaluate cross-reactivity and identify tolerable analgesics for the patients, acetaminophen and/or celecoxib oral provocation tests were performed in a similar manner for the aspirin-intolerant patients on separate days (if the former test was positive, the next test was performed with at least 7 days interval). An acetaminophen oral challenge was performed with the following dose-escalating schedule: 300 mg (or 325 mg if only a 325 mg tablet was available), 600 mg (or 650 mg), and 900 mg (or 975 mg). The celecoxib dose-escalating schedule was as follows: 100 and 200 mg. The interval of each dose; timing to check FEV1, BP, and the patient's symptoms and signs; and criteria for a positive test were identical to those of the aspirin oral provocation test.

Classification of NSAID hypersensitivity

NSAID hypersensitivity reactions were divided into four types according to the classification proposed recently by a group of

experts representing the European Network Drug Allergy (ENDA) and European Network on Hypersensitivity to Aspirin and Nonsteroidal Anti-Inflammatory Drugs (HANNA) as follows:[13] 1) aspirin-exacerbated respiratory disease (AERD; the same as NSAID-induced rhinitis/asthma): respiratory reactions such as rhinorrhea, nasal congestion, bronchospasm, wheezing, and dyspnea induced by aspirin and NSAIDs in patients with underlying asthma and/or chronic rhinosinusitis and nasal polyps; 2) aspirin-exacerbated chronic urticaria (AECU; the same as NSAID-exacerbated urticaria/angioedema): urticaria and/or angioedema exacerbated by aspirin and NSAIDs in patients with chronic urticaria; 3) aspirin-induced acute urticaria/angioedema (AIAU; the same as multiple NSAID-induced urticaria/angioedema): urticaria and/or angioedema induced by various NSAIDs, including aspirin, in subjects without a history of underlying chronic skin and/or respiratory disease; and 4) NSAID-induced blended reaction (NIRD): mixed or blended reactions induced by various NSAIDs but that do not clearly fall into any of the proposed categories, such as anaphylactic reactions induced by multiple NSAIDs or blended reactions in patients with both asthma/chronic rhinosinusitis and chronic urticaria.

Statistical analysis

An analysis of variance or the Kruskal-Wallis test (nonparametric) for continuous variables and a chi-square test or Fisher's exact test (nonparametric) for categorical variables were used to compare the clinical characteristics and cross-reactivity to acetaminophen/celecoxib according to the type of NSAID hypersensitivity. The *t*-test, chi-square test, and Fisher's exact test (nonparametric) were performed to compare clinical characteristics between acetaminophen and celecoxib-intolerant and -tolerant patients. Statistical analyses were performed using SPSS ver. 18.0 (SPSS, Inc., Chicago, IL, USA); a P value of <0.05 was deemed to indicate statistical significance.

RESULTS

Demographic and clinical characteristics of study subjects

A total of 180 patients with hypersensitivity to aspirin and NSAIDs were enrolled. Their mean age was 37.4±14.4 years, and 76 (42.2%) were male. A total of 114 (63.3%) patients had undergone both acetaminophen and celecoxib provocation tests. Thirty-five (19.4%) patients had undergone provocation test with acetaminophen alone. Thirty-one (17.2%) had undergone provocation test with celecoxib alone. Thirty-five (19.4%) had underlying asthma, 30 (16.7%) had chronic rhinosinusitis, and 62 (34.4%) had chronic urticaria. NSAIDs hypersensitivity was diagnosed by a positive oral aspirin provocation test result in 131 (72.8%) patients and a convincing clinical history of aspirin and/or other NSAID-induced hypersensitivity reaction in 49 (27.2%). Twenty-eight (15.6%) patients were classified into the AERD group, 54 (30.0%) into the AECD group, 82 (45.6%) into the AIAU group, and 16 (8.9%) into the NIRD group (Table 1).

Table 1. Demographic and clinical characteristics of study population (N=180)

Age (year)	37.4±14.4
Male	76 (42.2)
Total IgE (IU/mL) (N=134†)	394.6±739.8
Atopy (N=96*)	79 (82.3)
Underlying disease†	
Asthma	35 (19.4)
Allergic rhinitis	82 (45.6)
Chronic rhinosinusitis	30 (16.7)
Nasal polyp	15 (8.3)
Chronic urticaria	62 (34.4)
History of anaphylaxis	31 (17.2)
Food allergy	9 (5.0)
Atopic dermatitis	6 (3.3)
Diagnosis of NSAIDs hypersensitivity	
Aspirin oral provocation test	131 (72.8)
Convincing clinical history	49 (27.2)
Classification of NSAIDs hypersensitivity	
NSAIDs-induced rhinitis/asthma	28 (15.6)
NSAIDs-exacerbated urticaria/angioedema	54 (30.0)
Multiple NSAIDs-induced urticaria/angioedema	82 (45.6)
NSAIDs-induced blended reaction	16 (8.9)

Data are presented as number (percentage) or mean±SD.
*Numbers of subjects who were evaluated; †Numbers of subjects who have a documented medical history of underlying disease.

