

ORIGINAL ARTICLE

Safety of selective cyclooxygenase-2 inhibitors and a basic non-steroidal anti-inflammatory drug (NSAID) in Japanese patients with NSAID-induced urticaria and/or angioedema: Comparison of meloxicam, etodolac and tiaramide

Naoko INOMATA,¹ Hiroyuki OSUNA,² Junko YAMAGUCHI,³ Masahito ONODA,³ Yoshihiro TAKESHITA,³ Yoshiyuki CHIBA,⁴ Takeshi KAMBARA,⁵ Zenro IKEZAWA³

¹Department of Dermatology, Yokohama City University Hospital, ²Hiro Clinic, ³Department of Environmental, Immuno-Dermatology, Yokohama City University, School of Medicine, Yokohama, ⁴Department of Dermatology, Kanagawa Cancer Center, Kanagawa,

⁵Department of Dermatology, Yokohama City University General Medical Center, Yokohama, Japan

ABSTRACT

The identification of a safe and reliable alternative for patients with non-steroidal anti-inflammatory drug (NSAID)-induced urticaria/angioedema is a frequent problem for dermatologists and other practitioners. Cyclooxygenase-2 (COX-2) inhibitors have been reported to be safe for NSAID-intolerant patients from the US and Europe but not all of them have yet been approved for use in Japan. It was our objective to investigate the clinical manifestations of oral NSAID challenges in Japanese patients with histories of urticaria and/or angioedema after the intake of NSAIDs and to find safe alternative drugs, including COX-2 inhibitors and a basic anti-inflammatory drug. Twenty subjects suspected NSAID-induced urticaria/angioedema from histories were included in a double-blind or single-blind, placebo-controlled oral challenge protocol using NSAIDs. Skin prick tests using NSAIDs, which were dissolved in saline, were conducted. The mean age of the patients was 37.3 years; 14 patients were female. The results of other challenge tests showed that the most frequently intolerated drugs was loxoprofen (100%), followed by acetyl salicylic (94.4%), etodolac (53.3%), diclofenac (50%), acetaminophen (38.5%), meloxicam (33%), and tiaramide (21.4%). Urticaria and angioedema were induced after aspirin intake in 83.3% and 22.2% of patients, respectively, whereas an asthmatic response was seen in 5.6%. Skin prick tests with NSAIDs were 100% negative. This study showed that among the NSAIDs that are available in Japan and that were investigated in this study, tiaramide, which does not inhibit COX, is the relatively safe alternative drug for Japanese patients with NSAID-induced urticaria and/or angioedema. Furthermore, meloxicam seems to be better tolerated than etodolac between two selective COX-2 inhibitors.

Key words: angioedema, aspirin intolerance, non-steroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitor, urticaria.

INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID) intolerance, which occurs in approximately 1% of the general population, is a relatively common disease.^{1,2} Therefore, determining and suggesting

a safe, alternative anti-inflammatory agent for an NSAID-intolerant patient seems to be a common problem in clinical practice. In the last few years, the selective cyclooxygenase-2 (COX-2) inhibitors, such as meloxicam and especially very selective ones (rofecoxib and celecoxib) are reported to be

Correspondence: Naoko Inomata, MD, PhD, Department of Dermatology, Yokohama City University Hospital, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan. Email: ninomata@med.yokohama-cu.ac.jp

Received 14 June 2006; accepted 29 September 2006.

among the safest alternatives for patients with NSAID-induced urticaria (UR) and/or angioedema (AE), although reactions to these drugs have also been reported.³⁻⁶ COX-2 inhibitors have not been approved, and those available in Japan are two drugs, meloxicam and etodolac. We should determine the safe alternatives available in Japan for patients with NSAID-induced UR and/or AE.

In this study, we assess the clinical characteristics of drug challenges and the safety of meloxicam and etodolac in 20 Japanese patients with NSAID-induced UR and/or AE. In addition, we also used tiaramide, which shows an anti-inflammatory effect without inhibition of COX, for challenges.

SUBJECTS AND METHODS

Patients

The consecutive Japanese patients with histories of UR and/or AE after NSAID intake (six male and 14 female), who underwent challenge tests with aspirin and/or other NSAIDs at Yokohama City University Hospital between 1 August 2001 and 31 March 2006, were enrolled; one of which was described previously.⁷ Data regarding age, gender, clinical characteristics of NSAID intolerance and other accompanying diseases (chronic urticaria, bronchial asthma, rhinosinusitis or nasal polyps) were collected from reliable histories (Table 1). The following examination and challenges with aspirin and/or NSAIDs were performed after informed consent was obtained from the patients.

