

THE MANY FACES OF NSAID REACTIONS

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large group of common over-the-counter and prescription medications. As a group, NSAIDs are a common cause of drug hypersensitivity. However, the challenge is that the spectrum of hypersensitivity reactions to NSAIDs is varied, including classic IgE- and non-IgE-mediated reactions to individual NSAIDs, intolerance to all cyclooxygenase-1 inhibitors (COX-1 inhibitors) and delayed T-cell reactions to single or multiple NSAIDs. Allergy work-up and management differ based on understanding the phenotype and mechanism. In this case series we describe three different reactions to an individual NSAID – diclofenac. This highlights the clinical presentation, work-up and distinct management necessitated by each case.

Keywords: nonsteroidal anti-inflammatory drugs, NSAIDs, drug hypersensitivity

CASE 1

A 21-year-old woman with no known background of allergy or chronic medical illnesses presented to her local emergency room (ER) in the early hours of the morning with severe musculoskeletal shoulder pain. An intramuscular injection of 75 mg of diclofenac (Biotec Laboratories) was given as therapy, but within less than five minutes she developed clinical features of anaphylaxis, including severe hypotension (blood pressure 70/30 from a normal blood pressure at triage), diffuse urticaria, dyspnoea and wheezing. She received immediate treatment with 1 mL of 1 : 1 000 epinephrine intramuscularly, 2 L of intravenous fluid (plasmalyte B), 100 mg of hydrocortisone intravenously, 25 mg promethazine intravenously, and salbutamol nebulisation. No tryptase measurements were taken at the event, but the clinical diagnosis was anaphylaxis secondary to diclofenac. She responded well to treatment, was monitored in the ER, and later discharged.

She was seen subsequently by orthopaedics and diagnosed with a left-shoulder osteoid osteoma (benign bony tumour) and was started on paracetamol (acetaminophen) and ibuprofen for analgesia, which she tolerated. On review at the allergy clinic, she had no history of asthma, angioedema, urticaria or any other previous drug or food allergies. This was the patient's first known exposure to diclofenac. She had previously used aspirin and ibuprofen (both potent COX-1 inhibitors) with no adverse reactions. A sulphido-leukotriene release assay (ie cellular antigen stimulation test (CAST)) was performed and the results were positive for diclofenac and weakly positive for paracetamol (acetaminophen). The diagnosis of a single-NSAID Type-I hypersensitivity reaction to diclofenac was confirmed. Management should take the form of avoidance of

all preparations of diclofenac and a MedicAlert® bracelet with an anaphylaxis action plan. She was counselled to read drug labels as diclofenac can be present in polycomponent over-the-counter medication.

CASE 2

A 52-year-old woman presented as an outpatient with the history of poorly controlled diabetes mellitus (Type 2) and chronic backpain related to underlying osteoarthritis. She had had a previous spinal fusion and her chronic pain management required regular self-medication with paracetamol (acetaminophen) and tramadol. She denied the use of NSAIDs.

She was referred to our allergy clinic from her local hospital following a presentation to ER with anaphylaxis complicated by loss of consciousness (unfortunately, treatment notes from the facility were not available). No mast-cell tryptase was taken at the time of the event, but the total IgE was elevated at 626 kU/L (mean 13.2 kU/L for adults). The patient had eaten her regular biryani (a mixed rice dish originating on the Indian subcontinent) before taking paracetamol and diclofenac. This raised the concern that additives or spices in the biryani may have acted as a cofactor with diclofenac, resulting in anaphylaxis. Interestingly, she reported that since adolescence she has experienced periods of spontaneous urticaria responding to antihistamine therapy, for which she has not sought medical advice. According to her, there are no obvious triggers for this and the urticaria resolves rapidly with antihistamines. She denied angioedema and does not have any known allergies.

This history is suggestive of chronic spontaneous urticaria (CSU). CAST testing was done for various NSAIDs and food

additives at six weeks after the event, and all the tests were negative (see Table I). It is important to note that if CASTs are performed earlier than six weeks after an allergic reaction, the results may be falsely positive. The patient successfully passed an aspirin challenge (maximal dose 300 mg) on both an empty stomach and after having eaten biryani. Her back pain has been well controlled on paracetamol (acetaminophen) and she has been counselled to avoid diclofenac. An anaphylaxis action plan and MedicAlert® bracelet were issued to her. She still enjoys her local biryani regularly without any hypersensitivity reactions.

