

Aspirin-Exacerbated Cutaneous Disease

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KEYWORDS

- Aspirin • Angioedema • Chronic urticaria • Cyclooxygenases • Leukotrienes
- NSAIDs

KEY POINTS

- About one-third of patients with chronic urticaria experience exacerbation of cutaneous symptoms when they take aspirin and other nonsteroidal anti-inflammatory drugs.
- Most of these individuals are tolerant to weak inhibitors of cyclooxygenase (COX)-1 such as acetaminophen and to preferential and selective inhibitors of COX-2.
- The mechanisms of urticaria and angioedema induced by nonsteroidal anti-inflammatory drugs (NSAIDs) observed in patients with chronic spontaneous urticaria/angioedema involve the inhibition of COX-1.
- Patient management includes avoidance of classic NSAIDs, the use of drugs that do not inhibit COX-1 for symptomatic relief of pain, fever, and inflammation, and the pharmacologic treatment of chronic urticaria.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a chemically heterogeneous group of substances that interfere with inflammatory processes by blocking the function of a group of enzymes called cyclooxygenases. Under physiologic conditions, arachidonic acid (AA) derived from cell membrane phospholipids by the action of phospholipases is metabolized to produce potent inflammatory mediators through 2 major pathways. The first of these is the cyclooxygenase (COX) pathway, which participates in the conversion of AA into prostaglandins and thromboxanes. The second is the lipoxygenase pathway.

There are 2 COX isoforms, COX-1 and COX-2. COX-1 is the constitutive isoenzyme, which is present in all cells, and whose actions are inhibited by aspirin

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(acetylsalicylic acid or ASA) and all classic NSAIDs. COX-2, the inducible isoform, is present exclusively in inflammatory and immune cells, is upregulated after stimulation by cytokines, growth factors, bacterial lipopolysaccharides, tumor promoters, and other factors, and is inhibited by the classic NSAIDs and also by the new preferential (nimesulide, meloxicam) and selective (coxibs) COX-2 inhibitors. The second metabolic route for AA is the 5-lipoxygenase (5-LO) pathway, which converts AA to cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄).

Hypersensitivity reactions to NSAIDs are a major cause of morbidity worldwide. Most studies show that reactions to aspirin and NSAIDs are the second leading cause of drug hypersensitivity reactions, after antibiotics (especially β -lactams), for hospitalized as well as ambulatory patients.¹

Recently the European Network of Drug Allergy (ENDA), the Interest Group on Drug Hypersensitivity of the European Academy of Allergy and Clinical Immunology (EAACI), and the European Network on Hypersensitivity to Aspirin and NSAIDs (HANNA) proposed an updated classification of hypersensitivity reactions to NSAIDs based on timing of initiation, clinical picture, and pharmacologic pattern of the reaction. There were at least 2 previous articles that proposed for the first time a systematic understanding of the various clinical and pharmacologic patterns of reactions induced by NSAIDs.^{2,3} In the new classification, reactions to NSAIDs are divided into immediate (occurring after minutes to several hours of drug exposure) and delayed (appearing more than 24 hours after drug intake).⁴

Aspirin-exacerbated cutaneous disease (AECED) is characterized by flares of urticaria and angioedema induced by aspirin and other NSAIDs in patients who suffer chronic spontaneous urticaria. This picture should be distinguished from acute cross-reactive urticaria and angioedema occurring in patients who are otherwise healthy, which is now designated as urticaria and angioedema induced by multiple NSAIDs.⁵

PHARMACOLOGIC OVERVIEW OF NSAIDS

As previously mentioned, AA is metabolized to produce potent inflammatory mediators by 2 enzymatic pathways: the COX and the 5-LO pathways. NSAIDs are a group of medications that antagonize inflammation by interfering with the function of cyclooxygenases. The inhibition of COX-1 results in a shunting of AA metabolism toward the 5-LO pathway, with enhancement of the production of cysteinyl leukotrienes.