Cross-reactivity to acetaminophen

Acetaminophen provocation tests were performed in 149 patients with NSAID hypersensitivity (24 patients with AERD, 41 with AECD, 72 with AIAU, and 12 with NIRD). The overall rate of cross-reactivity to acetaminophen was 24.8%. There was a significant difference in the cross-reactivity to acetaminophen according to the type of NSAID hypersensitivity. Cross-reactivity was highest in the AECU group (43.9%), followed by the AERD (33.3%), NIBR (16.7%), and AIAU (12.5%) groups. Characteristics of adverse reactions to acetaminophen were very similar to those to aspirin and other NSAIDs, but generally milder. Patients with underlying AERD showed only respiratory symptoms in terms of cross-reactivity to acetaminophen. In addition, patients with AECU and AIAU showed only cutaneous symptoms, such as urticaria or angioedema, in terms of their cross-reaction. The provocative cumulative dose of acetaminophen was >1,000 mg in each group, and there were no significant differences among the groups (Table 2). However, 14 of 38 patients with cross-reactivity showed adverse reactions to <1,000 mg of acetaminophen. Moreover, 4 patients showed hypersensitivity reactions to <325 mg of acetaminophen.

Table 2. Cross-reactivity to acetaminophen according to the types of NSAIDs hypersensitivity

	Total (N=149)	AERD (N=24)	AECU (N=41)	AIAU (N=72)	NIBR (N=12)	*P* value
Age (year)	37.2±14.6	45.2±14.2	36.9±14.2	32.1±13.0	37.2±14.6	0.02
Male	65 (43.6)	7 (29.2)	13 (54.2)	39 (54.2)	6 (50.0)	0.049
Log (total IgE) (IU/mL)	5.2±1.3	4.9±1.4	5.6±1.5	5.1±1.1	5.2±0.7	0.200
Cross-reactivity to AAP	37 (24.8)	8 (33.3)	18 (43.9)	9 (12.5)	2 (16.7)	0.001
Characteristics of cross-reaction to AAP*						
Respiratory	9 (24.3)	8 (100.0)	0	0	1 (50.0)	<0.001
Cutaneous	28 (75.7)	0	18 (100.0)	9 (100.0)	1 (50.0)	<0.001
Provocative cumulative dose of AAP (mg)	1,146.3±545.0	1,173.8±420.1	1,177.5±483.6	1,020.0±755.5	1,387.5±583.4	0.813

AERD, aspirin exacerbated respiratory disease (NSAIDs-induced rhinitis/asthma); AECU, aspirin exacerbated chronic urticaria (NSAIDs-exacerbated urticaria/angioedema); AIAU, aspirin-induced acute urticarial/angioedema (multiple NSAIDs-induced urticaria/angioedema); NIBR, NSAIDs-induced blended reaction; AAP, acetaminophen.
*Analyses were performed in the patients with cross-reaction to AAP (8 patients with AERD, 18 with AECU, 9 with AIAU, and 12 with NIBR).

Table 3. Cross-reactivity to celecoxib according to the types of NSAIDs hypersensitivity

	Total (N=145)	AERD (N=23)	AECU (N=46)	AIAU (N=63)	NIBR (N=13)	*P* value
Age (year)	38.1±14.8	44.5±13.0	38.0±15.7	37.0±15.0	32.2±11.0	0.079
Male	63 (43.4)	8 (34.8)	14 (30.4)	34 (54.0)	7 (53.8)	0.063
Log (total IgE) (IU/mL)	5.1±1.3	4.8±1.4	5.4±1.5	5.0±1.1	5.5±0.7	0.356
Cross-reactivity to celecoxib	15 (10.3)	2 (8.7)	8 (17.4)	4 (6.3)	1 (7.7)	0.307
Characteristics of cross- reaction to celecoxib*						
Respiratory	3 (20.0)	2 (100.0)	0	1 (25.5)	0	0.020
Cutaneous	13 (86.7)	0	8 (100.0)	4 (100.0)	1 (100.0)	0.010
Provocative cumulative dose of celecoxib (mg)	263.3±138.2	300.0±0.0	293.8±167.8	225.0±95.7	100.0	0.460

AERD, aspirin exacerbated respiratory disease (NSAIDs-induced rhinitis/asthma); AECU, aspirin exacerbated chronic urticaria (NSAIDs-exacerbated urticaria/angioedema); AIAU, aspirin-induced acute urticarial/angioedema (multiple NSAIDs-induced urticaria/angioedema); NIBR, NSAIDs-induced blended reaction.
*Analyses were performed in the patients with cross-reaction to celecoxib (2 patients with AERD, 8 with AECU, 4 with AIAU, and 1 with NIBR).

