

Hypersensitivity reactions to anthranilic acid derivatives 17

Montserrat Fernandez-Rivas, MD; Belén de la Hoz, MD; Manuela Cuevas, MD, PhD*; Ignacio Davila, MD; Santiago Quirce, MD, PhD; and Eloy Losada, MD, PhD

Anthranilic acid derivatives are a group of nonsteroidal antiinflammatory drugs that include glafenine and fenamates. We report a woman who had immediate adverse reactions to glafenine and meclofenamate sodium.

Skin prick and intradermal tests were performed with solutions of glafenine and meclofenamate in phosphate-buffered saline (PBS) and with the drugs bound to human serum albumin (HSA). Prick and intradermal tests with PBS solutions were negative for both drugs as were prick tests with HSA solutions. Intradermal tests with HSA-glafenine, however, were positive at 20 minutes, and at 6 and 24 hours. Intradermal tests with HSA-meclofenamate elicited a positive response at 6 and 24 hours. These tests were negative when performed in control subjects. A leukocyte histamine release test and a RAST assay were negative for both drugs. The patient was challenged following a double-blind placebo-controlled oral procedure and tolerated therapeutic doses of aspirin, indomethacin, ibuprofen, dipyron, diclofenac, piroxicam, and acetaminophen. The oral challenge with glafenine and meclofenamate reproduced the reactions (eliciting doses: 50 mg and 15 mg, respectively), and the patient also reacted to 30 mg of mefenamic acid, an anthranilic acid derivative she had never previously received.

This is an exceptional case of selective adverse reactions to glafenine and fenamates, anthranilic acid derivatives, in a patient tolerating aspirin and other cyclooxygenase inhibitors. Our study implicates an immunologic mechanism, and the existence of cross-reactivity between the drugs (or some active metabolite generated in vivo).

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAID) are a group of extensively used drugs often implicated in a variety of adverse reactions.¹ As all these drugs share the ability to inhibit the cyclooxygenase of the arachidonic acid metabolism,² it has been postulated that these adverse responses to NSAID are due to an idiosyncratic reaction resulting from the inhibition of the cyclooxygenase pathway.¹

This hypothesis cannot explain all the adverse reactions to NSAID. There is a well defined group of patients who present selective reactions to pyrazolones but tolerate aspirin and other prostaglandin inhibitors, in which a type I immunologic mechanism seems plausible.³ In this sense, zomepirac and tolmetin have

been implicated in anaphylactoid reactions. The clinical presentation of the reported cases is suggestive of an IgE pathogenesis, although the immunologic studies were negative.⁴⁻⁶

We report a woman who presented selective or adverse reactions to glafenine and meclofenamate sodium, two anthranilic acid derivatives, with good tolerance of aspirin and other cyclooxygenase inhibitors. An immunologic mechanism is possibly implicated.

CASE REPORT

Two years before consultation a 49-year-old woman received glafenine, 400 mg twice each day, due to back pain. After 2 weeks of treatment, and within 30 minutes of the morning dose, she experienced generalized urticaria, cough, chest tightness, throat hoarseness, nausea, and vomiting. The patient received methylprednisolone and diphenhydramine and her symptoms resolved over several hours. Glafenine was discontinued.

Three months before consulta-

tion in our department the patient received meclofenamate sodium, 100 mg each day, for knee pain. Within 30 minutes of the fourth dose she began to notice progressive urticaria, edema of her eyelids and lips, and hoarseness. She responded well to symptomatic treatment. Meclofenamate was stopped.

The patient had previously tolerated aspirin, acetaminophen (paracetamol) and dipyron, but she had not taken any NSAID after the last adverse reaction to meclofenamate.

There was no personal or family history of atopy. Review of systems was unremarkable. Physical examination was normal. Routine laboratory tests were normal. There was no peripheral eosinophilia. Total IgE was 4 IU/mL (IgE EIA, Pharmacia, Sweden). Complement determinations (C3, C4, CH50) were within normal limits. Skin prick tests to common aeroallergens (Ben-card, UK) were negative, and a basal spirometry was normal, with FVC of 93% and FEV₁ of 103% of predicted values.

Skin prick and intradermal tests

From the Allergy and Immunology* Departments, Ramón y Cajal Hospital. Madrid, Spain.

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were performed with glafenine and meclofenamate in PBS (phosphate buffered saline) and with these two drugs conjugated with HSA (human serum albumin) according to the method of Levine and Ovary.⁷ All the solutions had a final concentration of 1 mg/mL. The 1-mg/mL solution and three tenfold dilutions were tested for each drug. The positive control was histamine phosphate 10 mg/mL for prick tests and 0.1 mg/mL for intradermal tests (Dome-Hollister-Stier, Miles Spain). The negative controls were PBS and PBS-HSA. Skin tests were read at 15 minutes for prick tests and 20 minutes for intradermal tests, and then all of them at 6, 24, and 48 hours. For prick tests we considered a reaction positive if the wheal size induced by the drug was 3 mm larger than the negative control.⁸ For intradermal tests we used the grading system from Norman⁹ and a 2+ reaction was considered positive.