Aspirin and the classic NSAIDs inhibit both COX isoforms, COX-1 and COX-2, whereas the new preferential (nimesulide, meloxicam) and selective (coxibs: rofecoxib, etoricoxib, valdecoxib, parecoxib, lumiracoxib) COX-2 inhibitors do not interfere with (or inhibit weakly) COX-1, and are better tolerated by the gastrointestinal tract because they do not reduce significantly the synthesis of prostaglandin E₂ in the stomach.

Recently, new COX isoenzymes that are preferentially inhibited by acetaminophen, pyrazolones, and antipyrine have been described as COX-1 variants and designated COX-2b and COX-3.^{6,7} In **Box 1**, a classification of NSAIDs according to their COX inhibitory properties is presented.

ASPIRIN-EXACERBATED CUTANEOUS DISEASE

Definition and Prevalence

Urticaria is characterized by the sudden appearance of wheals. Wheals are cutaneous swelling of variable size, almost invariably surrounded by a reflex erythema, with associated itching or, sometimes, a burning sensation of transient nature, with the skin

Box 1**Classification of NSAIDs according to their selectivity for COX isoenzymes****Weak COX inhibitors**

Acetaminophen, pyrazolone, salsalate

Inhibitors of COX-1 and COX-2

Piroxicam, indomethacin, sulindac, tolmetin, ibuprofen, naproxen, penopropfen, meclofenamate, mefenamic acid, diflunisal, ketoprofen, diclofenac, ketorolac, etodolac, nabumetone, oxaprozin, flurbiprofen

Preferential COX-2 inhibitors

Nimesulide, meloxicam

Selective COX-2 inhibitors

Celecoxib, rofecoxib, valdecoxib, etoricoxib, parecoxib, lumiracoxib

returning to its normal appearance in 1 to 24 hours. Angioedema can be defined as a sudden and pronounced swelling of the deep dermis and subcutaneous tissue or mucous membranes, with a painful rather than an itching sensation, and a slower resolution rate (up to 72 hours).^{8,9}

Urticaria and angioedema are classified according to their duration into acute (less than 6 weeks) and chronic (longer than 6 weeks), and are classed as spontaneous and inducible on the basis of the presence or absence of inducing factors.⁸

Two subsets of patients who develop cross-reactive urticaria and/or angioedema during placebo-controlled oral challenges with aspirin or NSAIDs have been described.¹⁰ First, NSAIDs may cause acute episodes of urticaria/angioedema in cross-reactive patients only when exposed to the drug.¹¹ These patients do not have chronic idiopathic urticaria, belong to the group designated as multiple NSAID-induced urticaria, and are the focus of an article elsewhere in this issue.⁴

On the other hand, aspirin and NSAIDs may also aggravate preexisting chronic spontaneous urticaria/angioedema.^{12–16} Analogous to aspirin-exacerbated respiratory disease (AERD), this condition has been designated as aspirin-exacerbated cutaneous disease or AECD, to denote that chronic urticaria evolves independently of the intake of aspirin and NSAIDs, and that those drugs are not the cause but the exacerbating factor for the hives.⁵ In fact, from 21% to 30% of patients with chronic spontaneous urticaria (CSU) develop hives after receiving NSAIDs,¹⁷ with active CSU increasing the risk of reacting to NSAIDs.¹⁸ Furthermore, Asero¹⁵ observed that the reaction to aspirin/NSAIDs may precede the onset of episodes of chronic urticaria. This observation means that some patients classified as being normal actually have latent chronic idiopathic urticaria, which is temporarily exacerbated by NSAIDs, long before the disease declares itself.

Patients with AECD react to drugs that exert an inhibitory effect on COX-1 and generally are tolerant to selective COX-2 inhibitors.^{19,20} A genetic predisposition for cutaneous NSAID hypersensitivity may play a role in AECD, because various investigators have observed the association between various genetic polymorphisms and this disease.^{21,22}

Pathogenesis

CSU and angioedema, previously known as chronic idiopathic urticaria, are characterized by the recurrent appearance of wheals or subcutaneous tissue edema lasting

longer than 6 weeks. Other forms of chronic urticaria that should be distinguished from CSU are the inducible urticarias such as those induced by physical agents (cold, pressure, heat, sunlight, vibration, aquagenic) and other inducible urticarias such as cholinergic, contact, and exercise-induced urticaria.⁸

Although the mechanisms of CSU are not completely understood, chronic inflammation of the skin and deep dermis with the release of several inflammatory mediators is responsible for the cutaneous swelling, generally surrounded by erythema, and the itching/burning sensation characteristic of the wheals. In most patients there is no identifiable exogenous stimulus leading to the production of hives, although in some patients nonspecific environmental triggers such as exercise, climatic changes, and emotional stress are present.

