

Selective adverse reactions to diflunisal

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Background and Objective: Diflunisal is a difluorophenyl derivative of salicylic acid. We report two patients who presented immediate adverse reactions to diflunisal (Dolobid) that consisted of generalized urticaria and chest tightness.

Methods: Diflunisal was conjugated to human serum albumin in order to perform in vivo and in vitro tests (skin prick and intradermal tests, leukocyte histamine release, and RAST). The patients were challenged following a single-blind, placebo-controlled oral procedure with diflunisal and other nonsteroidal antiinflammatory drugs.

Results: Skin tests with diflunisal were negative as were leukocyte histamine release tests and RAST in both patients. They tolerated therapeutic doses of aspirin, salsalate, salicylamide, lysine acetylsalicylate, acetaminophen, dipyron, and propyfenazone. The oral provocation with diflunisal elicited an immediate response at the cumulative dose of 400 mg in both patients.

Conclusion: These are two exceptional cases of selective adverse reactions to diflunisal with good tolerance to other salicylates and nonsteroidal antiinflammatory drugs. Thus, the inhibition of cyclooxygenase does not seem to be the mechanism involved. The pathogenic mechanism implicated in the reaction remains unclear, both idiosyncratic and immunologic mechanisms could explain our patients' adverse responses.

INTRODUCTION

Salicylates are the oldest and most commonly used family of nonsteroidal anti-inflammatory drugs.¹

Diflunisal is a salicylate with analgesic and anti-inflammatory activity and it is used in osteoarthritis and musculoskeletal pain.² It is a derivative of salicylic acid with an extra difluorophenyl group at the C5 position but it lacks the D-acetyl group¹ (Fig 1).

This drug has pharmacologic actions similar to aspirin and other nonsteroidal anti-inflammatory drugs as it is able to inhibit the cyclooxygenase of arachidonic acid metabolism from intact human platelets. Diflunisal is 37 times less potent than aspirin.²

Inhibition of the cyclooxygenase pathway has been considered the mechanism implicated in adverse reactions to nonsteroidal anti-inflammatory

drugs,³ as all drugs in the group share this property.⁴ There are, however, some cases⁵⁻⁸ of selective reactions to one drug or the family of nonsteroidal anti-inflammatory drugs with good tolerance to other cyclooxygenase inhibitors, which cannot be explained by this hypothesis.

We report here two patients who had selective adverse reactions to diflunisal with good tolerance to other salicylates and other nonsteroidal anti-inflammatory drugs.

CASE REPORTS

We present two patients, 70- and 74-year-old women, who developed itching of the hands and feet and generalized urticaria 30 minutes after the intake of one tablet of Dolobid (diflunisal, 500 mg) (Merck Sharp & Dohme de España, S.A., Madrid, Spain). One patient also developed chest tightness and tongue angioedema. Both responded to 0.3 mg epinephrine subcutaneously, 40 mg methylprednisolone, and 5 mg dexchlorpheniramine intramuscularly in an emergency room.

Both patients had previously tolerated aspirin and pyrazolones, but they had not taken any nonsteroidal anti-inflammatory drugs after the adverse reaction to diflunisal. They did not know whether they had taken diflunisal previous to the described adverse reactions.

Skin prick tests to a battery of common inhalants (including pollens, molds, mites, and cat and dog dander) (Ifidesa-Aristegui, Bilbao, Spain) were negative in both patients. Neither of them had a personal or family history of atopy. Total IgE in patient 1 was 101 IU/mL and 9 IU/mL in subject 2 (CAP System, Pharmacia, Uppsala, Sweden).

MATERIAL AND METHODS

Skin prick and intradermal tests were performed with diflunisal in a saline solution and with this drug conjugated with human serum albumin according to the method of Levine and Ovary.⁹ All the solutions had a final concentration of 1 mg/mL. This solution and three tenfold dilutions were tested. The positive control was histamine dihydrochloride, 10 mg/mL for prick tests and 0.1 mg/mL for intradermal tests (Ifidesa-Aristegui, Bilbao, Spain). The negative control was saline solution. Skin tests were read at 15 minutes for prick tests and 20 minutes for intradermal tests, and then at six and 24 hours. Five atopic and eight nonatopic subjects were used as controls.

We performed a leukocyte histamine release test with conjugated diflunisal according to the automated fluorimetric method.¹⁰ Diflunisal was tested at 0.32, 1.6, 8, 40, 200, and 1,000 µg/mL. The drug did not fluoresce. Two atopic patients were tested in the same assay.

Cyanogen bromide-activated filter paper discs were coupled with conjugated diflunisal at a concentration of 1

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mg/mL according to the method of Ceska et al.¹¹ The discs were incubated for 24 hours at 4 °C with the patients' sera (50 µL serum/disc). Afterwards a standard RAST was carried out according to the manufacturer's instructions (Phadebas RAST, Pharmacia, Uppsala, Sweden). Five atopic patients with elevated IgE and four nonatopic subjects were used as controls.