Cross-reactivity to celecoxib

Celecoxib provocation tests were performed in 145 patients with NSAID hypersensitivity (23 patients with AERD, 46 with AECD, 63 with AIAU, and 13 with NIRD). The overall rate of cross-reactivity to celecoxib was 10.3%, and there was no significant difference in cross-reactivity to celecoxib among the groups, although cross-reactivity in the AECU group was highest by 17.4%. Like the cross-reactions to acetaminophen, the characteristics of cross-reactions to celecoxib were similar to those of adverse reactions to aspirin and other NSAIDs and were generally mild. A difference in the provocative dose of celecoxib according to the type of NSAID hypersensitivity was not found among the celecoxib cross-reactors (Table 3).

Risk factors for cross-intolerance to acetaminophen or celecoxib

There were no differences in age, gender, total IgE level, and atopy status between patients with cross-reaction to acetaminophen or celecoxib and patients tolerant to these drugs. Patients with acetaminophen cross-intolerance had a higher prevalence of chronic urticaria as their underlying disease compared with acetaminophen-tolerant patients (odds ratio [OR], 3.5; 95% confidence interval [CI], 1.6-7.6). AECU was the most significant high-risk type of NSAID hypersensitivity for acetaminophen cross-intolerance (OR, 3.7; 95% CI, 3.7-8.1), whereas AIAU was the most significant low-risk type (OR, 0.3; 95% CI, 0.1-0.6). Chronic urticaria was also significantly more prevalent in patients with celecoxib intolerance (OR, 3.1; 95% CI, 1.1-9.4). Intolerance to 1 alternative drug was significantly associated with intolerance to another alternative drug. Celecoxib intolerance was more prevalent in patients with acetaminophen intolerance, and the OR was as high as 11.6 (95% CI, 2.8-46.6). There were no significant differences in other underlying diseases between patients cross-intolerant to acetaminophen or celecoxib and patients tolerant to these agents (Table 4).

DISCUSSION

NSAIDs are one of the most common causes of adverse drug reactions and are responsible for 21% to 25% of reported adverse drug events, which include immunologic and nonimmunologic hypersensitivity reactions.[15,16] Hypersensitivity reactions

Table 4. Comparison of clinical characteristics between patients cross-intolerant to acetaminophen or celecoxib and tolerant patients

	AAP-intolerant (N=37)	AAP-tolerant (N=112)	*P* value*	Celecoxib-intolerant (N=15)	Celecoxib-tolerant (N=130)	*P* value†
Age (year)	36.8±14.2	37.3±14.8	0.862	40.3±15.3	37.8±14.8	0.537
Male	12 (32.4)	53 (47.3)	0.113	6 (40.0)	57 (43.8)	0.776
Log (total IgE)	5.1±1.3	5.2±1.3	0.686	4.3±1.8	5.2±1.2	0.173
Atopy	18/22 (81.8)	54/64 (84.4)	0.748	4/5 (80.0)	59/71 (83.1)	1.000
Underlying disease						
Asthma	9 (24.3)	92 (17.9)	0.389	4 (26.7)	23 (17.7)	0.481
Allergic rhinitis	18 (48.6)	51 (45.5)	0.742	7 (46.7)	57 (43.8)	0.835
Chronic rhinosinusitis	8 (21.6)	16 (14.3)	0.293	5 (33.3)	20 (15.4)	0.139
Nasal polyp	6 (16.2)	7 (6.2)	0.089	2 (14.3)	11 (8.5)	0.626
Chronic urticaria	20 (54.1)	28 (25.0)	0.001	9 (60.0)	42 (32.3)	0.033
History of anaphylaxis	2 (5.4)	4 (3.6)	0.638	1 (6.7)	7 (5.4)	0.592
Food allergy	4 (10.8)	22 (19.6)	0.220	3 (20.0)	20 (15.4)	0.708
Atopic dermatitis	2 (5.4)	4 (3.6)	0.638	0 (0.0)	5 (3.8)	1.000
Types of NSAIDs hypersensitivity						
AERD	8 (21.6)	16 (14.3)	0.293	2 (13.3)	21 (16.2)	1.000
AECU	18 (48.6)	23 (20.5)	0.001	8 (53.3)	38 (29.2)	0.078
AIAU	9 (24.5)	63 (56.3)	0.001	4 (26.7)	59 (45.4)	0.166
NIBR	2 (5.4)	10 (8.9)	0.731	1 (6.7)	12 (9.2)	1.000
Intolerance to celecoxib or AAP‡	9/30 (30.0)	3/84 (3.6)	<0.001	9/12 (75.0)	21/102 (20.6)	<0.001