Oral challenges

Double-blind or single-blind, placebo-controlled challenge tests were used for provocation tests. All patients, except two with life-threatening reactions after aspirin intake, underwent challenges with aspirin. Subjects underwent further tests with other COX-1/2 inhibitors with the drugs exerting little or no inhibitory activity on COX-1, including acetaminophen, etodolac, meloxicam and tiaramide. Increasing doses (starting with 1/20 of the therapeutic dose, except for case 8, where we used 1/40 of the therapeutic dose, and increasing the dose step by step to 1/10, 1/5, 1/2 and a full measure of the therapeutic dose, except for case 5, where we used 1/8, 1/3, 1/2 and a full measure of the therapeutic dose) were administered under strict hospital

surveillance at more than 3-h intervals, until the daily therapeutic dose was cumulatively reached. The drugs were applied up to the following therapeutic doses recommended in Japan: 1.0 g lactose (placebo); 1.0 g aspirin; 200 mg acetaminophen; 25 mg diclofenac; 60 mg loxoprofen; 200 mg ibuprofen; 200 mg etodolac; 10 mg meloxicam; and 100 mg tiaramide. Antihistamines were withdrawn 3 days before the test. The patients fasted 3 h before and during challenges. Only the appearance of unequivocal UR and/or AE was considered as a positive reaction. The patients with chronic urticaria were challenged when no or a few eruptions were observed without treatment. A few wheals and eruption exceeding approximately fivefold after NSAID ingestion was considered a positive reaction.

Skin prick tests

To evaluate whether hypersensitivity to NSAID would be mediated by immunoglobulin (Ig)E, skin prick tests (SPT) with these drugs were carried out. Responses of all SPT were interpreted according to European Academy of Allergy and Clinical Immunology guidelines.⁸ All SPT with drugs of therapeutic dose, which were crushed to powders and dissolved with 1 ml saline, were carried out.

Autologous serum skin test (ASST)

Sera were obtained from venous blood samples by centrifugation at $1710 \times g$ for 10 min. Fifty microliters of autologous serum were injected intradermally into the volar aspect of the forearm. Skin reactivity was evaluated by using a histamine intradermal test of 20 μ L at the concentration of 10 μ g/mL. Fifty microliters of saline solution were used as a negative control. All injection sites were scored at 30 min after injection. The test result was considered positive when the mean diameter of the erythema with autologous serum was at least 4 mm larger than the mean erythema of the wheal elicited by the negative control or when it was the same as the mean diameter of the erythema elicited by histamine.⁹

RESULTS

Patients

The demographic data, clinical characteristics of the patients, the NSAID that the patients were

Table 1. Characteristics of 20 patients with a history of intolerance to aspirin and/or other NSAID

Patient no.	Age (years), gender	Drugs responsible for the reactions (by history)	Reactions due to responsible drugs (by history)		CU	ASST	Nasal polyp
			Cutaneous	Extracutaneous			
1	76F	DIC, LOX	UR	DY	+	-	-
2	41F	ASP	UR	-	+	NT	-
3	49F	TIA, PRA	UR	DY	-	NT	-
4	58M	IBU	UR	-	+	NT	+
5	27M	ASP	AE	-	-	NT	NT
6	28F	ASP	UR/AE	BA	-	NT	-
7	32F	ASP, IND	UR/AE	DY	+	NT	-
8	51F	DIC, LOX	UR	BA, CO	-	-	-
9	5F	ASP	UR/AE	BA, Dy, CO, AB, HE	+	NT	NT
10	59M	DIC, LOX	UR	DY, CO, FE	-	NT	NT
11	30F	ASP, IBU	UR	DY	+	-	-
12	41M	ASP, ACE	UR	DY	+	-	-
13	34F	Unknown	UR	-	+	-	-
14	38M	ASP, LOX	UR	DY	-	+	-
15	27F	ASP, IBU	UR/AE	DY	-	NT	-
16	35F	ASP, LOX	UR/AE	DY	+	+	NT
17	42F	ASP, LOX	UR	-	+	NT	-
18	30F	LOX	UR	BA	+	NT	NT
19	18F	ASP, ACE	UR	-	-	-	NT
20	32M	IBU	UR	DY	+	NT	NT
Positive			UR: 19/20	BA: 4/20	12/20	2/8	1/13
No			AE: 6/20	DY: 11/20 CON: 2/20 ABD: 1/20			

ASP, aspirin; DIC, diclofenac; LOX, loxoprofen; IBU, ibuprofen; ACE, acetaminophen; ETO, etodolac; MEL, meloxicam; TIA, tiaramide; TIAP, tiaprofenic acid; PRA, pranoprofen; UR, urticaria; AE, angioedema; DY, dyspnea; CO, loss of consciousness; BA, bronchial asthma; AB, abdominal pain; HE, headache; FE, fever; CU, chronic urticaria; ASST, autologous serum skin test; NT, not tested.

intolerant to, and reactions occurring after the intakes of the drugs the patients were intolerant to by reliable history, are given in Table 1.