Different hypotheses have been postulated to explain the mechanisms involved in CSU, including psychosomatic factors, food and additive intolerance or allergy, autoreactivity or autoimmunity, and poorly understood disturbances of basophils and immunoglobulin E (IgE).

Patients with chronic urticaria associated with aspirin-induced urticaria/angioedema react to various NSAIDs that have a different chemical composition but share the ability to inhibit COX-1. Usually they are tolerant to COX-2 inhibitors.^{20,23}

The mechanisms responsible for the production of aspirin/NSAID-induced exacerbations of chronic urticaria and angioedema involve the inhibition of COX-1, as demonstrated by Mastalerz and colleagues.²⁴ These investigators observed that patients with CSU who experience disease exacerbations when exposed to aspirin have increased basal levels of urinary LTE₄ (uLTE₄) when compared with aspirin-tolerant CSU patients. Further increases of uLTE₄ occur in the group of aspirin-sensitive patients after oral aspirin challenge. It is postulated that the inhibition of COX-1 by NSAIDs results in a decreased prostaglandin production, enhanced inflammatory mediator release in the skin, and symptoms.²⁵ Because leukotriene receptor antagonists are able to inhibit these reactions, it is likely that the increased cysteinyl leukotriene production contributes to the inflammatory process.^{26,27}

It is presently accepted that chronic urticaria is associated with autoimmune diseases, especially chronic autoimmune thyroiditis.²⁸ Furthermore, 5% to 10% of patients with CSU have circulating immunoglobulin G (IgG) anti-IgE, which is functional and induces mediator release from mast cells and basophils on cross-linking of receptor-bound IgE,²⁹ and 30% to 40% of patients have IgG antibody to the α subunit of the high-affinity IgE receptor itself.³⁰ The presence of these circulating autoantibodies is usually demonstrated by means of an autologous intradermal skin test with the patient's serum or plasma.

The presence of positive autologous serum and plasma skin tests suggests an association between CSU, autoimmunity, and aspirin hypersensitivity.^{16,31} Another interesting observation has been recently reported by Ye and colleagues,³² who observed an association between IgE immune response to toxic shock syndrome toxin (TSST)-1 and aspirin sensitivity in patients with chronic urticaria.

A genetic predisposition for NSAID cutaneous hypersensitivity has been observed in various populations, and polymorphisms of HLA antigens (HLA-DRB1*1302 and HLA-DB1*069), neutrophil-related genes, LTC₄ synthase, 5-LO, Fc ϵ RI, and histamine *N*-methyltransferase have been suggested as genetic markers for NSAID-induced urticaria/angioedema.^{21,22,33–35}

Clinical Picture

In AECD wheals and/or angioedema usually appear after 1 to 4 hours of drug administration, but in case an injectable form of the drug (eg, ketoprofen or dipyrone) is

administered by the parenteral route the clinical picture may begin earlier and be more severe. Rarely late reactions can occur. Individual hives tend to disappear within a few hours but may persist for several days.

Prognostic factors for longer duration and increased severity of CSU are the presence of concomitant angioedema, positivity of autologous serum skin test, and comorbidity with physical urticaria.

Quiralte and colleagues¹¹ reported that the most common clinical presentation of cutaneous NSAID hypersensitivity is eyelid (periorbital) angioedema. To illustrate the clinical presentation of patients with AECD, 2 cases are described in **Boxes 2** and **3**.

It is unusual that AERD and AECD coexist in the same patient, and these 2 phenotypes are generally regarded as different clinical entities. However, Isik and colleagues³⁶ observed that in some patients asthma and nasal polyposis may co-occur in patients with CSU and NSAID hypersensitivity, although it should be emphasized that this association is rarely present.

