
Cutaneous reactions to nonsteroidal anti-inflammatory drugs

A review

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The nonsteroidal anti-inflammatory drugs are one of the most commonly prescribed classes of drugs used in medical practice. This review discusses the diverse cutaneous reactions associated with nonsteroidal anti-inflammatory drugs. Adverse cutaneous reactions occur most frequently with benoxaprofen, piroxicam, sulindac, meclofenamate sodium, zomepirac sodium, and phenylbutazone. The most serious adverse cutaneous reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis, appear to be most often associated with sulindac and phenylbutazone. Tolmetin and zomepirac sodium, two structurally similar pyrrole derivatives, have been associated with a disproportionate number of cases of anaphylactoid reactions. Among the currently marketed nonsteroidal anti-inflammatory drugs, piroxicam appears to have the highest rate of phototoxic reactions. This phototoxic eruption is most often vesiculobullous. (*J AM ACAD DERMATOL* 12:866-876, 1985.)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed classes of drugs used in medical practice. About 70 million prescriptions for NSAIDs were dispensed from retail pharmacies in 1982. This number represents almost 5% of the total prescription market.* In a national survey of ambulatory medical care conducted in 1981, seven of the NSAIDs were among the 100 drugs most commonly ordered or provided by physicians. Aspirin was ranked sixth and ibuprofen twelfth (see Table

I for trade names). Naproxen, sulindac, indomethacin, zomepirac sodium, and phenylbutazone were also among the 100 most frequently prescribed drugs.* The number of NSAIDs available to practitioners has grown steadily in the past 10 years. In 1973 there were only four NSAIDs available by prescription; by 1982 there were twelve NSAIDs on the market.† The indications, mechanisms of action, pharmacology, efficacy, and toxicity of the newer NSAIDs have been reviewed.¹⁻⁵ These reviews, however, give limited attention to adverse cutaneous reactions to NSAIDs. Cutaneous reactions to antirheumatic drugs have been reviewed, but these reviews have adequately discussed only two of the NSAIDs introduced since 1965.^{6,7}

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*Baum C, Kennedy DL, Rorbes MB, Jones JK: Drug utilization in the U.S.: 1982 Fourth Annual Review. Washington, DC, 1983, U.S. Department of Health and Human Services, pp. 25-46.

*Koch H: Drugs most frequently used in office practice: National Ambulatory Medical Care Survey, 1981. *Vital and Health Statistics of the National Center for Health Statistics Advance Data*, No. 89, April 15, 1983.

†Baum C, Kennedy DL, Rorbes MB, Jones JK: Drug utilization in the U.S.: 1982 Fourth Annual Review. Washington, DC, 1983, U.S. Department of Health and Human Services, pp. 25-46.

Table I. Trade names of NSAIDs

Class	Generic name	Registered trade name(s)
Salicylates	Aspirin	*
	Diflunisal	Dolobid
Heterocyclic acetic acids	Indomethacin	Indocin
	Sulindac	Clinoril
	Tolmetin	Tolectin
	Zomepirac sodium	Zomax
Propionic acid derivatives	Ibuprofen	Motrin; Rufen; Advil;† Nuprin†
	Naproxen	Naprosyn; Anaprox
	Fenoprofen	Nalfon
	Benoxaprofen	Oraflex
Anthranilic acids	Mefenamic acid	Ponstel
	Flufenamic acid	‡
	Meclofenamate sodium	Meclomen
Pyrazolones	Phenylbutazone	Azolid; Butazolidin
	Oxyphenbutazone	Oxalid; Tandearil
Oxicams	Piroxicam	Feldene

*Too numerous to list.

†Over the counter.

‡Investigational.

In this report we review the literature on the toxicity of NSAIDs, with emphasis on adverse cutaneous reactions. We have attempted to concentrate on NSAIDs introduced since 1965. Aspirin, indomethacin, and phenylbutazone have been included because they are so widely used.

