



A Case of Nonsteroidal Anti-Inflammatory Drug-Induced Anaphylaxis Confirmed by Skin Testing

Jaechun Lee*

Department of Internal Medicine, College of Medicine, Jeju National University, Jeju, Korea

*Corresponding author: Jaechun Lee, docu@hanmail.net

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are collectively a major culprit of drug-induced hypersensitivity. No reliable diagnostic tests, other than a direct challenge, are available for detecting the hypersensitivity. Cross-reactivity among NSAIDs that inhibit cyclooxygenase-1 is common. However, in rare cases, the mechanism underlying hypersensitivity can be understood from the immunological point of view, without involving cross-reactivity of NSAIDs or even with a positive skin test for an NSAID. A 55-year-old woman was referred to the Emergency Department for anaphylaxis. She suffered from generalized hives, chest tightness, and hypotension a few minutes after intramuscular injection of diclofenac. One year ago, she had experienced a similar reaction after intramuscular injection of aceclofenac. Thereafter, she had been taking naproxen as needed to relieve her osteoarthritis pain, without having an adverse reaction. To confirm drug hypersensitivity and to find alternative drugs, provocation tests were performed with acetaminophen, celecoxib, and lysine-aspirin. All tests were negative, and a skin prick test with diclofenac was also negative. However, intradermal injection of 0.05 mL (37.5 mg/mL) diclofenac provoked an anaphylactic shock and resulted in her admission. Here, we report a rare case of single NSAID-induced anaphylaxis, which was only triggered by acetic acid derivatives of NSAIDs, presumably by an immunoglobulin E-mediated reaction.

Keywords

Nonsteroidal anti-inflammatory drugs
Drug hypersensitivity
Anaphylaxis
Diclofenac
NSAID-induced hypersensitivity

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs commonly used for the control of

inflammation and pain. Although the various drugs in the NSAID class have different chemical structures, cross-reactivity between NSAIDs is common due

to their common pharmacological mechanism of cyclooxygenase-1 inhibition ^[1]. In this case, selective cyclooxygenase-2 inhibitors were used as an alternative ^[2].

Some NSAIDs do not cross-react with other classes of NSAIDs. Immunoglobulin E (IgE)-mediated hypersensitivity reactions to these drugs may occur, termed single NSAID-induced urticaria/angioedema or anaphylaxis, and are very rare ^[3].

This case presents the report concerning a patient with a single NSAID-induced anaphylaxis confined to a single chemical class, confirmed by skin testing and provocation testing.

2. Case presentation

A 55-year-old female patient was brought to the Emergency Department with suspected anaphylactic shock. She had received an intramuscular injection of diclofenac for osteoarthritis pain control at another clinic, and within minutes developed signs and symptoms of generalized urticaria, chest tightness, and hypotension. She was treated with epinephrine bolus, glucocorticoid bolus, and antihistamine bolus in the Emergency Department of an external hospital, and was referred to our allergy clinic due to rapid recovery of symptoms and signs.

She had a history of similar symptoms and signs after receiving intramuscular injection of aceclofenac for joint pain control one year ago and was taking naproxen as needed for joint pain control, which did not cause any adverse effects.

Three weeks after the anaphylaxis, a drug-induced test was planned to identify the causative drug(s) of the adverse drug reaction and to identify alternative medications for pain control. After admission to the surgery center, paracetamol (Denogan injection, Yungjin Pharm., Seoul, Korea), celecoxib (Celebrex, Pfizer Inc., New York, NY, USA), and lysine-aspirin (Arthalgyl injection, Il-Yang Pharm, Yongin, Korea) were administered sequentially, under close medical

observation, in the following order: intravenously (total dose 1.5 g), orally (total dose 200 mg), intravenously (cumulative dose 841.5 mg), and orally (500 mg) ^[4]. All provocation tests were negative.

During the next outpatient visit, a skin prick test using undiluted diclofenac (37.5 mg/mL; Cafenac injection, Hana Pharm., Seoul, Korea) was performed, showing negative result. Immediately after intradermal injection (0.05 mL) using the undiluted solution, swelling and redness appeared at the injection site, and local pruritus was observed. Within 10 minutes, the anaphylactic reaction recurred. Her blood pressure dropped to 69/47 mmHg. She also developed generalized urticaria, and complained of pruritus, palpitations and chest tightness.

Epinephrine, systemic steroids, and antihistamines were immediately administered, but symptoms and signs were not fully controlled, necessitating one day of inpatient observation.

Anaphylaxis with intramuscular aceclofenac, intramuscular diclofenac, and intradermal diclofenac, and tolerance to oral naproxen, oral celecoxib, intravenous lysine-aspirin, oral aspirin, and intravenous paracetamol all pointed to the diagnosis of a single NSAID-induced anaphylaxis of the acetic acid derivative group (**Table 1**).

Further skin testing and provocation tests with other NSAIDs were recommended, but the patient refused further testing for fear of recurrence of the anaphylaxis. A medicine safety card was issued and she was counselled to strictly avoid future exposure to NSAIDs of the acetic acid derivative class.

3. Summary

NSAIDs are classified in two ways based on their relative degree of inhibition of cyclooxygenase isoenzymes and similarity of chemical structure (**Table 1**).

The mechanisms of NSAID-induced adverse drug reactions can be attributed to the degree of inhibition of

Table 1. Nonsteroidal anti-inflammatory drugs classification according to chemical structure and pharmacological activity in inhibition of cyclooxygenase isoenzymes ^[1,5].