CASE 3

A 44-year-old male with a background history of recently diagnosed gout presented at his local ER with an acute gouty flare of his right knee. On presentation he had a small knee effusion which was drained and uric acid crystals were observed in the synovial fluid. After the drainage of the knee effusion, he complained of ongoing severe pain and the on-call doctor administered 75 mg intramuscular diclofenac (Biotec Laboratories). Less than five minutes after this injection, he developed severe angioedema of the face and larynx, and required intubation for airway protection. He did not develop urticaria, bronchospasm or cardiovascular symptoms. He required mechanical ventilation for three days while the angioedema resolved and was then discharged home to follow-up at the allergy clinic. Mast-cell tryptase was again not done at the time of the event.

On review the patient denied any prior exposure to diclofenac and had previously used aspirin with no adverse events. He had no personal or family history of prior angioedema or urticaria and had no known allergies. A diagnosis of single-NSAID angioedema was made with no cross-intolerance to other

Cox-1 NSAIDs. At the allergy clinic we screened for hereditary angioedema: complement C4 were normal, as was a baseline mast cell tryptase. All CASTs (performed more than two months after the event) for paracetamol, salicylates, lys-aspirin and food mixes were negative. He successfully completed an aspirin challenge (to a dose of 300 mg) with no adverse reaction.

We have optimised his gout treatment and counselled him to avoid diclofenac and to read carefully the ingredients of any over-the-counter medication for gouty flares, as these commonly contain diclofenac. He was issued a MedicAlert® bracelet and has an anaphylaxis action plan.

DISCUSSION

NSAIDs are among the most commonly used medications globally and are present in many over-the-counter preparations. NSAIDs act via modulation of the cyclo-oxygenase (COX) pathway and inhibition of the production of prostaglandins and thromboxane. These actions result in anti-thrombotic, analgesic, anti-pyretic and anti-inflammatory effects.¹ This class of drugs contains a variety of agents with differing chemical structures, resulting in variable inhibition of COX-1 and COX-2 pathways.^{1,2} For instance, aspirin is a potent COX-1 inhibitor, whereas diclofenac has equipotent COX-1 and COX-2 inhibition and celecoxib is selective for COX-2 inhibition.^{3,4} NSAIDs are one of the most common reported drug 'allergies';³ however, global prevalence is unknown.⁵

Adverse reactions to NSAIDs are diverse and can include – but are not limited to – gastritis, dyspepsia, diarrhoea, constipation, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis, erythema multiforme, erythema nodosum, bullous leukocytoclastic vasculitis, photosensitivity, acute renal

TABLE I: SUMMARY OF CHARACTERISTICS AND RESULTS OF CASE SERIES

CASE	AGE	GENDER	CO-MORBIDITIES	CULPRIT DRUG	PRESENTATION	CAST RESULTS
1	21	Female	Osteoid osteoma	Diclofenac	Type 4 (Table II): Anaphylaxis with cutaneous and respiratory involvement	Diclofenac: 57 pg/mL (positive) Lys-aspirin: 0 pg/mL Ibuprofen: 0 pg/mL Acetaminophen: 19 pg/mL (weakly positive)
2	52	Female	Osteoarthritis Previous spinal fusion surgery Recently diagnosed diabetic	Diclofenac	Type 4: Anaphylaxis	Diclofenac: 0 pg/mL Lys-aspirin: 0 pg/mL Ibuprofen: 0 pg/mL Acetaminophen: 0 pg/mL Sodium salicylate: 0 pg/mL Tartrazine: 70 pg/mL (negative) Sodium benzoate: 0 pg/mL Sodium nitrite: 0 pg/mL
3	44	Male	Gout	Diclofenac	Type 3: Angioedema with laryngeal oedema	Mast-cell tryptase baseline: 4.2 µg/L C4: 0.42 g/L Diclofenac: 0 pg/mL Lys-aspirin: 0 pg/mL Ibuprofen: 0 pg/mL Acetaminophen: 0 pg/mL Sodium salicylate: 16 pg/mL (negative) Food colourant mix I and II: ¹ 0 pg/mL Sodium benzoate: 0 pg/mL Sodium nitrite: 0 pg/mL

¹ Food colourant mix I includes: quinoline yellow, sunset yellow FCF, chromotrope B, amaranth and new coccine. Food colourant mix II includes: erythrosine, patent blue V, indigo carmine and brilliant black.

failure, interstitial nephritis, aseptic meningitis, hypersensitivity pneumonitis, thrombocytopaenia, liver dysfunction, urticaria, angioedema and anaphylaxis.^{2,6} This diverse presentation of a common class of drugs can complicate the diagnosis of NSAID hypersensitivity.