The literature that we have summarized is necessarily composed largely of case reports. Special caution must be exercised in assessments of causality based on case reports.⁸ Many of the adverse cutaneous reactions described in this review were recently summarized from reports by dermatologists to the American Academy of Dermatology's Adverse Drug Reaction Reporting System (ADRRS), a system for spontaneous adverse drug reaction reports under Food and Drug Administration sponsorship.⁹ The ADRRS was instituted in 1980 to encourage dermatologists to report new, unusual, and serious suspected adverse reactions to drugs. Reports can be made with the use of a toll-free telephone number (1-800-323-1473). Confidentiality of both reporter and patient is assured.

The nonsteroidal anti-inflammatory drugs can be divided into several chemically related classes (Fig. 1). The salicylates are the oldest and most

widely used class of NSAIDs, and aspirin is the standard to which most NSAIDs are compared for the treatment of rheumatoid arthritis.¹⁻³ Diflunisal is a derivative of aspirin with an extra difluorophenyl group at the C5 position and no D-acetyl group. Indomethacin is a heterocyclic acetic acid derivative (or indole); sulindac is an indene derivative of indomethacin. Tolmetin and zomepirac acid are structurally similar heterocyclic acetic acids (or pyrroles) with a structural resemblance to indomethacin but with actions and toxicity more similar to the propionic acid derivatives.^{*3} With the exception of benoxaprofen, the propionic acid derivatives are a homogeneous group with similar uses, actions, and toxicity.¹⁻³ The anthranilic acid derivatives share the unique ability to both inhibit prostaglandin synthesis and block prostaglandin action.^{1,2} Phenylbutazone is a pyrazole derivative. Piroxicam is the only enolic acid derivative of the oxicam class currently available in the United States. NSAIDs in the same chemical class often produce similar adverse cutaneous reactions (Table II).

*Mendelis P: Abuse potential associated with nonsteroidal anti-inflammatory drugs. ADR Highlights, pp. 82-85, June 8, 1982.

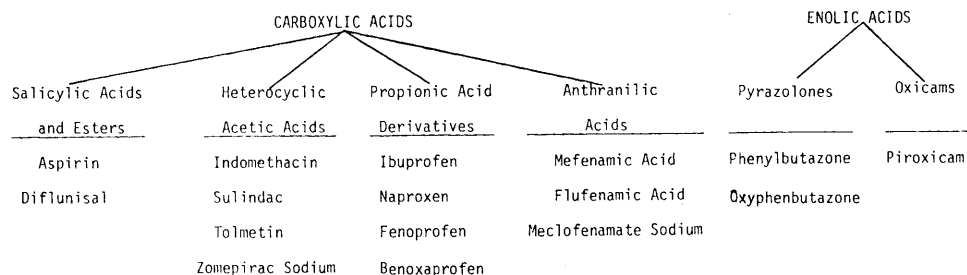


Fig. 1. Families of nonsteroidal anti-inflammatory drugs.

Salicylates

Aspirin is indicated for the treatment of rheumatoid arthritis and of the arthritis and serositis of systemic lupus erythematosus (SLE), as well as for analgesia.^{1,10,11} Aspirin is metabolized by the hepatic microsomal enzymes and excreted in the urine; its elimination from the body follows complex, dose-dependent, first- and zero-order kinetics.^{12,13} At low doses, salicylate is conjugated with glycine to form salicylurate, which is excreted in the urine. This pathway is saturated at higher doses. Once this pathway becomes saturated, small increments in aspirin dose may produce large increments in serum salicylate levels.^{1,12}

Gastric irritation (dyspepsia, erosions, ulcers, and bleeding) is the most common side effect of aspirin.¹⁻³ Tinnitus and deafness are frequent with high-dose therapy. Aspirin can provoke asthma in aspirin-sensitive (intolerant) patients, who often have histories of vasomotor rhinitis, nasal polyps, and asthma.^{1-3,14-16} This aspirin-induced asthma (also known as aspirin disease) has a nonimmunologic basis and, most importantly, may be precipitated by all of the prostaglandin-inhibiting NSAIDs.^{1-3,14,16-18} Renal disease and hepatotoxicity have been reported with aspirin¹; blood dyscrasias are also reported but are rare.⁴