Chemical classification		Pharmacological classification		
Chemical group	Example drugs	Relative COX-inhibition	Example drugs	
Salicylic acid derivatives	Aspirin Salsalate	Strong COX-1 inhibitors	Aspirin Ibuprofen	
Para-aminophenol	Acetaminophen		Indomethacin	
Acetic acid derivatives	Indomethacin Sulindac Etodolac Diclofenac Aceclofenac	Poor COX-1 inhibitors	Sulindac Naproxen Meclofenamate Diclofenac Aceclofenac Ketoprofen Piroxicam Mefenamic acid	
Propionic acid derivatives	Ibuprofen Naproxen Ketoprofen		Acetaminophen Salsalate	
Fenamic acid derivatives	Mefenamic acid Meclofenamate		Preferential COX-2 inhibitors	Meloxicam Nimesulide
Enolic acid derivatives	Piroxicam Meloxicam phenylbutazone			
Selective COX-2 inhibitors	Celecoxib Parecoxib Etoricoxib		Selective COX-2 inhibitors	Celecoxib Parecoxib Etoricoxib

Diclofenac and aceclofenac are pharmacologically classified in the same group as aspirin and naproxen, in terms of inhibition of cyclooxygenase-1 (COX-1), but it is not related to either substance in its chemical structure. Drugs in bold are the tested ones in this report. Abbreviation: COX, cyclooxygenase.

cyclooxygenase-1 according to the first classification and the immune response according to the second classification ^[5].

If an immediate-type hypersensitivity reaction occurs, as a result of the intake of a single NSAID or NSAIDs of the same chemical group, it can be diagnosed as a single NSAID-induced hypersensitivity reaction. However, these patients are resistant to other NSAIDs with less chemical similarity to the NSAID in question ^[1]. Hypersensitivity reactions to single NSAIDs have been reported only to the pyrazolones, paracetamol, ibuprofen, diclofenac, and naproxen ^[3]. In 53 patients with hypersensitivity to propyphenazone, a drug of the pyrazolone class,

skin tests were positive in 83% of cases, and serum-specific IgE was detected in 58% of patients by enzyme-linked immunosorbent assay ^[6]. Serum-specific IgE has not been detected in patients taking NSAIDs other than pyrazolones ^[1]. In 59 patients with a history of hypersensitivity to diclofenac, detection of specific IgE to diclofenac itself or its metabolites was attempted, but none was detected ^[7].

In Korea, patients with diclofenac-induced anaphylaxis were skin-tested with various NSAIDs within 3 days of anaphylaxis, but the results all showed negative ^[8]. Lee *et al.* ^[9] reported that a patient who was resistant to aspirin had anaphylaxis to diclofenac alone. Skin tests with diclofenac were negative. In a

total of nine patients with diclofenac hypersensitivity, including seven anaphylactic cases registered with the Allergy Vigilance Network in France over an 11-year period, four intradermal test-positive cases suggestive of an IgE-mediated reaction were reported. In one patient with a negative intradermal test, anaphylaxis was reproduced through oral provocation test^[10].

As the previous literature review indicates, hypersensitivity reactions to single NSAIDs are very rare and no standardized diagnostic protocol has been proposed. Kowalski *et al.*^[3] suggested that skin prick testing with diclofenac should be performed in patients who are resistant to aspirin and are hypersensitive to diclofenac; if negative, a concentration-dependent intradermal test should be performed. NSAIDs, including diclofenac, are recommended for terminal testing with powdered drug and intradermal testing at a concentration of 0.1 mg/mL^[11]. To avoid systemic hypersensitivity reactions such as the one presented in this case, intradermal testing should be performed with the recommended dilutions and, if negative, escalated to full strength.

Aceclofenac is a prodrug of diclofenac and is similar in chemical structure to diclofenac (Figure 1). A case of anaphylaxis after taking aceclofenac tablets for osteoarthritis was positive for skin testing with aceclofenac, but resistant to other NSAIDs, including diclofenac^[12].

In this case, immediate-type hypersensitivity reactions were confirmed by skin testing with the culprit drug, diclofenac injection. Intradermal testing alone can cause anaphylaxis and should be done with caution and under medical observation. This patient developed anaphylaxis due to diclofenac and aceclofenac, which belong to the acetic acid derivatives in the chemical classification of NSAIDs. Other commonly used NSAIDs in the acetic acid derivatives group include indomethacin and ketorolac, but further testing was not available to prove hypersensitivity to these drugs. Tolerance to NSAIDs other than acetic acid derivatives has been demonstrated by actual use and provocation test.

In conclusion, we report the first case in Korea of a single NSAID-induced anaphylaxis to diclofenac and aceclofenac, which are the NSAIDs of acetic acid derivative group, and the first case of an NSAID-induced IgE-mediated hypersensitivity reaction using skin tests.

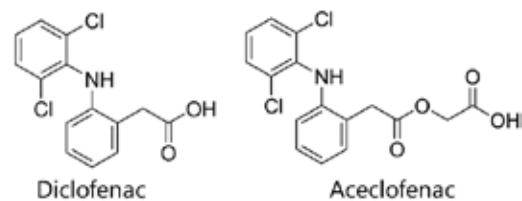


Figure 1. Chemical structures of diclofenac and aceclofenac

Disclosure statement

The author declares no conflict of interest.

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