AAP, acetaminophen; AERD, aspirin exacerbated respiratory disease (NSAIDs-induced rhinitis/asthma); AECU, aspirin exacerbated chronic urticaria (NSAIDs-exacerbated urticaria/angioedema); AIAU, aspirin-induced acute urticaria/angioedema (multiple NSAIDs-induced urticaria/angioedema); NIBR, NSAIDs-induced blended reaction.

*AAP-intolerant vs AAP-tolerant; †Celecoxib-intolerant vs celecoxib-tolerant; ‡Intolerant to celecoxib for the comparison between AAP-intolerant and AAP-tolerant, and intolerant to AAP for the comparison between celecoxib-intolerant and celecoxib-tolerant.

to NSAIDs may have different pathogenic mechanisms and various clinical manifestations, including urticaria, angioedema, anaphylaxis, and delayed-type skin eruptions.[13] Two most common presentations of aspirin/NSAID hypersensitivity are bronchial asthma and urticaria/angioedema. They are elicited by inhibition of COX-1 and alteration of eicosanoid biosynthesis, which is differentiated from other adverse reactions to NSAIDs by its allergy mechanism.[3,13] These common types of reactions are frequently accompanied by underlying asthma and chronic rhinosinusitis/nasal polyps (known as the aspirin triad) and chronic urticaria.[3] Aspirin and NSAIDs can precipitate or aggravate symptoms in 4.3% to 21% of adult asthmatics and 27% to 35% of patients with chronic urticaria.[2,17,18] The cornerstone of current management for this type of aspirin/NSAID hypersensitivity is avoidance of cross-reacting NSAIDs and the use of alternative drugs.[13] Therefore, identification of non-cross-reacting alternative analgesics for individual patients is crucial for the management of NSAID-sensitive patients.

In the present study, we found that acetaminophen and celecoxib, which has been recognized as a relatively safe drug, also induced adverse reactions in 24.8% and 10.3% of patients with NSAID hypersensitivity, respectively. Previous studies revealed that acetaminophen, which is a COX-3 inhibitor with a weak effect on COX-1, may elicit adverse reactions at a high dose in some patients with NSAID hypersensitivity.[6] Low doses of acetaminophen (<600 mg) were relatively safe, with a prevalence of adverse reactions of 1% to 8.4%.[6] Settipane *et al.*[7] reported that 34% of patients with aspirin-induced asthma reacted to acetaminophen at doses of 1,000 to 1,500 mg. A recent review of EAACI/ENDA and GA2LEN/HANNA classified acetaminophen into group B (NSAIDs cross-reacting in a minority of hypersensitive patients) in terms of its cross-reactive type and recommended low-dose acetaminophen (<1,000 mg) in patients with aspirin-sensitive asthma and a challenge test before regular use.[13] However, few studies have been conducted in patients with NSAID-exacerbated urticaria/angioedema to date, and the cross-reactivity of acetaminophen according to the type of NSAID hypersensitivity has not been demonstrated clearly. In our study, the cross-reaction rates differed significantly according to the type of NSAID hypersensitivity. AECU was the most common type of acetaminophen cross-reaction (43.9%). AERD showed a cross-reaction rate similar to that in a previous report (33.3%), and the cross-reaction rate of AIAU was lowest (12.5%). Although most previous studies focused on AERD, our results suggest that AECU is another clinically important type of cross-reaction to acetaminophen. The characteristics of their cross-reactions

were identical to those of their original reaction, and the mean provocative doses of acetaminophen in all types of NSAID hypersensitivity were >1,000 mg. However, we found several cases of cross-reaction provoked by a low dose of acetaminophen. Although most reactions were mild compared with those induced by NSAIDs, these findings suggest that precautions and challenge testing before the administration of acetaminophen are needed in patients with AECU, AIAU, or AERD in clinical practice, as recommended by EAACI/ENDA and GA2LEN/HANNA.[13]