Cutaneous reactions to aspirin have been extensively reviewed in the past.^{6,7,15} Aspirin is a common cause of acute urticaria, aggravation of chronic urticaria, and purpura. Aspirin is estimated to be the cause of 5% to 10% of acute and chronic urticaria cases.⁶ Twenty-two percent of patients with chronic urticaria were made worse by aspirin challenge.¹⁹ In most cases, aspirin-induced urticaria has a nonimmunologic basis and can be in-

duced by other NSAIDs, as well as by azo dyes (i.e., tartrazine) and sodium benzoate. Patients who developed anaphylactoid reactions to zomepirac sodium, some of which were fatal anaphylaxes, often had previous urticarial reactions to aspirin. Easy bruisability and purpura result from the irreversible effect of aspirin on platelet function. Aspirin has been uncommonly associated with many cutaneous reactions that include pruritus, fixed drug eruptions, erythema multiforme (EM), aphthous stomatitis (especially with chewable aspirin),¹⁵ and erythema nodosum.^{6,7,15} Case reports of aspirin-induced pustular psoriasis, scarlatiniform erythema, angioedema, anaphylactoid purpura, and dyshidrosis have appeared in the literature.^{6,7,15}

Diflunisal is indicated for analgesia, osteoarthritis, and, on the basis of limited studies, rheumatoid arthritis.²⁰⁻²³ Diflunisal has uricosuric effects. A half-life of 8 to 12 hours makes twice-daily therapy possible with diflunisal. Upper gastrointestinal side effects are common but may be less frequent than with aspirin. Headaches occur in 3% of patients treated with diflunisal.^{20,24} Cholestatic jaundice and several cases of interstitial nephritis associated with diflunisal have been reported.^{20,25,26}

Rashes or pruritus occur in 3% to 5% of patients taking diflunisal. Urticaria and an exanthem are the most common rashes.²¹ At least seven cases of Stevens-Johnson syndrome associated with diflunisal use have been reported.^{26,27} Chan et al²⁶ reported a patient in whom erythroderma and interstitial nephritis were detected 2 weeks after diflunisal therapy had been discontinued. Causality in this case was not clearly established.

Heterocyclic acetic acids

Introduced into the U.S. market in 1965, indomethacin is currently indicated and widely used for a host of conditions including tendonitis, bursitis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, enteropathic arthritis,¹ rheumatoid arthritis,²⁸ gout,²⁹ osteoarthritis, and fever.¹⁻³ Although the serum half-life of indomethacin is only 2 hours, its duration of action is longer because it is stored in the tissues.³⁰ In addition to gastric intolerance, central nervous system (CNS) side effects (headache, dizziness, confusion, depression, drowsiness, hallucinations, depersonalization, seizures, and syncope) are common with indomethacin.^{1-3,31,32} In one report 47% of patients complained of CNS side effects and 20% stopped the drug because of CNS reactions.³² Indomethacin has been associated with worsening renal function,¹⁻³ pseudotumor cerebri, and ocular disease.³³ Toxic hepatitis^{1,5} and blood dyscrasias,^{4,5} although reported, are rarely associated with indomethacin. A report of the development of impaired immunity in several children who received high doses of indomethacin has nearly precluded the use of indomethacin in children.³⁴

Cutaneous reactions to indomethacin are infrequent.^{2,6,7,31} The most common cutaneous reaction to indomethacin is a morbilliform drug eruption,^{6,7} which occurs more frequently in elderly persons.³⁵ Both urticaria and, less commonly, angioedema have been reported,^{6,7} especially in aspirin-sensitive patients.³⁶ Pruritus has also been reported. Stomatitis was reported to be common by Bailin and Matkaluk⁶ but appears to be relatively uncommon and is most often associated with blood dyscrasias.⁷ Periorbital edema has been described but is rarely reported in the literature.^{6,7,32} Thrombocytopenic purpura occurs and is "not uncommon."^{6,7} Marsh et al³⁷ have reported two cases of vasculitic purpura caused by indomethacin and also mentioned two additional patients who probably had indomethacin-induced cutaneous vasculitis. Recently O'Sullivan et al³⁸ reported a case of toxic epidermal necrolysis (TEN) after indomethacin use. In a recent study, which cited 135 reactions to NSAIDs as reported to the ADRRS, only one was an adverse cutaneous reaction to indomethacin.

