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# Anaphylaxis to diclofenac: nine cases reported to the Allergy Vigilance Network in France

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## Abstract

Nine cases of diclofenac hypersensitivity recorded by the Allergy Vigilance Network in France from 2002 to 2012 were studied. Data from history, symptoms, skin tests, basophil activation tests, and oral challenge (OC) were recorded. Grade 3 severe anaphylactic reactions occurred in seven cases of nine. IgE-dependent anaphylaxis was confirmed in six cases: positive intradermal tests ($n = 4$), a syndromic reaction during skin tests ($n = 1$), and one case with grade 1 reaction and negative skin tests had an anaphylactic shock to the OC. A nonimmune reaction was suspected in one case. An IgE-dependent mechanism may be the predominant cause of adverse reactions to diclofenac. Allergy skin tests must be carried out sequentially at the recommended concentrations. BATs may be helpful because they can support the diagnosis of anaphylaxis. Given the risks of a direct challenge to diclofenac, OC to aspirin should be performed first to exclude a nonimmunologic hypersensitivity to NSAIDs. Tests for specific IgEs to most frequently used NSAIDs such as diclofenac and ibuprofen are urgently needed.

Hypersensitivity to NSAIDs is related to immunologic and nonimmunologic mechanisms. Hypersensitivity, expressed by cutaneous signs, is usually related to a nonimmunologic mechanism. However, IgE-dependent hypersensitivity may occur. Its frequency varies, depending on the NSAID (1, 2).

We report nine cases of hypersensitivity to diclofenac, recorded by the Allergy Vigilance Network from 2002 to 2012. The results of skin tests, laboratory tests, and oral challenge are presented.

## Material and methods

The methodology of case collection has been previously reported (3). Briefly, the data include age, sex, medical history, grade of the reaction, emergency treatment modalities, skin tests, laboratory tests, and oral challenge (OC) (3, 4).

Skin tests were performed in seven cases according to the guidelines (5, 6). First-line measures included prick tests, followed by intradermal test (IDT) to Voltarène® from 25 μg/ml to 25 mg/ml. Three patients underwent basophil activation tests (BATs). OC was performed in hospital centers to diclofenac (1), to aspirin (2), and to celecoxib (1).

## Case reports

The case reports concern five men and four women with a mean age of 60 years (range: 46–77 years) (Table 1).

Seven patients presented with clinical signs of severe anaphylactic reactions: six anaphylactic shock and one laryngeal angioedema that could be classified as grade 3. One patient presented generalized urticaria, nausea, abdominal pain, and faintness (grade 2). One patient had generalized erythema (grade 1).

Time to reaction varied depending on the route of administration: 30 s after intravenous administration (No. 4), five to ten minutes after intramuscular injection (Nos. 2 and 3), from five minutes to five hours after oral administration (mean time to reaction: 90 min) (Nos. 1, 5, 6, 8, and 9), and 30 min for one patient after contact with the ocular mucosa (No. 7).

Seven patients were managed by the mobile emergency unit (MEU) and then transferred to a hospital emergency department for 12–24 h. One was already in hospital in a surgical department. Epinephrine was administered to five patients, and vascular filling and oxygen in one case (Table 1).

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**Table 1** Clinical signs of diclofenac hypersensitivity in nine patients