On the other hand, celecoxib and selective COX-2 inhibitors are reportedly very safe,[8-10,19] and the reviews of EAACI/ENDA and GA2LEN/HANNA classified them as group C (NSAIDs well tolerated by all hypersensitive patients) in AERD.[13] However, several case reports of adverse reactions induced by celecoxib in patients with aspirin-sensitive asthma, especially uncontrolled asthma, have been published.[20-22] Moreover, in terms of NSAID-induced urticaria/angioedema, previous studies showed inconsistent results.[5,6,13] Many studies reported that COX-2 inhibitors are tolerated by all patients, but some revealed that celecoxib and rofecoxib induced skin reactions in 2% to 9.6% of patients with aspirin-induced urtiaria/angioedema.[5] A recent study[11] reported that 24% of patients with NSAID-intolerant urticaria/angioedema and intolerance to acetaminophen, and 6% of patients with NSAID-intolerant urticaria/angioedema and tolerance to acetaminophen were intolerant to etoricoxib. In the present study, there were 2 cases (8.7%) of adverse respiratory reactions to celecoxib in patients with AERD. In addition, the cross-reaction rate to celecoxib in AECD was as high as 17.4%, although the reactions were mild and limited to cutaneous symptoms. The mechanism of celecoxib intolerance is unclear because celecoxib does not lose its selectivity despite the dose being increased.[5] However, our data suggest that selective COX-2 inhibitors can also provoke adverse reactions in a minority of patients with both aspirin/NSAID-induced asthma and urticaria/angioedema, and physicians should be aware of the possibility of cross-reaction. We believe that it would be better to recommend an oral challenge test prior to prescription or take precautions when patients take the first dose of a COX-2 inhibitor as an alternative to NSAIDs.

Few reports are available for risk factors of cross-reaction between acetaminophen and celecoxib. A history of anaphylactoid reactions induced by NSAIDs and an atopic status were reported as risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders.[23] In our study, age, gender, atopic status, and total IgE were not associated with cross-reactions to acetaminophen and celecoxib. Underlying chronic urticaria was the key risk factor for cross-reactions to both acetaminophen and celecoxib. AECD was also detected as a risk factor for acetaminophen hypersensitivity, but the cross-intolerance may be more closely related to underlying chronic urticaria rather than NSAID-induced cutaneous reaction given the low risk in AIAU individuals. Acetaminophen and selective COX-2 inhibitors seem to have a similar risk of cross-intolerance in NSAID hypersensitivity. These data are consistent with a recent study conducted by Dona *et al.*,[11] which showed a higher prevalence of cross-reaction to etoricoxib in patients with both NSAID and paracetamol intolerance.

This study had several limitations. First, challenge tests for acetaminophen and celecoxib were not performed in a placebo-controlled, blinded manner. Thus the possibility of false-positive reactions exists, which may have contributed to the high rate of cross-reactivity. However, to minimize the effect of the open provocation method, we regarded the provocation test as positive when only objective changes in signs were detected. Second, the time interval between each challenge dose in the common protocol we used in our clinic was shorter than that recommended by a consensus report.[14] No analysis of the exact provocative dose was available. Instead, we used the provocative cumulative dose to evaluate the threshold of tolerability to acetaminophen and celecoxib. Third, our study included only patients who had undergone oral provocation tests. We could not perform the provocation test on all aspirin-sensitive patients who visited our clinic because some of them refused to undergo the challenge, for various reasons. The majority may have been tolerant to acetaminophen and celecoxib, but were not included in the analysis in this study. Selection bias is possible due to their exclusion and may have affected our results. Finally, as a limitation of the retrospective nature of the electronic medical record review, atopic status, total IgE, and the presence of chronic rhinosinusitis and nasal polyps were not evaluated thoroughly in some patients. These were assessed only in those for whom such information was available in the medical records.

Nevertheless, to our knowledge, our study is the first report of the prevalence and risk factors of cross-intolerance to acetaminophen and celecoxib in an Asian population. Our results provide valuable information for physicians prescribing alternative drugs to aspirin/NSAID-sensitive patients in clinical practice. In summary, acetaminophen and celecoxib may induce adverse reactions in a non-negligible portion of NSAID-sensitive patients. The prevalence of cross-intolerance to acetaminophen differs according to the type of NSAID hypersensitivity. Underlying chronic urticaria was a risk factor for cross-intolerance to both acetaminophen and celecoxib. Intolerance to acetaminophen was associated with intolerance to celecoxib. Physicians should be aware of the possible cross-reactions of these alternative drugs and consider oral challenge tests to confirm patients' tolerance of drugs.

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