Table II. Commonly reported cutaneous reactions by drug class

Drug class	Common cutaneous reactions*
Salicylates	Acute urticaria Chronic urticaria (aspirin) Purpura (aspirin) Exanthem (diflunisal)
Heterocyclic acetic acids	Exanthem EM TEN (sulindac) Anaphylactoid reactions (zomepirac sodium, tolmetin)
Propionic acid derivatives	Pruritus Photosensitivity (benoxaprofen) Photoonycholysis (benoxaprofen) Milia (benoxaprofen) EM TEN (benoxaprofen)
Anathranilic acids	Pruritus (sodium meclofenamate) Exanthem (sodium meclofenamate)
Pyrazolones	EM TEN (phenylbutazone) Exanthem (phenylbutazone) Pruritus (phenylbutazone) Fixed drug reaction
Oxicams	Photosensitivity (piroxicam) Vesicobullous (piroxicam) Henoch-Schönlein purpura (piroxicam) Pruritus (piroxicam)

*Specific drugs appear in parentheses if reaction is not common to entire class.

cin. This report was a case of photosensitivity induced by indomethacin that was proved by rechallenge and by positive photopatch testing.⁹

Sulindac was developed as a potent anti-inflammatory agent with less gastrointestinal and CNS toxicity than indomethacin. Current indications include rheumatoid arthritis,^{1,3} osteoarthritis,^{1,3,39} gout, and ankylosing spondylitis.² After absorption, sulindac is converted by the liver into an active sulfide derivative. Since the active sulfide derivative has a serum half-life of 18 hours, sulindac can be given twice a day. Sulindac and the active sulfide derivative are metabolized in the liver and excreted in the urine and feces.⁴⁰ There

is enterohepatic recirculation of sulindac and its metabolites.⁴⁰ Sulindac produces fewer upper gastrointestinal and CNS side effects than indomethacin, but constipation, fatigue, and dry mouth are more frequent.³⁹ More importantly, however, toxic hepatitis, which is often accompanied by rashes (see below), continues to be reported.^{5,41,42} In addition, "numerous reports"⁵ of sulindac-associated blood dyscrasias have appeared.^{5,43} Sulindac has also been associated with pancreatitis^{5,44,45} and anaphylaxis.^{46,47} Aseptic meningitis has occurred in patients with SLE who were given sulindac.^{5,45,46}

Rashes occur in 3% to 9% of patients taking sulindac.^{48,49} EM (Stevens-Johnson syndrome) and TEN have been reported with considerable frequency.^{45,48-50} In at least one case, association with sulindac was proved with rechallenge,⁴⁵ and there have been at least two deaths.^{9,45} In most cases, EM or TEN began within 2 to 3 weeks after sulindac was taken for the first or second time. Patients with sulindac-induced EM-TEN often have fever and occasionally have concomitant hepatitis.⁴⁵ Morbilliform drug eruptions are common with sulindac and often occur in patients with toxic hepatitis^{41,42} or other systemic hypersensitivity reactions. Pruritus is a common cutaneous reaction to sulindac and may occur without a rash or as a harbinger of EM-TEN, a morbilliform drug eruption,^{41,45,46} or anaphylaxis.⁴⁷ Stomatitis,^{40,46} facial and oral erythema,⁴² urticaria,⁴⁷ a pernio-like reaction,⁵¹ and fixed drug eruptions^{9,52} have all been reported with sulindac use. Petechiae, exfoliative erythroderma, photosensitivity, and two cases of serum sickness are adverse cutaneous reactions associated with sulindac that have recently been reported to the ADRRS.⁹

Tolmetin is a relatively new NSAID currently used for rheumatoid arthritis and ankylosing spondylitis.^{1,2} Tolmetin causes upper gastrointestinal toxicity, headache, and dizziness but is better tolerated than aspirin.¹⁻³ Toxicologic effects of tolmetin are most noteworthy for a substantial number of reported anaphylactoid reactions.^{6,53} Meningitis in patients with SLE,⁶ nephrotic syndrome,⁵⁴ and agranulocytosis^{6,55} have also been reported in association with tolmetin.