Prick and intradermal tests with PBS solutions were negative for both drugs, as well as prick tests with HSA drug solutions. Intradermal tests with HSA-glafenine, however, were positive at 20 minutes, 6, and 24 hours. No immediate response was obtained with intradermal tests with meclofenamate conjugated to HSA, but a positive response was observed when reading at 6 and 24 hours. (Table 1). The 48-hour read-

ing was negative for both drugs. These skin tests were performed on ten control subjects with negative results.

We performed a leukocyte histamine release test with glafenine and meclofenamate HSA solutions according to the method of Siraganian¹⁰ and with the modifications previously described.¹¹ The assay was negative for both drugs.

Cyanogen bromide activated filter paper discs were coupled with glafenine and meclofenamate HSA solutions at a concentration of 1 mg/mL, according to the method of Ceska et al.¹² The discs were incubated (in duplicate) for 24 hours with the patient's serum. Afterwards a standard RAST technique was undertaken following the manufacturer's instructions (Phadebas RAST Pharmacia, Uppsala, Sweden). Human serum albumin discs were used as controls. The assay was also performed with sera from five control subjects who tolerated both drugs, and with total IgE similar to the patient's. There was no difference between the cpm obtained in the patient and the controls.

The patient was challenged with progressively increasing doses of aspirin up to 500 mg with good tolerance. She also tolerated indomethacin, 50 mg; diclofenac, 50 mg; ibuprofen, 400 mg; piroxicam, 10 mg; dipyrrone, 575 mg; and acetaminophen, 650 mg. She was chal-

lenged with glafenine, meclofenamate, and mefenamic acid, an anthranilic acid derivative she had never previously received. The three anthranilic acid derivatives induced adverse reactions with the following eliciting doses: glafenine, 50 mg; meclofenamate, 15 mg; and mefenamic acid, 30 mg. The three reactions were similar, appeared at 60 minutes after drug ingestion, and consisted of an urticarial rash on the face and thorax, irritative cough, and hoarseness. There were no changes in basal spirometry or blood pressure. The reactions were treated with an antihistamine and a single dose of corticosteroids and she stayed under observation for the subsequent three hours with complete recovery. Before the provocative tests the patient gave written, fully informed consent. She was carefully monitored and full emergency therapy was available. All the drugs were administered in white opaque gelatin capsules, following a double-blind placebo-controlled oral procedure. Only one drug or placebo (lactose, 100 mg) was given on any one day. After a positive provocation the next drug challenge was separated by at least seven days.

DISCUSSION

We report a patient who presented selective adverse reactions to two anthranilic acid derivatives, glafenine and meclofenamate sodium, as was demonstrated by a double-blind placebo-controlled oral challenge. She tolerated aspirin and other NSAIDs: indomethacin, diclofenac, dipyrrone, ibuprofen, piroxicam, and acetaminophen. All these drugs belong to different chemical families and are known to have diverse effects on prostaglandin biosynthesis^{2,15,16}; thus cyclooxygenase inhibition was excluded as the implicated mechanism in our patient's adverse reactions.

The anthranilic acid derivatives are a group of NSAIDs that includes glafenine, antrafenirle, floctafenine, and the fenamates (mefenamic, flu-

Table 1. Intradermal Tests with HSA-Conjugated Drugs

Drug	Reading		
	20 minutes	6 hours	24 hours
Glafenine, mg/mL			
0.001	0	±	±
0.01	0	±	±
0.1	1+	2+	2+
1.0	2+	4+	4+
Meclofenamate, mg/mL			
0.001	0	0	0
0.01	0	±	±
0.1	0	1+	1+
1.0	0	3+	2+

Grading system according to Norman.⁹

fenamic, etofenamic, and meclofenamic acids) (Fig 1). They are all able to inhibit cyclooxygenase. In contrast to the other aspirin-like drugs some of the fenamates, especially meclofenamic acid, appear to antagonize certain effects of prostaglandins.^{15,16} This latter characteristic could explain the reactions of the patient admitting that she exhibits a unique biochemical defect. As far as we know, this property has not been described for glafenine.

In an attempt to examine the underlying mechanisms, we performed skin tests, a leukocyte histamine release, and a RAST assay with the two implicated drugs. Histamine release test and RAST were negative. Skin tests performed with solutions of glafenine and meclofenamate in PBS without HSA were negative. Intradermal tests with HSA solutions of glafenine and meclofenamate gave positive responses. We considered that HSA working as a carrier for the drugs (haptens) would be better to elicit an allergic cutaneous reaction, as was finally the case. Prick tests were again negative, but we obtained positive responses in the intradermal tests at 20 minutes for glafenine and at 6 and 24 hours for both drugs.