Diagnosis

A medical history and physical examination are helpful to establish the diagnosis of chronic urticaria. Recurrent wheals with or without angioedema lasting for more than 6 weeks, usually in the absence of precipitating factors, are typically associated with CSU, and initial complementary studies are oriented to rule out concomitant systemic diseases and the presence of triggering or exacerbating factors. Present guidelines suggest performing a set of screening tests that includes a differential blood count, liver function tests, erythrocyte sedimentation rate, and C-reactive protein. An explicit recommendation in the guidelines is to inquire early specifically about drug intake temporarily associated with cutaneous symptoms, and more especially about NSAIDs.⁸

Box 2

Case report

A 42-year-old male patient was referred to the Allergy clinics in January 2011 after complaining of eyelid and lip edema appearing 2 hours after the ingestion of ibuprofen, 400 mg, which was taken for toothache. During the medical interrogation the patient reported having recurrent tongue and facial edema for the last 4 years without any identifiable triggering agent, and palpebral angioedema induced by sodium diclofenac. Prednisone, 50 mg every day for 5 days and fexofenadine, 180 mg for 1 month were indicated.

Two months later the patient returned to the emergency room because of eyelid edema and cough (**Fig. 1**). Treatment with intravenous hydrocortisone, 100 mg and chlorpheniramine, 10 mg were given, and at the time of discharge prednisone, 50 mg for 5 days and cetirizine, 10 mg for 1 month were prescribed.

Laboratory investigations done on March 3, 2011: Complement: CH₅₀ 113.5 units/mL. C3 133 mg/dL. C4 38.3 mg/dL. Hematologic values and blood chemistry: within normal limits. Stools: cysts of *Giardia lamblia*.

Treatment: (1) Cetirizine 10 mg every day for 3 months. (2) Nitazoxanide 500 mg twice a day for 3 days. (3) Avoidance of NSAIDs that inhibit COX-1. (4) Acetaminophen for mild pain or fever. Celecoxib for inflammation or moderate to severe pain.

Diagnosis: (1) Chronic angioedema. (2) AECD. (3) Giardiasis.

Comments: No confirmatory provocation tests were considered pertinent for this patient because the history was clearly indicative of chronic spontaneous angioedema aggravated by 2 cross-reacting NSAIDs. Oral challenges with acetaminophen and celecoxib were tolerated.

Box 3**Case report**

A 28-year-old male patient consulted because he had recurrent itchy wheals predominantly on the lower limbs for 8 years, with increased frequency and severity for the last 6 weeks (Fig. 2). The skin lesions were occasionally accompanied by lip edema.

The patient referred that the wheals increased after taking analgesics, including aspirin and dipyrrone. There were no other previous or current significant medical problems.

Routine *laboratory* investigations included hematological tests, erythro sedimentation rate, blood chemistry, urinalysis, and coprologic evaluation. All resulted negative or within normal ranges.

Management: (1) Levocetirizine 5 mg every day. (2) Prednisone 50 mg every day for 6 days. (3) Avoidance of classic NSAIDs. (4) Alternative drugs for pain, fever, and inflammation: acetaminophen or meloxicam.

Diagnosis: CSU/angioedema exacerbated by NSAIDs (AECD).

Comments: A test for tolerance is recommended to make sure that alternative NSAIDs can be used with safety in these patients. It has been observed that if doses of alternative NSAIDs are increased (eg, >1000 mg of acetaminophen), cutaneous reactions may occur.

Patient questioning and examination may provide information for further testing to investigate infectious diseases (for example, *Helicobacter pylori*, parasites), in vivo or in vitro tests for IgE-mediated allergy to environmental or food allergens, autoantibodies (including thyroid antibodies), tests for thyroid function, and specific tests for physical urticarias. Intradermal tests with autologous serum or plasma allow the confirmation of mast cell-activating autoantibodies (anti-Fc ϵ I or anti-IgE) or other serum factors able to induce mediator release in the skin, and to confirm CSU-associated autoimmunity or autoreactivity. Skin biopsy is generally indicated only for differential diagnosis from other skin diseases, and especially from urticarial vasculitis.