There are few reports of cutaneous reactions to tolmetin in the literature. A macular hypersensi-

tivity eruption has been reported.* Pruritus and urticaria have occurred in association with tolmetin-associated anaphylactoid reactions,^{56,57} and a case of TEN associated with tolmetin use was reported to the ADRRS.⁹

Zomepirac sodium is a prostaglandin-inhibiting, nonnarcotic analgesic that is structurally similar to tolmetin.⁵⁸⁻⁶⁰ In 1983 zomepirac sodium was voluntarily withdrawn from the market because of reports of fatal anaphylactoid reactions.^{5,53,61} These reactions occurred most frequently in patients with a history of hypersensitivity reactions to aspirin who used zomepirac sodium intermittently. Zomepirac sodium also causes upper gastrointestinal and CNS side effects,⁶² may worsen renal function,⁶² has induced asthma in aspirin-sensitive patients,^{5,63} and causes urogenital symptoms.^{59,62}

In one long-term study, rashes were reported in 6.4% of 405 patients taking zomepirac sodium for 3 months or more.⁶² Reported cutaneous reactions to zomepirac sodium include urticaria,⁶² stomatitis,⁶⁴ and serum sickness.⁶⁵ Several adverse cutaneous reactions to zomepirac sodium were reported to the ADRRS; most of these were anaphylactoid in nature (anaphylaxis, urticaria, and angioedema). A case of TEN, three cases of EM, and five cases of exanthems or morbilliform eruptions associated with zomepirac sodium were reported to the ADRRS.⁹

Propionic acid derivatives

Ibuprofen is a substituted phenylalkanoic acid indicated for analgesia, osteoarthritis, rheumatoid arthritis, gout, and dysmenorrhea.^{1-3,66,67} In 1984 ibuprofen became available without prescription. Ibuprofen causes less gastrointestinal toxicity than aspirin⁶⁶ but has been associated with meningitis when given to patients with SLE.^{5,68} A reversible toxic amblyopia⁶⁹ and a case of papillary necrosis⁷⁰ have been reported with ibuprofen. Blood dyscrasias^{5,71} and hepatitis^{5,66} are rare.

Cutaneous reactions to ibuprofen are infrequent.⁶ A "maculopapular" drug eruption may occur, especially in patients with SLE.^{72,73} Bar-Sela et al⁷⁴ reported a patient who had the onset

*Ehrlich G: Rheumatoid arthritis: Long-term therapy with tolmetin sodium. *Orthopedics Digest* 4:416-424, 1976.

of a lupus-like syndrome with a morbilliform eruption and a positive antinuclear antibody titer concomitant with the start of ibuprofen use. The rash and symptoms resolved when ibuprofen was withdrawn, but the antinuclear antibody titer remained positive. It is uncertain whether the patient's SLE was ibuprofen induced. Sternlieb and Robinson⁷⁵ reported a patient with bullous EM (Stevens-Johnson syndrome) and toxic hepatitis after ibuprofen use. At the time of that report (1978), five additional cases of EM and TEN had been reported to The Upjohn Co. (Kalamazoo, MI). Alopecia occurred in a group of black patients reported by Meyer.⁷⁶ The alopecia was limited to those patients taking ibuprofen who also used hair straighteners. Pruritus is probably the only common cutaneous reaction to ibuprofen. Urticaria, angioedema, and psoriasiform palmar dermatitis have also been reported.⁶ Photosensitivity and onycholysis, reported by Bailin and Matkaluk⁶ as common reactions to ibuprofen and fenoprofen, have not been described in the literature. A vesiculobullous eruption, a fixed drug eruption, and leukocytoclastic vasculitis are adverse cutaneous reactions to ibuprofen that were reported to the ADRRS.⁹