The two patients were challenged following a single-blind, placebo-controlled oral procedure with aspirin, diflunisal, salsalate, lysine acetylsalicylate, salicylamide, acetaminophen, dipyrone, and propyfenazone. The drugs were administered in white opaque gelatin capsules. Progressively increasing doses with 1-hour intervals were given until reaching the therapeutic dose. After the last dose the patient remained under observation for three hours. Only one drug or placebo was given on any one day. After a positive reaction, the next oral challenge was separated by at least 2 weeks. The provocation protocol was started with placebo (lactose four capsules). If well tolerated, aspirin was administered on a second day. If no reaction was observed, diflunisal was given on a third day, continuing the drug administrations in the order mentioned above. Diflunisal was administered at 50, 100, and 250 mg. The oral drug challenges were performed under medical observation and fully emergency therapy was available. Written informed consent was given by both patients.

RESULTS

Skin prick and intradermal tests with diflunisal in a saline solution and conjugated with human serum albumin were negative. Leukocyte histamine release and RAST gave negative results. All these tests were negative in control patients. In the oral challenge both patients reacted with diflunisal, but tolerated the rest of salicylates and other nonsteroidal anti-inflammatory drugs (Table 1).

Thirty minutes after the administration of 250 mg of diflunisal (cumulative dose 400 mg), patient 1 had itching of her hands and feet, mild

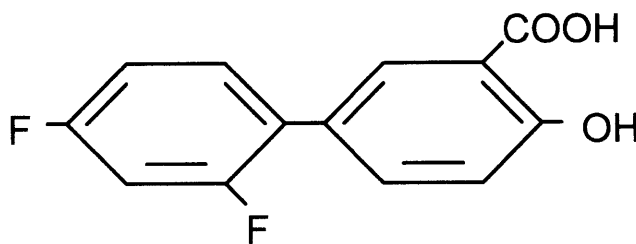


Figure 1. Diflunisal, 5-(2,4)-difluorophenyl salicylic acid.

generalized urticaria, and chest tightness. There were no changes in spirometry and blood pressure from basal values. She was treated with 5 mg dexchlorpheniramine and 40 mg methylprednisolone intramuscularly and the reaction subsided in the following two hours. The patient did not have any late response.

Patient 2 developed, 15 minutes after the administration of 250 mg diflunisal (cumulative dose 400 mg), itching of her hands and feet with some wheals on the wrist. She was treated with 5 mg dexchlorpheniramine and 40 mg methylprednisolone intramuscularly and the reaction subsided in the following two hours. No late response was observed.

DISCUSSION

We report two exceptional patients who presented selective adverse reactions to diflunisal with good tolerance to other salicylates and nonsteroidal anti-inflammatory drugs as was demonstrated by oral challenge. In the literature reviewed (Comprehensive Medline /1983–1993/), we have only

found one report of an anaphylactoid reaction caused by this drug.¹²

As both patients tolerated aspirin and other nonsteroidal anti-inflammatory drugs, inhibition of the cyclooxygenase pathway is excluded as the implicated mechanism.

In order to study the mechanism involved, we performed skin tests, histamine release, and RAST with diflunisal conjugated to human serum albumin. Although these tests gave negative results, an immunologic mechanism cannot be ruled out. This is a common finding with the majority of drugs because their determinants are unstable and/or unknown.¹³

Diflunisal is metabolized differently from aspirin and the other salicylate derivatives.¹⁴ It is not metabolized to salicylic acid by cleavage of the two aromatic rings and there is no evidence of loss of fluoride atoms.^{2,12} Thus, the metabolites generated are different from those of other salicylates. This biochemical characteristic may explain the negativity of the immunologic tests performed with the native drug, and could also be the basis for the lack of

Table 1. Results

	Patient 1	Patient 2
Prick tests	Negative	Negative
Intradermal tests	Negative	Negative
Histamine release	Negative	Negative
RAST	Negative	Negative
Oral challenge		
Diflunisal (cumulative dose 400 mg)	Positive	Positive
Other non-steroidal anti-inflammatory drugs*	Negative	Negative

* Aspirin, salsalate, l. acetylsalicylate, salicylamide, acetaminophen, and dipyrone, propyfenazone.

clinical reactivity observed in our patients to other salicylates.

In conclusion, we present two exceptional cases of immediate selective reactions to diflunisal. The studies performed indicate that cyclooxygenase inhibition is not implicated, but we could not elucidate the mechanism involved. Both an immunologic and an idiosyncratic response to diflunisal metabolites could explain our patients' selective reactions.

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