

An Expanded Profile of Cutaneous Reactions to Nonsteroidal Anti-inflammatory Drugs

Reports to a Specialty-based System for Spontaneous Reporting of Adverse Reactions to Drugs

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● The nonsteroidal anti-inflammatory drugs are widely used in the United States and are a frequent cause of cutaneous reactions. Since December 1980, dermatologists have reported 135 of these drug reactions to a specialty-based Adverse Drug Reaction Reporting System. Reactions to piroxicam were most frequently reported; the majority of reactions to this drug were vesiculobullous and occurred most often in sun-exposed areas. Other reactions to nonsteroidal anti-inflammatory drugs not previously recognized include serum sickness, exfoliative erythroderma, and photosensitivity associated with sulindac; toxic epidermal necrolysis was reported with tolmetin, zomepirac sodium, and piroxicam. Fixed drug eruptions were noted with ibuprofen and naproxen, and photosensitivity was reported with sulindac and indomethacin. These findings illustrate the usefulness of a specialty-based system for spontaneous reporting of new and serious adverse reactions to drugs.

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IN THE past decade, many new nonsteroidal anti-inflammatory drugs (NSAIDs) have been introduced into the United States and are now widely used to treat a variety of conditions, including inflammatory and degenerative musculoskeletal disorders. Several comprehensive reviews discuss the indications, mechanisms of ac-

tion, pharmacology, efficacy, and toxicity of these drugs.^{1,5} However, these reviews are limited in their attention to cutaneous reactions to NSAIDs. Bailin and Matkaluk⁶ have reviewed the cutaneous reactions to rheumatological drugs, but have discussed only two of the NSAIDs introduced since 1965.

Since its inception in December 1980 through July 1983, the Adverse Drug Reaction Reporting System (ADRRS), a system administered by the American Academy of Dermatology for the spontaneous reporting of suspected adverse reactions to drugs, has received 135 reports of adverse

cutaneous reactions to NSAIDs. This study presents reactions to NSAIDs reported to the ADRRS, with emphasis on newly reported cutaneous reactions.

METHODS

The ADRRS of the American Academy of Dermatology was organized in late 1980 to facilitate the reporting of new, unusual, or serious suspected adverse drug reactions. To simplify and encourage reporting, a toll-free telephone number (1-800-323-1473) is available 24 hours each day, seven days a week. During business hours, this telephone is answered by a trained project assistant in the American Academy of Dermatology's office. During other hours, a voice-activated answering machine is available. Reporters and patients are assured of confidentiality, and each reporter is furnished with a transcript of their report for verification. Telephone reports account for more than 90% of reports received from December 1980 through July 1983. Written reports account for the remainder.

All reports are reviewed for completeness by a board-certified dermatologist. If needed, supplementary information may also be requested from the reporter. Completed reports are classified according to established algorithms for judging the type, severity, and outcome of reactions based on a standard vocabulary.⁷ Reports are also classified by the degree of causality between each drug and its adverse

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Table 1.—Cutaneous Reactions to Nonsteroidal Anti-inflammatory Drugs Classified by Clinical Morphological Findings in 135 Reported Patients*

Reaction	Drugs							
	Piroxicam	Zomepirac Sodium	Sulindac	Benoxaprofen	Meclofenamate Sodium	Ibuprofen	Naproxen	Tolmetin
Vesiculobullous	29	...	...	...	1	1	2	...
Toxic epidermal necrolysis	...	1	2	1†	...	...	...	1
Erythema multiforme	3	3	3	...	2	1	1	...
Exfoliative erythroderma	...	...	1	1	1	...	...	...
Anaphylaxis	...	4	...	...	...	...	...	...
Angioedema	...	2	...	...	...	2	1	...
Urticaria	1	7	1	...	1	4	1	1
Serum sickness	...	...	2	...	...	...	1	...
Vasculitis	1	...	...	...	2	1	...	...
Purpura-petechiae	...	1	2	...	2	...	...	1
Photosensitivity	36	...	1	3	1	...	...	...
Fixed drug	...	1	1	...	1	1	...	...
Exanthem‡	10	5	4	2	11	...	1	1
Pruritus, with rash	11	3	1	...	7	...	...	...
Skin pain	...	1	2	...	...	...	...	...
Nail disorder	...	...	...	5	...	...	...	...
Rash, unspecified and other§	8	...	1	6	1	...	...	...
Total	100	28	21	18	30	10	7	4

* Reported to the Adverse Drug Reaction Reporting System. Excluded from Table 1 is one reaction to indomethacin (photosensitivity) and two persons with reactions to fenoprofen (rash and pruritus).

†Indicates skin necrosis.

‡Includes macular drug eruption, maculopapular rash, morbilliform eruption, and "drug rash."