Naproxen has been shown to be efficacious for analgesia and for treatment of rheumatoid arthritis, osteoarthritis of hip and knee, gout, and dysmenorrhea.^{1-3,77} Plasma half-life of naproxen is 12 to 18 hours, which makes twice-daily dosage possible.^{1-3,6,78} Naproxen's toxicity profile is similar to ibuprofen, but CNS side effects (lightheadedness, headache, and vertigo) are more common.¹⁻³

Rashes occur in approximately 5% of patients taking naproxen.⁶ Pruritus is the most common cutaneous reaction to naproxen,⁶ and in one extended study it occurred in 94 of 672 patients (14%).⁷⁹ Grennan et al⁸⁰ reported a case of cutaneous vasculitis in a patient taking naproxen and noted that six other cases had been reported to Syntex Laboratories, Inc. (Palo Alto, CA). Heyman et al⁸¹ reported a lichen planus-like eruption, confirmed by biopsy, that developed in a patient 10 days after naproxen was started. These authors noted that three additional cases of lichen planus associated with naproxen had been reported to Syntex. Purpura, urticaria, hyperhidrosis, and "dermatitis" have also been described in patients

taking naproxen.^{6,80} EM, a vesicobullous eruption, and a fixed drug eruption were new adverse cutaneous reactions associated with naproxen use and reported to the ADRRS.⁹

Fenoprofen is indicated for the treatment of rheumatoid arthritis, gout, osteoarthritis, and analgesia.^{1-3,82} The drug's toxicity is very similar to the other propionic acid derivatives. Lipoid nephrosis and interstitial nephritis have been reported in five patients by Finkelstein et al.⁸³

There are few reports of adverse cutaneous reactions to fenoprofen in the literature. Hypersensitivity rashes occur.^{1,2} Pruritus, urticaria, and a vesiculobullous eruption were reported to the ADRRS.⁹

Shortly after its well-publicized entry into European and United States markets, the product license of benoxaprofen was suspended because the drug caused fatal cholestatic hepatitis, especially in elderly persons.⁸⁴⁻⁸⁶ Benoxaprofen had been used for rheumatoid arthritis, osteoarthritis,^{1-3,87,88} ankylosing spondylitis,⁸⁹ and psoriasis.^{90,91} Unlike most other NSAIDs, which act principally by inhibiting prostaglandin synthetase, benoxaprofen is a 5-lipoxygenase inhibitor. Benoxaprofen is a weak inhibitor of prostaglandin synthetase. A plasma half-life of 25 to 32 hours makes once-daily therapy feasible. The plasma half-life in elderly persons may be as long as 148 hours.⁸⁷ Benoxaprofen is metabolized in the liver and excreted in the urine as the glucuronide and in the feces.⁹² Upper gastrointestinal tract side effects are common, especially in elderly persons.^{87,93}

Cutaneous reactions are the most common side effects of benoxaprofen and account for 70% of all reported side effects.⁹³ Photosensitivity, initially reported in only 9% of 1,681 patients in one study,⁹⁴ occurs in all fair-skinned white persons exposed to sunlight after recommended doses.^{87,94,95} The photosensitivity has an action spectrum of 310 to 340 nm and is experienced as immediate itching, burning, and erythema.⁹⁶⁻¹⁰⁰ Onycholysis occurs in 8% to 13% of patients taking benoxaprofen^{93,94} and has occurred without exposure of the affected nail to sunlight.^{96,100,101} The onycholysis begins distally, is usually incomplete, and improves when the drug is withdrawn. Cysts and milia are common in pa-

tients taking benoxaprofen^{87,93,102} and have been reported in up to 5.3% of patients.⁹³ Hypertrichosis has occurred in approximately 1% of benoxaprofen-treated patients,^{87,93,103} and increased nail growth has been observed.^{87,93,103} EM (Stevens-Johnson syndrome) has been associated with benoxaprofen.^{87,104,105} Fenton and English¹⁰⁶ reported cases of TEN, leukopenia, and thrombocytopenic purpura that complicated benoxaprofen therapy. Pruritus and urticaria are not uncommon.^{94,99} Psoriasis and prurigo nodularis have improved in some patients treated with benoxaprofen.^{90,91,107}