Allergic reactions are IgE-mediated and symptoms include urticaria, angioedema and anaphylaxis. Typically, these patients have had at least one exposure to the culprit drug. It is important to note that IgE-mediated allergic reactions have not been described for aspirin.⁵ The COX-1 inhibitors most commonly implicated in anaphylaxis are ibuprofen (United States); diclofenac (France) and the pyrazole NSAIDs such as phenylbutazone (Spain).^{5,7} Pseudo-allergic reactions are non-immune-mediated reactions that are related to the degree of the COX-1 inhibiting effect of a drug. In susceptible individuals these reactions will occur with any NSAID that inhibits COX-1; however, the exact mechanism of action is unknown.⁶ NSAID-induced hypersensitivity reactions have been reviewed and classified by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on NSAIDs Hypersensitivity⁸ (see Table II).

The classification of NSAID hypersensitivity reactions can be difficult as the presentation is variable, with overlapping features.

A thorough history is paramount and the clinician must establish whether the patient has underlying rhino-sinusitis, asthma or chronic urticaria. It is also important to determine whether the patient had ever taken NSAIDs prior to the reaction, and whether the reaction is caused by a single NSAID or multiple types. This can be difficult as various NSAIDs are ubiquitous in over-the-counter medication.

Unfortunately, there are no validated in-vitro or skin-testing methods available for NSAID hypersensitivity reactions, and negative CAST results do not exclude clinical hypersensitivity. If a definitive diagnosis is required, then a drug (NSAID) challenge can be done. However, this is usually reserved for patients who require future NSAID therapy – for instance, aspirin as secondary prevention of cardiovascular events. Drug challenges to culprit drugs in Type 4 and 5 reactions (see Table II) should be avoided due to increased risk of anaphylaxis and severe cutaneous drug reactions.⁵ A suggested diagnostic strategy is to use an aspirin challenge protocol in Type 1–3 reactions, if indicated. This would require close monitoring of vital signs while giving 150 mg aspirin orally. This is followed by three hours of observation and then giving a further 300 mg aspirin followed by a further three-hour observation period. If the patient can tolerate aspirin, then they can use any class of NSAIDs apart from the culprit NSAID. If the patient has a reaction to aspirin, they are classified as having

TABLE II: CLASSIFICATION OF NSAID REACTIONS BY THE EAACI TASK FORCE ON NSAIDS HYPERSENSITIVITY⁸

TYPE	CULPRIT NSAID	PRESENTATION	COMORBIDITIES	ONSET	MECHANISM OF ACTION
Type 1: NSAID-induced asthma and rhinitis	Multiple COX-1-inhibiting NSAIDs	• Rhinitis • Bronchospasm • Laryngospasm • Facial flushing • Periorbital oedema • Conjunctival injection • Nausea/vomiting • Diarrhoea • Hypotension	Asthma Rhinosinusitis Nasal polyps Aspirin-exacerbated respiratory disease	Delayed (30 minutes – 3 hours)	COX-1 inhibition (pseudoallergic)
Type 2: NSAID-induced urticaria/ angioedema in chronic spontaneous urticaria	Multiple COX-1- inhibiting NSAIDs	• Urticaria and/or angioedema	Chronic urticaria	Delayed (30–90 minutes)	COX-1 inhibition (pseudoallergic)
Type 3: NSAID-induced urticaria/ angioedema in otherwise asymptomatic individuals	Multiple COX-1- inhibiting NSAIDs. These patients can usually tolerate highly selective COX-2 inhibitors	• Urticaria and/or angioedema	Nil	Delayed (30–90 minutes)	COX-1 inhibition (pseudoallergic)
Type 4	Single NSAID other than aspirin (rarely NSAID with similar molecular structure)	• Cutaneous and respiratory symptoms • Anaphylaxis	Nil	Immediate	IgE-mediated
Type 5: Single NSAID-induced delayed reactions (SNIDR)	Single NSAID other than aspirin (rarely NSAID with similar molecular structure)	• Cutaneous (mostly) with wide spectrum, from maculopapular rash to drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) • Fixed drug eruption • Nephritis	Nil	Variable: usually after 24 hours of NSAID exposure	T-cell-mediated

a pseudoallergic reaction as aspirin has not been implicated in Type 4 reactions (anaphylaxis).⁵ It is important to note that in all three of these cases a serum mast-cell tryptase was not taken at the time of the reaction. Emergency physicians should be made aware of the utility of this test in confirming an IgE-mediated allergic response.

Management of NSAID reactions depends on the severity of symptoms and the classification of the reaction. Acute, severe reactions should be managed acutely as per emergency

protocols. If the patient had severe symptoms, then avoidance of that drug should be advised and the patient should be referred to an allergist/immunologist if ongoing use of the culprit NSAID is required. When reviewing the patient, it is important to educate them regarding which NSAIDs (if any) are safe to use— and to provide them with a list of safe and/or unsafe NSAIDs.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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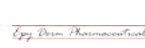


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