| Case report | Sex | Age (years) | Past history | Associated factors | Route of administration/ time to reaction | Clinical reaction | Emergency management |
|---|---|---|---|---|---|---|---|
| 1 | M | 50 | – | β-blocker eye drops | p.o 5 h | Anaphylactic shock (Loss of consciousness and cardiovascular collapse) | EU |
| 2 | M | 50 | Acute generalized urticaria after application of diclofenac gel | – | IM 5 min | Anaphylactic shock | MEU then EU Epinephrine |
| 3 | W | 77 | – | β-blocker eye drops ARA-2 | IM 10 min | Anaphylactic shock | Home visit by GP EU Epinephrine Hospitalization for 24 h |
| 4 | M | 68 | Malaise and skin rash a few minutes after taking diclofenac p.o. | – | IV 30 s | Anaphylactic shock | Surgery department. Epinephrine |
| 5 | W | 53 | – | β-blocker p.o. | p.o. 45 min | Anaphylactic shock | Home visit by GP EU Epinephrine Hospitalization for 12 h |
| 6 | M | 70 | – | β-blocker p.o. Aspirin Alcohol | p.o. 10 min | Anaphylactic shock | MEU then EU Epinephrine Monitoring for 14 h |
| 7 | W | 65 | Serious systemic reaction to celecoxib | – | Hand contact with eye mucosa (gel) 30 min | Laryngeal AO (Facial AO, malaise with tachycardia) | MEU then EU Monitoring for 12 h |
| 8 | M | 46 | – | Ranitidine | p.o. 5 min | Grade 2 anaphylaxis (Urticaria, nausea, abdominal pain, and lipothymic malaise) | Consultation at GP then MEU then EU Monitoring for 17 h |
| 9 | W | 59 | Urticaria and angioedema recurring without drug intake | – | p.o. (75 mg) 1 h 30 | Grade 1 anaphylaxis (Generalized erythema) | – |

p.o., *per os*; EU, emergency unit; MEU, mobile emergency unit; ARA2, angiotensin receptor antagonist.

**Table 2** Allergy tests in nine cases of diclofenac hypersensitivity

| Case | Prick tests | IDT | Syndromic reaction to skin test | BAT | OC | Diagnosis* |
|---|---|---|---|---|---|---|
| 1 | – | + at 2.5 mg/ml | – | + | Negative OC to aspirin | Confirmed anaphylaxis |
| 2 | nd | nd | nd | nd | nd | Plausible anaphylaxis |
| 3 | – | Negative up to 1 mg/ml | – | – | Negative OC to celecoxib (cumulative dose: 200 mg) | Plausible anaphylaxis |
| 4 | – | + at 0.25 mg/ml (skin tests to other drugs used general anesthesia: negative) | – | nd | Negative OC to aspirin | Confirmed anaphylaxis |
| 5 | – | + at 25 mg/ml | – | nd | nd | Confirmed anaphylaxis |
| 6 | – | – at 0.025 mg/ml | Intense and diffuse pruritus | nd | nd | Confirmed anaphylaxis |
| 7 | nd | nd | nd | nd | nd | Uncertain mechanism |
| 8 | – | + at 25 mg/ml for diclofenac | Acute urticaria and palmar pruritus | + | nd | Confirmed anaphylaxis |
| 9 | – | – at 0.25 mg/ml | – | Not interpretable | + at 25 mg: anaphylactic shock within 5 min (palmar and conjunctival erythema, diffuse pruritus, tachycardia, and hypotension) | Confirmed anaphylaxis |

nd, not done.

*Decision criteria for diagnosis: Anaphylaxis confirmed by positive skin tests ± syndromic reaction when skin tests ± positive TAB ± positive OC; Plausible anaphylaxis only based on the rapid time to onset of symptoms (anaphylactic shock); and Uncertain mechanism when history of reaction to other NSAIDs.

Associated factors were reported for four patients: treatment with β-blockers (two in eye drops and two via the oral route). One of these patients was also taking an ARA-2, and another (No. 6) also took aspirin and alcohol. A past history of skin reactions to diclofenac was recorded in two cases (Nos. 2 and 4) and a systemic reaction to celecoxib in one case (No. 7).

Seven patients had allergy tests (Table 2). IDTs were positive in four patients at 0.25 mg/ml, 2.5 mg/ml, and 25 mg/ml. Patient No. 8 presented abdominal urticarial and palmar pruritus twenty minutes after IDT. In patient No. 6, diffuse and intense pruritus was elicited by IDT at 0.025 mg/ml. BAT was positive twice (Nos. 1 and 8). Skin tests and BAT were negative for two patients (Nos. 3 and 9). For patient No. 9, OC was positive at 25 mg with onset of pruriginous palmar erythema, conjunctival erythema, then extension of skin rash with marked angioedema, cardiovascular collapse (BP: 74/47 mmHg), and tachycardia (112/min) preceded by sinus bradycardia for one minute. This patient was treated with epinephrine (1 mg IM), Solumedrol (120 mg IV), Polaramine (dexchlorpheniramine) (one vial IV), vascular filling (1 Lof Ringer's lactate), oxygen, and aerosolized salbutamol.