Anthranilic acids

Mefenamic acid and flufenamic acid are indicated for rheumatoid arthritis, dysmenorrhea, and analgesia.¹⁻³ The fenamic acids inhibit prostaglandin synthetase and block prostaglandin action. In addition to upper gastrointestinal side effects and platelet dysfunction common to all NSAIDs, mefenamic acid and flufenamic acid cause diarrhea in 12% to 15% of patients.¹⁻³ Coombs' test-positive hemolytic anemia occurs more commonly with mefenamic acid. Nephrotoxicity has occurred with both drugs, especially in elderly persons.¹⁻³ Since seizures have occurred with mefenamic acid overdose, the drug should be avoided in patients with epilepsy.¹⁰⁸⁻¹¹⁰ Marrow hypoplasia has been described. Neither drug is recommended for long-term use.¹⁻³

Cutaneous reactions are not common with mefenamic acid or flufenamic acid. Hypersensitivity rashes, urticaria, and pruritus occur but are not common.¹¹¹ No adverse cutaneous reactions to mefenamic acid were reported to the ADRRS.⁹ Flufenamic acid is not marketed in the United States.

Sodium meclofenamate has been used for rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.*†⁵ Meclofenamic acid has weak secretory laxative properties and causes diarrhea in

11% to 46% of patients.*¹¹² Upper gastrointestinal side effects, anemia, and abnormal liver function tests have all been reported.*†

Rashes occur in 3% to 9% of patients taking meclofenamate sodium.*^{112,113} Several cases of EM after meclofenamate sodium use have been reported.^{9,113} Drug-induced exanthem, often accompanied by pruritus, was the most common cutaneous reaction to sodium meclofenamate reported to the ADRRS. Exfoliative erythroderma, vasculitis, fixed drug eruption, a vesiculobullous eruption, urticaria, purpura and/or petechiae, and photosensitivity were also reported.⁹

Oxicams

Piroxicam is indicated for the treatment of rheumatoid arthritis, osteoarthritis, gout, and ankylosing spondylitis.^{2,5,87,114-116} A plasma half-life of 50 hours makes once-daily therapy possible.⁸⁷ Upper gastrointestinal side effects are common. When more than 20 mg of piroxicam is given per day, or when the drug is given with aspirin,^{87,117-120} the incidence of ulcers is unacceptably high (16% to 33%). Worsening renal function and blood dyscrasias have also been reported.^{5,87,121}

In one large study, rashes occurred in 2.4% of patients taking piroxicam.¹¹⁸ Several cases of an apparently unique photosensitivity caused by piroxicam have been reported.^{9,122,123} The photosensitive eruption is most often vesiculobullous but may be maculopapular, lichenoid, or nonspecific, and it is often pruritic. More than half of the reported eruptions occurred in sun-exposed areas and within 3 days of the patient's first exposure to piroxicam. There was often a history of increased sun exposure. The rash is frequently accompanied by a stinging or burning sensation. These features suggest a phototoxic mechanism. Three cases of EM associated with piroxicam were reported to the ADRRS. Several piroxicam-associated drug-induced exanthems were also reported to the ADRRS. Alopecia, eczematous dermatitis, and

*Dresner AJ: Multicenter studies with sodium meclofenamate in the U.S. and Canada. *Curr Ther Res* 23(suppl):90-106, 1978.

†Eberl R: European studies of sodium meclofenamate for the treatment of ankylosing spondylitis. *Curr Ther Res* 23(suppl):126-130, 1978.