§"Other" includes lichenoid, one reaction; granulomatous, one; eczematous, one; alopecia, two; and pruritus without rash, two.

||A patient may have more than one cutaneous reaction. Therefore, the sum of the reactions may be greater than the total number of patients reported.

reaction (eg, remote, possible, probable, and definite).⁸ Each cutaneous reaction is classified by a dermatologist and diagnosed on clinical grounds that include morphological findings and distribution. The majority of cases, however, are not confirmed through histological findings.

Each report and its evaluation is entered into Medical Information Storage and Retrieval, a system that permits retrieval of reactions on the basis of type of reaction, suspected drug, or patient characteristics.⁹

RESULTS

From December 1980 to July 1983, the ADRRS received 135 reports of adverse drug reactions that were judged to be possibly (18%), probably (71%), or definitely (11%) related to NSAIDs. Reactions to NSAIDs represented 13% of all reactions reported to the ADRRS during this period.

Cutaneous reactions to NSAIDs reported to the ADRRS are summarized in Table 1. Adverse cutaneous reactions were reported most commonly to piroxicam, zomepirac sodium, sulindac, meclofenamate sodium, and benoxaprofen. These five drugs accounted for 116 of the 135 adverse cutaneous reactions reported. The relative number of new NSAIDs prescriptions dispensed between July

1981 and June 1983 and the ratio of the number of adverse reaction reports received by the ADRRS to the number of new prescriptions dispensed for each NSAID are given in Table 2. According to this index, benoxaprofen, piroxicam, meclofenamate sodium, sulindac, and zomepirac sodium have the highest rates of reactions reported relative to the number of new prescriptions dispensed during this period.

Reactions to benoxaprofen included two serious eruptions: toxic epidermal necrolysis and exfoliative erythroderma. More than half of reported eruptions associated with benoxaprofen suggested photosensitivity. In one patient, histological examination of a biopsy specimen from a sun-exposed area showed cutaneous damage deep enough to result in prominent sweat gland necrosis. Because of the adverse effects associated with its use, benoxaprofen was withdrawn from the United States market in August 1982.

The highest total number of adverse cutaneous reactions to NSAIDs were reported in association with piroxicam. Five piroxicam reactions were severe enough to require bed rest or hospitalization. More than two

thirds of piroxicam reactions were of a distribution or character that suggested photosensitivity. Twenty-four (67%) of the 36 reactions that suggested photosensitivity were vesiculobullous or eczematous in nature. Other eruptions attributed to piroxicam that occurred in sun-exposed areas had a variety of morphological features, including nine maculopapular eruptions and one lichenoid eruption. Stinging or burning were frequently reported in association with piroxicam eruptions. Another characteristic of these eruptions was their rapid onset; more than half of the vesiculobullous or eczematous eruptions in sun-exposed areas occurred within three days of the patient's first exposure to piroxicam, which suggests a phototoxic mechanism. Alopecia was also reported in association with use of this drug (Table 1).

Meclofenamate sodium has the highest reaction rate relative to new prescriptions for NSAIDs available in the United States before 1980. More than two thirds of eruptions associated with this drug were exanthems, and pruritus was prominent (Table 1). Pruritus was also noted in one patient who did not have an eruption. Photosensitivity was not a prominent

Table 2.—Ratio of Reactions Reported to the ADRRS* to Relative Number of New Prescriptions Dispensed

Drug	Relative No. of New Prescriptions Dispensed†	No. of Persons With Reactions Reported to ADRRS	Ratio of Reactions Reported to Relative Prescriptions Dispensed
Benoxaprofen	1.0	15	15
Piroxicam	5.7	49	8.6
Meclofenamate sodium	2.7	15	5.6
Sulindac	8.4	18	2.1
Zomepirac sodium	10.7	19	2.1
Tolmetin	3.4	3	0.9
Naproxen	14.2	6	0.4
Fenoprofen	5.0	2	0.4
Ibuprofen	26.9	7	0.3
Indomethacin	12.7	1	0.1

*ADRRS indicates Adverse Drug Reaction Reporting System.

†Market and prescription data © copyright 1981-1983, IMS America Ltd. Benoxaprofen had the smallest number of prescriptions dispensed from July 1981 to June 1983. The number of prescriptions for all other drugs are expressed as a multiple of the number of benoxaprofen prescriptions for this period.