Anaphylaxis was confirmed in six patients: four by skin tests (positive IDT) (with two cases confirmed by BAT), one with a syndromic reaction due to IDT, and another one due to OC. Anaphylaxis was plausible for two patients. A nonimmunologic hypersensitivity was suspected for patient No. 7 because he had a past history of reaction to celecoxib. However, it was not confirmed because an OC to aspirin was not performed.

## Discussion

In Europe, severe anaphylaxis affects between one and three people per 10 000 inhabitants every year, with a death rate of 0.65–2% (7). Drugs are one of the main causes. Of the 333 cases of drug-induced hypersensitivity reported to the Allergy Vigilance Network between 2002 and 2010, 33 cases (10%) were related to NSAIDs and aspirin. For nine of these 33 cases, diclofenac was incriminated (3).

Diclofenac is a phenylacetic acid derivative belonging to the group of arylcarboxylic acids. VOLTARENE® is available as tablets, solutions for IM injection, suppositories, eyedrops, skin gels, and plasters.

The published cases of diclofenac-induced anaphylaxis include oral, rectal forms, and injectable solution (8). Patient No. 7 in our study presented laryngeal angioedema after contact with ocular mucosa.

In a study of 744 cases of drug-induced anaphylaxis, NSAIDs were the second cause of anaphylaxis, after antibiotics. Diclofenac was the only NSAID significantly associated with anaphylactic reactions (9–11). Cases of fatal reactions have been reported (8, 12). Our study confirms the severity with six of nine patients presenting with anaphylactic shock and AS in another one induced by OC.

Two mechanisms may be involved in immediate hypersensitivity reactions to NSAIDs: IgE-dependent allergy and nonimmunologic hypersensitivity to aspirin and NSAIDs caused by impaired metabolism of leukotrienes (1, 2).

Nonimmunologic hypersensitivity is suspected if skin tests and BAT are negative. The diagnostic is plausible when there

is history of reactions to one or several other NSAIDs. It can be proved if the OC to 500 mg aspirin is positive (1, 2, 6).

The IgE-dependent mechanism can be determined from immediate positive skin tests and by *in vitro* tests (5, 6, 13). There is no reference concentration for skin tests to diclofenac guaranteeing their specificity. Among the nine cases studied here, the concentration of 25 mg/ml was always negative in skin prick tests. Positive IDTs were observed at 0.25 mg/ml, 2.5 mg/ml, and 25 mg/ml dilutions. For patient No. 6, negative IDT at 0.025 mg/ml elicited a syndromic reaction, an observation already quoted (14).

In a single study reporting diclofenac hypersensitivity reaction, the search results for specific IgEs based on haptenation of protein carriers was negative (15). Screening for NSAID-specific IgEs is not available. However, we report two positive BATs suggesting IgE-dependent hypersensitivity.

On the basis of these results and the published guidelines, anaphylactic accidents involving diclofenac should be carefully managed. Firstly, skin prick tests should be performed, and if test results are negative, IDT starts with 0.025 mg/ml and increases gradually to 25 mg/ml. BATs may be helpful (13). OC does involve certain risks (16). OC to aspirin should be performed as a safer procedure, and its negativity would discard a nonimmunologic hypersensitivity, thus rendering the hypothesis of IgE-dependent anaphylaxis plausible. As an IgE-dependent mechanism may be predominant, tests for specific IgEs to diclofenac are urgently needed.

## Author contributions

We state that all authors have equally contributed to the allergy testing of cases. Julia Picaud, Etienne Beaudouin, and D-Anne Moneret-Vautrin have written the paper. All authors agree with the paper.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

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