*Preston S: Safety of sodium meclofenamate. *Curr Ther Res* 23(suppl):107-112, 1978.

†Smith T: Clinical pharmacology studies of sodium meclofenamate. *Curr Ther Res* 23(suppl):42-50, 1978.

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vasculitis were also reported.⁹ Several cases of Henoch-Schönlein purpura after piroxicam use have been reported in the literature.^{87,124} Martin et al¹²⁵ reported a case of fatal pemphigus vulgaris that developed in a 73-year-old man 3 days after starting piroxicam, 20 mg daily.¹²⁵

Pyrazolones

Phenylbutazone is used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and gout. The plasma half-life of phenylbutazone is variably reported as either 22 hours³ or 60 to 80 hours.² Phenylbutazone is metabolized in the liver and excreted in the urine and feces. One of its metabolites, oxyphenbutazone, is an active NSAID and has a plasma half-life of 70 to 80 hours.³ Upper gastrointestinal side effects occur in approximately 20% of patients taking phenylbutazone.^{2,3} More importantly, marrow aplasia, fluid retention with congestive heart failure, and toxic hepatitis have all occurred with phenylbutazone.^{2-5,126}

Cutaneous reactions to phenylbutazone are many and varied and have been well reviewed by Bailin and Matkaluk⁶ and by Almeyda and Baker.⁷ Morbilliform hypersensitivity rashes can occur in conjunction with or separately from exfoliative dermatitis in approximately 4% of patients treated with phenylbutazone.⁷ These eruptions may be accompanied by an atypical lymphocytosis resembling acute mononucleosis.¹²⁷ Pruritus is a common reaction to phenylbutazone.^{6,7} There have been over 150 cases of EM-TEN associated with phenylbutazone.⁶ The pyrazolones are the only group of NSAIDs that commonly cause a fixed drug eruption.^{5,6,128} Although fixed drug eruptions are seen more commonly with oxyphenbutazone, cross-reactivity with phenylbutazone has also been demonstrated.¹²⁸ As with other NSAIDs, urticaria is not infrequent, especially in aspirin-sensitive patients.⁷ Buccal ulceration occurs with and without marrow dysplasia.⁷ Phenylbutazone has uncommonly been associated with a myriad of cutaneous reactions, including erythema nodosum,⁷ lichenoid erythroderma,⁷ acne neurotica,⁷ non-thrombocytopenic purpura,^{6,129} vasculitis,^{6,7} a hemorrhagic bullous eruption of the hands,¹²⁹ polyar-

teritis nodosa,⁶ photosensitivity,^{6,7} and an SLE-like syndrome.⁶

CONCLUSION

The NSAIDs cause diverse cutaneous reactions. Although NSAIDs in the same chemical class often produce similar cutaneous reactions, many exceptions exist. Aspirin, a salicylic acid, is a common cause of acute and chronic urticaria and purpura. Of the heterocyclic acetic acids, sulindac has been most frequently associated with a wide variety of adverse cutaneous reactions, including pruritus, exanthems, EM, and TEN. With the exception of benoxaprofen, which frequently causes phototoxic eruptions, the propionic acid derivatives are infrequently associated with rashes; pruritus is the only common cutaneous reaction seen with other members of this class of drugs. Drug-induced exanthem is seen commonly with the heterocyclic acetic acids, the pyrazolones, the anthranilic acids, and one of the salicylates, diflunisal. The pyrazolones are most commonly associated with fixed drug eruptions.

Much of the information summarized in this review was obtained from letters, case reports, or reports of adverse reactions occurring in small numbers of patients. One report, however, contained 135 adverse cutaneous reactions to NSAIDs that had been reported by dermatologists to the ADRRS of the American Academy of Dermatology.⁹ That report illustrates the utility of a specialty-based adverse drug reaction reporting system in accumulating, codifying, and reporting the spectrum of adverse reactions to drugs encountered in medical practice.

We thank the more than 500 dermatologists who have contributed reports to the Adverse Drug Reaction Reporting System of the American Academy of Dermatology.

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