AECD can be suspected from questioning the patient, because frequently the patient will refer a history of chronic spontaneous hives or angioedema accompanied



Fig. 1. A 42-year-old male patient with chronic angioedema and aspirin-exacerbated cutaneous disease (AECD). Observe the diffuse angioedema of the face, bilateral eyelid, and upper and lower lip.



Fig. 2. A 28-year-old male patient with chronic spontaneous urticaria and angioedema, and NSAID hypersensitivity (AECD) is shown. Observe the presence of generalized urticaria, which involves upper and lower limbs and the trunk.

by repeated exacerbations of urticaria/angioedema after taking different COX-1 inhibitors. When the relation between skin symptoms and NSAID administration is unclear, oral provocation tests with aspirin using standard protocols are useful to confirm AECD (**Table 1**).⁵ These challenges should not be performed during urticarial exacerbations, and are better done after at least 1 to 2 weeks during which the patient does not show any skin eruption.³⁷ The provocation test should be performed without interrupting the current treatment of chronic urticaria to avoid false-positive results due to reactivation of the underlying disease when therapy is discontinued (**Box 4**).

Other NSAIDs can be tested in a similar form, using protocols available in the literature.³⁸ There is no in vitro test presently validated for routine diagnosis of cutaneous

Table 1
Single-blind oral provocation test with acetylsalicylic acid (aspirin; ASA) for patients with urticaria and angioedema

Day 1	Day 2	Day 3	Day 4
Placebo	ASA 100 mg	ASA 325 mg	ASA 650 mg
Placebo	ASA 200 mg		

On days 1 and 2, doses are administered every 2 hours.

Skin scores are recorded every 2 hours.

Treatment of chronic urticaria is continued during the provocation test (for explanation see the section Diagnosis).

In Europe, the recommended ASA doses for testing are 71 mg, 117 mg, 312 mg, and 500 mg.³⁷

Box 4
Protocol for oral provocation test with NSAIDs (single- or double-blind)

Drugs or placebo concealed in identical opaque capsules are given on different days. Drug doses are administered 1 hour apart with a 3-hour observation period in the hospital. Doses for the different NSAIDs are shown in [Table 2](#).

Vital signs and pulmonary function (forced expiratory volume in 1 second, forced vital capacity, midexpiratory phase [25%–75%] of forced expiratory flow, and peak expiratory flow) are monitored at baseline and hourly for 3 hours. The skin, nose, eyes, and thorax are examined hourly and the presence of breathlessness, cough, wheezing, dysphonia, nasal or ocular itching, sneezing, rhinorrhea, nasal obstruction, and conjunctival erythema are investigated every hour by physical examination.

For urticaria and angioedema the percentage of skin involved is calculated as follows: head and neck 30%, chest 20%, abdomen 20%, upper limbs 15%, and lower limbs 15%. The test is considered positive if an increase of 20% or more from baseline is observed.

Previous treatment with antihistamines and/or anti-inflammatory drugs is maintained during the test to avoid false positives due to spontaneous exacerbations of urticaria and/or angioedema. The tests are done on an outpatient basis in a medical center with easy availability of medications and equipment required for the treatment of reactions that occur during the challenge.

NSAID hypersensitivity, although the basophil activation test and the sulfidoleukotriene release assay have been proposed for this task.³⁹

Management

The treatment of CSU and angioedema is based on preventive measures designed to reduce the effects of provoking and exacerbating factors, and on pharmacologic therapies. These treatments follow the guidelines proposed by international organizations and experts in the area.⁴⁰ The first choice is to use second-generation antihistamines in the usually recommended doses. If there is not a satisfactory response, the doses can be increased progressively every 2 weeks up to 4 times the regular dose. Add-on therapy with leukotriene receptor antagonists is the next step if there is no symptom improvement. In patients who do not respond, additional medications include anti-inflammatory, immunosuppressive, and biologic therapies. A new Position Paper on