Table 3.—Cutaneous Reactions to NSAIDs Reported to the ADRRS*

Drug	Newly Reported†	Previously Reported and Requiring Hospitalization or Bed Rest†
Sulindac	Exfoliative erythroderma, photosensitivity, serum sickness‡	Toxic epidermal necrolysis (2)
Tolmetin	Toxic epidermal necrolysis‡	...
Zomepirac sodium	Toxic epidermal necrolysis‡	Urticaria, exanthem, anaphylaxis
Ibuprofen	Vesiculobullous,‡ fixed drug	Vasculitis, erythema multiforme
Naproxen	Erythema multiforme, vesiculobullous (2), fixed drug	Serum sickness
Benoxaprofen	Alopecia	...
Piroxicam	Erythema multiforme (2), vesiculobullous (29),‡ photosensitivity (36)	Urticaria, maculopapular rash, rash (unspecified)
Indomethacin	Photosensitivity	...
Meclofenamate sodium	...	Erythema multiforme, vasculitis, vesiculobullous

*NSAIDs indicates nonsteroidal anti-inflammatory drugs; ADRRS, Adverse Drug Reaction Reporting System. Reactions included were not previously noted in the English literature or requiring hospitalization or bed rest.

†The number of cases reported appears in parenthesis if more than one case was reported.

‡Indicates at least one patient with reaction of this type who required hospitalization or bed rest.

occurrence with this drug; it was suspected in only one of 15 reported reactions. Vasculitic, purpuric, or petechial eruptions were noted in four cases, a rate significantly higher than that reported for other NSAIDs ($P < .05$, Fisher's exact test). Three serious reactions (erythema multiforme, vasculitis, and a vesiculobullous eruption) occurred in association with meclofenamate sodium exposure.

The majority of cutaneous reactions to zomepirac sodium were anaphylactoid in nature. Reactions to this drug that were reported to our system included four cases of anaphylaxis, two cases of angioedema, and seven cases of urticaria. Other new and serious reactions included a case

of toxic epidermal necrolysis, which had not been previously reported with this drug. Zomepirac acid was withdrawn from the US market in March 1983.

Sulindac was associated with a wide variety of adverse cutaneous reactions (Table 1). One eruption in a sun-exposed distribution suggested photosensitivity. This eruption, along with two other serious reactions, a case of a serum sickness-like syndrome and one of exfoliative erythroderma, had not been noted previously. The case of serum sickness, as well as two cases of toxic epidermal necrolysis, required bed rest or hospitalization.

Of the remaining five NSAIDs with new prescription rates at least as

great as that of benoxaprofen during this period, only two had more than five reported reactions: naproxen and ibuprofen. Since both of these drugs had relatively high prescription rates, there were relatively small ratios of reactions to new prescriptions (Table 2). Three previously unreported types of reactions (erythema multiforme, a vesiculobullous eruption, and a fixed drug eruption) were reported in association with naproxen. The latter two types of reactions were also newly reported to us with ibuprofen. Tolmetin, a NSAID structurally similar to zomepirac acid, was associated with toxic epidermal necrolysis, a reaction not previously reported with this drug. A case of indomethacin-related photosensitivity, which was established by rechallenge and photopatch testing, was also reported. Reactions reported to the ADRRS not previously reported in our review of the English literature, as well as those requiring hospitalization or bed rest, are summarized in Table 3. (A supplemental bibliography consisting of the 111 manuscripts we reviewed is available through NAPS.)

Two deaths occurred among those patients with adverse cutaneous reactions to NSAIDs reported to the ADRRS. Toxic epidermal necrolysis developed in an 81-year-old woman within 12 to 14 hours of taking zomepirac sodium for an unknown indication. She had no known previous exposure to zomepirac sodium. The patient died of complications of toxic epidermal necrolysis after a 14-day hospitalization. Toxic epidermal necrolysis developed in an 82-year-old woman 14 days after starting on a regimen of sulindac. She had no known history of previous exposure to sulindac and had not recently begun taking any other drugs. She died of complications of toxic epidermal necrolysis in eight days.

COMMENT

Nonsteroidal anti-inflammatory drugs, a chemically heterogeneous group of compounds, can cause a wide variety of cutaneous reactions. As a result of the cooperation of the dermatologists who shared their observations with the ADRRS, we have been able to expand our knowledge of the spectrum of cutaneous reactions associated with NSAIDs.

Unfortunately, spontaneous reports provide little information about the mechanisms responsible for adverse cutaneous reactions associated with NSAIDs. The wide variety of cutaneous reactions associated with many NSAIDs suggest that a variety of mechanisms may be responsible. Since NSAIDs affect the inflammatory pathway, it is conceivable that many of the observed cutaneous effects of these drugs result from alteration of this pathway rather than from classic hypersensitivity (immunologic) reactions.

Special caution should be taken when interpreting data on relative reaction rates calculated from spontaneous reports. Reactions associated with newly marketed drugs or those of unusual morphological features are more likely to be reported than are well-described reactions to older drugs. For example, cutaneous reactions, especially urticaria, are considered to be frequent with salicylates. However, physicians did not report reactions to salicylates to the ADRRS, and only one adverse cutaneous reaction to indomethacin was reported, which also suggests that reactions to drugs in use for a long period are less likely to be reported.