Oral challenges

Results of the challenge tests are summarized in Table 2. All patients had a positive response to one or several NSAID challenges. No reaction to a placebo was observed. All patients challenged with aspirin except one patient (case 19) were provoked by aspirin. In most cases (12/17, 70.6%), aspirin reactivity occurred following a dose of less than 200 mg. The respiratory symptoms and gastrointestinal symptoms occurred in five and one patients, respectively. No patients experienced hypotension and loss of consciousness. The time interval between the last intake of aspirin and the onset of symptoms was between 5 min and 6 h (mean, 1 h and 53 min). The time interval between aspirin intake and the onset of symptoms was less than 1 h in 8/17 patients reactive to aspirin, whereas it was more

than 1 h in all three patients in which AE occurred after aspirin challenge.

Nineteen aspirin reactors underwent a total of 48 further challenge tests with acetaminophen, etodolac, meloxicam and tiaramide, which induced UR and/or AE in 5/13, 8/15, 2/6 and 3/14 patients, respectively.

At least one safe alternative NSAID was eventually found in the cases challenged with all of these four drugs. One subject, case 19, tolerated aspirin and did not tolerate acetaminophen on oral challenge, although she had a history of UR induced by acetaminophen and aspirin. This subject underwent a total of two further challenges with alternative substances, and no reactivity was observed to meloxicam or tiaramide.

Skin prick tests and ASST

Skin prick test using NSAIDs were all negative in all patients. In addition, two of eight patients were positive on ASST.

Table 2. Results of oral challenges with aspirin and other NSAID (*n* = 20)

Case no.	NSAID								ASP challenge		
	Acid							Basic	Provoked dose (mg)	Time interval	Symptoms
	ASP	DIC	LOX	IBU	ACE	ETO	MEL	TIA			
1	+	NT	NT	NT	-	+	NT	-	50	3 h 30 min	UR, DY
2	+	NT	NT	NT	NT	-	NT	-	50	2 h	UR
3	+	NT	+	NT	+	-	-	+	100	45 min	UR, DY, DI
4	+	NT	NT	+	NT	-	NT	NT	200	5 min	UR
5	+	-	NT	NT	-	-	+	-	330	6 h	AE
6	NT	+	+	NT	-	+	NT	+	NT	NT	NT
7	+	NT	+	NT	-	-	NT	NT	50	1 h	AE, DY
8	+	NT	NT	NT	NT	+	NT	+	25	10 min	UR, BA
9	+	NT	NT	NT	+	NT	NT	NT	50	15 min	UR, DY, AB, HE
10	+	NT	+	NT	+	+	-	-	200	30 min	UR
11	+	+	NT	NT	+	+	+	-	50	1 h	UR
12	+	NT	NT	NT	NT	NT	NT	-	50	3 h	UR
13	+	NT	+	NT	-	-	NT	NT	200	4 h	UR
14	+	NT	+	NT	NT	-	NT	NT	1000	2 h 30 min	UR
15	+	-	+	-	-	+	NT	-	500	2 h 15 min	UR/AE
16	+	NT	+	NT	-	+	-	-	500	1 h	UR/AE
17	+	NT	NT	NT	-	+	NT	-	100	2 h	UR
18	NT	NT	NT	NT	NT	NT	NT	+	NT	NT	NT
19	-	NT	NT	NT	+	NT	-	-	-	-	-
20	+	NT	NT	+	NT	NT	NT	NT	1000	2 h	UR
Positive no.	17/18	2/4	8/8	1/2	5/13	8/15	2/6	3/14	Mean	Mean	
%	94.4	50	100	50	38.5	53.3	33.3	21.4	262 mg	1 h 53 min	

DISCUSSION

In this study, we evaluated the clinical characteristics of the oral challenges carried out in 20 Japanese patients with NSAID-induced UR and/or AE. Seventeen of 18 patients challenged with aspirin were provoked by aspirin. At least one safe alternative NSAID was eventually found in each of the cases challenged with acetaminophen, etodolac, meloxicam or tiaramide. Among NSAIDs used in this study, the most tolerable drug for the patients with aspirin-induced UR and/or AE seemed to be tiaramide, which exerts no COX inhibition, followed by meloxicam and acetaminophen.