In this case there are certain clinical characteristics that suggest an immunologic mediated reaction: the symptomatology, the timing of the reactions, the low eliciting doses, the reproduction of the reaction with a drug of the group never taken before. Further, the positive skin tests support this mechanism. We can hypothesize that reactive metabolites generated in vivo and bound to HSA could have acted as true immunogens eliciting positive intradermal tests. The leukocyte histamine release test and RAST negative results do not exclude hypersensitivity. If an in vivo generated metabolite is implicated in the adverse reactions of the patient, these tests would probably be negative.

Glafenine is an effective analgesic and has been extensively used in Europe. It has, however, often been found responsible for allergy-like reactions. The clinical pictures strongly suggest an immunologic reaction, but the underlying mechanism has not been elucidated.¹⁷⁻²² The fenamates have not gained widespread clinical acceptance. Meclofenamate is the third generation of the fenamates. They all cause frequent side effects, most of which are gastrointestinal.^{14,23,24}

In the literature reviewed (Comprehensive Medline 1966-1992) there are no reports of hypersensitivity reactions to meclofenamate. Further, the studies concerning glafenine "sensitivity" do not describe similar associated reactions with fenamates.¹⁷⁻²¹ To the best of our knowledge this is the first report of combined reactivity to glafenine and fenamates (meclofenamic and mefenamic acid) indicating the presence of cross-reactivity.

In conclusion, we report an exceptional case of selective adverse reactions to glafenine and fenamates, anthranilic acid derivatives, in a patient who tolerated aspirin and other cyclooxygenase inhibitors. Our study suggests that an immunologic mechanism was probably implicated and the existence of cross-reactivity between the drugs (or some active metabolites generated in vivo).

With this case report we would like to draw attention to the possibility of selective adverse reactions to one drug or family of NSAIDs. Similar restricted reactions have already been reported.³⁻⁶ The prostaglandin inhibition hypothesis does not explain these adverse responses, as these patients tolerate drugs that inhibit the cyclooxygenase of the arachidonic acid metabolism: they are probably mediated by an immunologic mechanism. To evaluate these patients completely we believe it is important to challenge them with aspirin and the implicated drug. If aspirin is well tolerated an idiosyncratic reaction, due to cyclooxygenase inhibition is excluded and this will indicate a safety of future administration of other NSAIDs.

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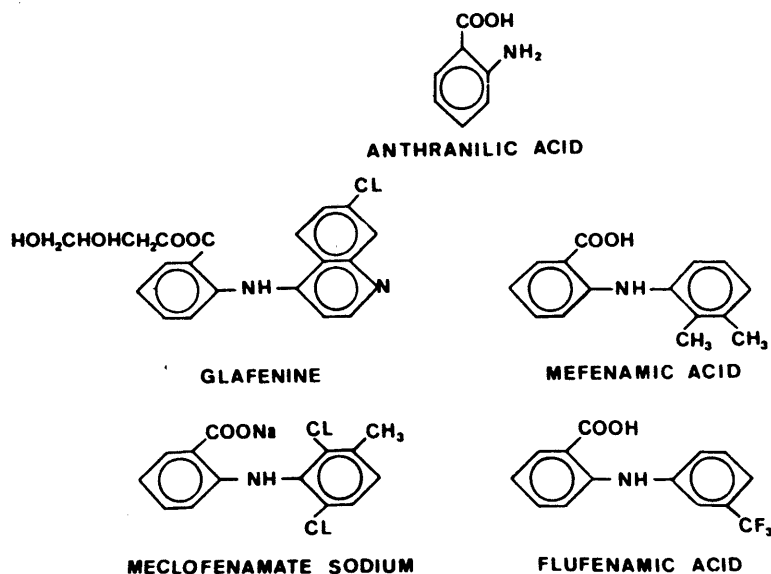


Figure 1. Anthranilic acid derivatives.

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Request for reprints should be addressed to:
 Montserrat Fernandez-Rivas
 Urb. Las Suertes 19, 4B.
 28400 Collado-Villalba
 Spain

NEARLY 50 YEARS AGO

"REGROWTH" OF TONSILS AND ADENOIDS AFTER REMOVAL LINKED TO ALLERGY

Prospective study of 136 children with allergic rhinitis who required tonsillectomy and adenoidectomy disclosed regrowth of lymphoid tissue in the tonsillar fossae or adenoidal area in only 4, all of whom were less than 3 years old and had had no previous specific treatment for allergy. Regrowth of such tissue occurred in 14 of 60 children in whom allergy was diagnosed only after tonsillectomy and adenoidectomy.

The authors inferred regrowth of such tissue after removal of tonsils and adenoids was strongly suggestive of allergy, and allergy management when indicated before surgery minimized the likelihood of regrowth.

Tonsillectomy and adenoidectomy are recommended now much less frequently than 50 years ago and it is well known that surgery is not effective for allergic rhinitis. Nevertheless, tonsils and adenoids are still removed, often without adequate evaluation or management of allergy.

—RMS

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