Serious reactions associated with sulindac use included two cases of serum sickness, a photosensitivity eruption, and one patient in whom exfoliative erythroderma developed. These reactions were all reported to the ADRRS but were not described in our literature search.

Tolmetin and zomepirac acid are structurally similar heterocyclic acetic acids (or pyrroles).^{3,10} Although only a single report associated with tolmetin use was reported to the ADRRS, this patient had a severe eruption of toxic epidermal necrolysis. Several adverse cutaneous reactions to zomepirac sodium were reported to the ADRRS. Most of these reactions were anaphylactoid in nature (anaphylaxis, urticaria, and angioedema). Because of the risk of anaphylactoid reactions, this drug was withdrawn from the US market. Other types of reactions reported to the ADRRS in association with zomepirac sodium included toxic epidermal necrolysis, exanthems, and morbilliform eruptions.

With the exception of benoxaprofen, the propionic acid derivatives

(ibuprofen, naproxen, and fenoprofen) are a homogenous group of drugs with similar uses, actions, and toxicity.¹³ Ibuprofen is the most widely dispensed NSAID in this drug class and has recently been made available as a nonprescription drug. Cutaneous reactions to ibuprofen seem to be infrequent.⁶ In addition to morbilliform eruptions, a vesiculobullous and a fixed drug eruption were reported to the ADRRS in association with ibuprofen. Naproxen is said to be a more frequent cause of cutaneous eruptions than is ibuprofen.⁶ Reactions to naproxen not previously noted in the literature included a fixed drug eruption, a vesiculobullous eruption, and a case of erythema multiforme that was reported to the ADRRS.

Shortly after its well-publicized entry into the US market, the product license of benoxaprofen was withdrawn because the drug caused fatal cholestatic hepatitis, especially in the elderly.¹¹⁻¹³ Cutaneous reactions are the most common side effects of benoxaprofen therapy and account for 70% of all reported side effects.¹⁴ During benoxaprofen's brief time on the US market, physicians reporting to the ADRRS noted 19 reactions, including alopecia, toxic epidermal necrolysis, and exfoliative erythroderma. Of the reported cases of photosensitivity associated with this drug, one was sufficiently severe to result in necrosis of the sweat glands.

The fenamic acids are anthranilic acid derivatives that share the unique ability to both inhibit prostaglandin synthesis and block prostaglandin action.¹² Meclofenamate sodium is the most widely used fenamic acid in the United States. Rashes are reported to occur in 3% to 9% of patients using this drug.¹⁵⁻¹⁷ The most common cutaneous reaction to meclofenamate sodium reported to the ADRRS was an exanthem usually accompanied by pruritus. Other reactions reported to our system included exfoliative erythroderma, vasculitis, a fixed drug eruption, a vesiculobullous eruption, urticaria, purpura-petechiae, and photosensitivity.

Piroxicam is the only enolic acid derivative of the oxicam class currently available in the United States. In one large study, rashes occurred in

2.4% of patients taking piroxicam.¹⁸ As detailed herein, several cases of a seemingly unique photosensitivity reaction caused by piroxicam have been reported.¹⁹ This photo-distributed eruption is most often vesiculobullous but may also be maculopapular or lichenoid, and is often pruritic. Three cases of erythema multiforme and cases of alopecia and vasculitis have all been reported to the ADRRS.

The ADRRS system represents a new mechanism for spontaneous reporting of suspected adverse drug reactions. Physicians, principally members of the American Academy of Dermatology, can use a toll-free telephone number to report suspected reactions. Reporter and patient confidentiality are guaranteed and a board-certified dermatologist reviews all reports and requests supplemental information. Although most diagnoses are not confirmed through histological findings and we cannot be sure of each report's true morphological features, more than 95% are made by trained dermatologists.

The usefulness of this system for the early recognition of potentially serious reactions is illustrated by the report of an anaphylactoid reaction associated with zomepirac acid sodium that was received during the first six months of operation. We reported these findings in a newsletter sent to all American Academy of Dermatology members and to the Food and Drug Administration almost two years before this drug was withdrawn from the US market. Also, during piroxicam's first summer on the market, we received reports of multiple vesiculobullous and eczematous reactions on sun-exposed surfaces. These observations led to a label change that indicated this potential adverse reaction.

This manuscript, which is based on 135 reactions reported to the ADRRS by more than 100 dermatologists, illustrates the potential usefulness of a specialty, society-based, controlled system for spontaneous reporting of adverse drug reactions. We believe that our system has helped to increase dermatologists' awareness of the importance of drugs in the etiology of cutaneous reactions. We also believe that additional specialty-based, controlled systems for spontaneous reporting of adverse drug reac-

ions could help to increase our knowledge of these reactions and help to ensure their rapid recognition, especially those reactions associated with newly marketed drugs.

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More than 500 dermatologists assisted by contributing reports to the Adverse Drug Reaction Reporting System of the American Academy

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