Non-steroidal anti-inflammatory drugs induce UR and/or AE in two clinical settings.¹⁰ In the first, acute urticaria develops within minutes to 24 h of ingestion in an otherwise healthy individual. In the second, patients with preexisting chronic urticaria experience a flare when exposed to NSAIDs. It is now generally accepted that inhibition of COX-1 is the most likely pathogenic mechanism involved in reactions to multiple chemically-unrelated substances, resulting

in overproduction of leukotrienes, and reactions to single drugs are possibly IgE mediated.^{11,12} There is evidence that selective COX-2 inhibitors are generally an acceptable alternative in patients with or without chronic idiopathic urticaria who experience UR and/or AE after ingesting one or multiple NSAIDs.³⁻⁶ However, COX-2 inhibitors available in US and Europe have not yet been approved in Japan. This study indicated that of the two COX-2-selective inhibitors available in Japan, meloxicam might be better tolerated than etodolac in NSAID-induced UR and/or AE. Further studies are needed to confirm this indication, as there are only six patients who were challenged with meloxicam. Surprisingly, in this study, acetaminophen, which weakly inhibits COX, was better tolerated than etodolac. On the basis of both clinical history and challenge-test results, we found that while tolerability of acetaminophen and meloxicam by NSAID-induced UR and/or AE patients with or without chronic urticaria was measured at 8.4–32.0%¹³⁻¹⁶ and 1.0–17.3%,¹⁷⁻²⁰ respectively, in Europe, it was 38.5% and 30.0%, respectively, in our Japanese study. Netti reported

that, based on challenge-test results in patients with histories of NSAID-induced UR and/or AE, tolerability of acetaminophen by the patients without chronic urticaria was 6.9% (5/72), whereas it was 19% (8/42) in the patients with chronic urticaria.²¹ These results indicated that patients with NSAID-induced UR and/or AE and chronic urticaria may be less tolerant of acetaminophen than patients with NSAID-induced UR and/or AE alone.

The mechanism of the anti-inflammatory effect exerted by tiaramide, which was developed and approved only in Japan, has not been elucidated yet, although it has been reported that tiaramide shows no inhibitory effect on COX. Tiaramide is tolerated by almost all patients reactive to aspirin. This result supported the COX theory that COX inhibition might be a key mechanism of NSAID-induced UR and/or AE. However, in three patients reactive to aspirin, skin reactions were also induced by tiaramide, indicating that in a part of patients NSAID-induced UR and/or AE might also be caused via a mechanism other than COX inhibition.

In this study, aspirin challenges were carried out as essential tests in all patients except those with life-threatening history induced by NSAIDs. We could not confirm whether they are multiple-reactors or single-reactors, as two patients did not allow themselves to be challenged by COX-1/2 inhibitors. The other 16 patients were challenged with multiple drugs including COX-1/2 inhibitors, resulting in their being confirmed as multiple-reactors. Asero suggested that in subjects with a history of UR induced by a single NSAID (other than aspirin) the diagnostic work-up should start with an aspirin challenge in order to detect single/multiple NSAID reactors.²²

The one patient who tolerated aspirin on challenge did not tolerate acetaminophen alone but did tolerate meloxicam and tiaramide, suggesting that she might be a single-reactor to acetaminophen. The skin prick test using NSAIDs including acetaminophen was negative in this patient. The mechanism of single drug-induced UR and/or AE may be allergic sensitization with the synthesis of IgE antibodies specific for the drugs that function as a hapten. However, to date, specific drug recognition based upon an IgE-mediated mechanism has been shown only in patients intolerant to pyrazolones.²³

In our study, chronic urticaria and ASST positivity accompanied NSAID-induced UR and/or AE in 60% and 28.6% of patients with NSAID-induced UR and/or AE, respectively. NSAID-induced UR occurs in approximately 20–55% of chronic idiopathic urticaria patients.^{24,25} Asero demonstrated that most patients with multiple NSAID intolerance and approximately one-third of those with single NSAID hypersensitivity are characterized by the presence of circulating histamine-releasing factors.²⁶

In conclusion, aspirin challenge might be a good indicator for differentiating multiple-NSAID reactors from a single-NSAID reactor. Furthermore, in multiple NSAID-reactive individuals, tiaramide could be the first choice as an alternative NSAID other than NSAID that weakly inhibit COX-1/2 or selective COX-2 inhibitors in Japan.