Table 2
Doses of NSAIDs used for oral provocation tests

Drug	Doses (mg)
Dipyrone	250, 500
Acetaminophen	250, 500, 1000
Ibuprofen	50, 100, 200
Diclofenac	25, 50
Ketoprofen	25, 50
Naproxen	125, 250
Nimesulide	50, 100
Meloxicam	7.5, 15
Celecoxib	100, 200
Rofecoxib	25, 50
Etoricoxib	60, 120

Table 3
Pharmacologic treatment of chronic urticaria and angioedema based on the quality of scientific evidence

Drug	Quality of Evidence	Strength of Recommendation
Nonsedating antihistamines	High	Strong (f)
Sedating antihistamines	High	Strong (a)
Increased doses of nonsedating antihistamines	Moderate	Weak (f)
Anti-H2 antihistamines	Moderate	Weak (f)
Oral corticosteroids (short courses)	Low	Weak (f)
Oral corticosteroids	Very low	Strong (a)
Leukotriene receptor antagonists (add on)	Low	Weak (f)
Anti-inflammatory agents: Dapsone Sulfasalazine Hydroxychloroquine Colchicine Mycophenolate mofetil	Low to very low	Weak (f)
Immunosuppressive agents: Cyclosporin A Methotrexate Cyclophosphamide	Moderate Very low Very low	Weak (f) Weak (f) Weak (f)
Biologic agents: Omalizumab Intravenous immunoglobulin	Moderate Low	Weak (f) Weak (f)

For cyclosporin A and omalizumab, the recommendation is stronger than for other immunosuppressive, anti-inflammatory or biologic therapies.

(f): recommendation for. (a): recommendation against.

Data from Sánchez-Borges M, Asero R, Ansotegui IJ, et al. World Allergy Organization position paper. Diagnosis and treatment of urticaria and angioedema—a worldwide perspective. World Allergy Organ J 2012;5:125–47.

the diagnosis and treatment of urticaria and angioedema of the World Allergy Organization presents therapeutic recommendations for urticaria and angioedema based on the grading of efficacy according to evidence-based medicine (Table 3).⁴¹ Out of presently available therapies for recalcitrant patients with CSU, cyclosporine A and omalizumab appear to deliver the best results when compared with the other drugs (Box 5).^{42,43}

Box 5
Management of aspirin-exacerbated cutaneous disease

- Avoidance of COX-1 inhibitors
- Weak COX-1 inhibitors (acetaminophen) for fever or mild pain
- Preferential COX-2 inhibitors (nimesulide, meloxicam) for pain and inflammation
- Selective COX-2 inhibitors (coxibs: rofecoxib, etoricoxib, celecoxib) for pain and inflammation
- Desensitization not usually recommended
- Management of CSU and angioedema as per guidelines⁴⁰

Avoidance of aspirin and classic NSAIDs is indicated for patients with AECD, but analogous to AERD the underlying chronic urticaria is not affected by drug elimination. All COX-1 inhibitors should not be prescribed, and alternative weak COX-1 inhibitors (acetaminophen) or preferential and selective inhibitors of COX-2 (nimesulide, meloxicam, coxibs), which are tolerated by most AECD patients, can be used for relief of pain, fever, and inflammation. Provocation tests are performed to confirm tolerance to these alternative anti-inflammatory drugs.^{19,23,44,45}

Aspirin desensitization, as used in patients with AERD, is not generally indicated for patients with cross-reactive aspirin-induced urticaria and angioedema, because persistent aspirin-induced hives are routine and desensitization almost never occurs (Table 3).⁴⁶

SUMMARY

About one-third of patients with CSU and angioedema who receive aspirin or the classic NSAIDs show exacerbation of their cutaneous disease. Most of these subjects can tolerate weak COX-1 inhibitors such as acetaminophen and inhibitors of COX-2.

The mechanisms of aspirin/NSAID-induced urticaria and angioedema observed in patients with chronic urticaria involve the inhibition of COX-1. Patient management includes avoidance of classic NSAIDs, use of non-COX-1 inhibitor NSAIDs for symptomatic relief of pain, fever, and inflammation, and pharmacologic treatment of chronic urticaria according to presently available guidelines.

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