REFERENCES

- 1 Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. *J Allergy Clin Immunol* 1977; **60**: 276–284.
- 2 Szczeklik A, Stevenson D. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003; **111**: 913–921.
- 3 Senna G, Bilo MB, Antonicelli L *et al.* Tolerability of three selective cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib and rofecoxib in NSAID-sensitive patients. *Allerg Immunol (Paris)* 2004; **36**: 215–218.
- 4 Zembowicz A, Mastalerz L, Setkowicz M, Radziszewski W, Szczeklik A. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol* 2003; **139**: 1577–1582.
- 5 Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Tolerance of nonsteroidal anti-inflammatory drug-sensitive patients to the highly specific cyclooxygenase 2 inhibitors rofecoxib and valdecoxib. *Ann Allergy Asthma Immunol* 2005; **94**: 34–38.
- 6 Pacor ML, Di Lorenzo G, Biasi D, Barbagallo M, Corrocher R. Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal anti-inflammatory drugs. *Clin Exp Allergy* 2002; **32**: 397–400.
- 7 Inomata N, Osuna H, Fujita H, Ogawa T, Ikezawa Z. Multiple chemical sensitivities following intolerance to azo dye in sweets in 5-year-old girl. *Allergol Int* 2006; **55**: 203–205.
- 8 Dreborg S. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989; **44**(suppl 10): 22–30.

- 9 Hide M, Kameyoshi Y. Autologous serum skin test for chronic urticaria. *Jpn J Clin Dermatol* 2004; **58**: 66–71.
- 10 Tan EK, Grattan CE. Drug-induced urticaria. *Expert Opin Drug Saf* 2004; **3**: 471–484.
- 11 Stevenson DD, Sanchez-Borges M, Szczeklik A. Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001; **87**: 177–180.
- 12 Stevenson DD, Simon RA, Zuraw BL. Sensitivity to aspirin and nonsteroidal anti-inflammatory drugs. In: Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER (eds). *Allergy. Principles Pract*, 6th edn. St Louis, MO: Mosby Inc, 2003; 169.
- 13 Ispano M, Fontana A, Scibilia J, Ortolani C. Oral challenge with alternative nonsteroidal antiinflammatory drugs (NSAIDs) and paracetamol in patients intolerant to these agents. *Drugs* 1993; **46**(Suppl 1): 253–256.
- 14 Asero R. Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. *Ann Allergy Asthma Immunol* 1999; **82**: 554–558.
- 15 Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000; **84**: 101–6.
- 16 Nettis E, Marcandrea M, Ferrannini A, Tursi A. Tolerability of nimesulide and paracetamol in patients with NSAID-induced urticaria/angioedema. *Immunopharmacol Immunotoxicol* 2001; **23**: 343–354.
- 17 Kosnik M, Music E, Matjaz F, Suskovic S. Relative safety of meloxicam in NSAID-intolerant patients. *Allergy* 1998; **53**: 1231–1233.
- 18 Quaratino D, Romano A, Di Fonso M *et al*. Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol* 2000; **84**: 613–617.
- 19 Sanchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, Perez CR. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001; **87**: 201–204.
- 20 Nettis E, Di Paola R, Ferrannini A, Tursi A. Meloxicam in hypersensitivity to NSAIDs. *Allergy* 2001; **56**: 803–804.
- 21 Nettis E, Colanardi MC, Ferrannini A, Tursi A. Update on sensitivity to nonsteroidal antiinflammatory drugs. *Curr Drug Targets Immune Endocr Metabol Disord* 2001; **1**: 233–240.
- 22 Asero R. Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. *Clin Exp Allergy* 2005; **35**: 713–6.
- 23 Himly M, Jahn-Schmid B, Pittertschatscher K *et al*. IgE-mediated immediate-type hypersensitivity to the pyrazolone drug propyphazone. *J Allergy Clin Immunol* 2003; **111**: 882–8.
- 24 Mastalerz L, Setkowicz M, Sanak M, Szczeklik A. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol* 2004; **113**: 771–5.
- 25 Societe Francaise de Dermatologie. Consensus Conference: management of chronic urticaria. Wednesday 8 January 2003. Institute Pasteur-Paris, France. Recommendation (short version). *Eur J Dermatol* 2003; **13**: 385–92.
- 26 Asero R, Tedeschi A, Lorini M. Autoreactivity is highly prevalent in patients with multiple intolerances to NSAIDs. *Ann Allergy Asthma Immunol* 2002; **88**: 468–72.