

# Anaphylactoid Reaction to Diflunisal

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are very widely prescribed agents, not only for the treatment of various rheumatological diseases, but also for less severe conditions such as dysmenorrhea, musculoskeletal complaints, and pain. Side effects are generally mild, with gastrointestinal distress being the most common. More severe reactions such as anaphylactoid reactions may occur, however. Although the Spontaneous Reporting System of the Food and Drug Administration has received reports of anaphylactoid reactions associated with almost all the nonsteroidal anti-inflammatory drugs marketed in the United States, such a reaction to diflunisal has not been reported in the literature. Diflunisal is a difluorophenyl derivative of salicylic acid but is not hydrolyzed to salicylate *in vivo*. It is not considered a true salicylate. It does, however, have pharmacologic actions similar to aspirin and other nonsteroidal anti-inflammatory drugs.

## Case Report

A 47-year-old woman presented with a chief complaint of left shoulder and neck pain following vigorous yard work. She was diagnosed as having musculoskeletal strain secondary to yard work and was prescribed heat, rest, and diflunisal, 1 g initially, followed by 500 mg every 12 hours. She denied any previous adverse reaction to drugs, and specifically had taken ibuprofen, naproxen, and aspirin in the past without complications. The patient had not used diflunisal previous to this occasion. She had no history of anaphylactic reactions, nasal polyps, or asthma. Approximately one hour after ingesting 1 g of diflunisal, she experienced itching of her hands and feet, lightheadedness, and subsequently collapsed at her desk. The patient was placed in a supine position on the floor by an office co-worker and her pulse was not palpable. As cardiopul-

monary resuscitation was initiated, she revived and was taken to the emergency room.

Upon arrival in the emergency room, the patient's blood pressure was 90/60 mmHg, pulse 76 beats per minute, respirations 16/min, and oral temperature, 96.5 °F (35.8 °C). She had an erythematous, urticarial, coalescent rash on her upper and lower extremities, face, trunk, and abdomen. Her lungs were clear without wheezing. She was treated with 0.3 mg of epinephrine subcutaneously and 25 mg of diphenhydramine intramuscularly. The pruritis rapidly resolved, and her blood pressure stabilized at 120/75 mmHg within 30 minutes. Approximately one hour later she was given a 1.0-mg epinephrine suspension subcutaneously and 200 mg of methylprednisolone intravenously. She was admitted to the intermediate care unit for observation and treated with 25 mg of hydroxyzine every four hours. A complete blood count (drawn after the patient received epinephrine) revealed a hemoglobin of 144 g/L (14.4 g/dL) a white cell count of  $23.2 \times 10^9/L$  ( $23,200/mm^3$ ) with 0.83 neutrophils, 0.14 lymphocytes, 0.02 monocytes and 0.01 eosinophils.

Approximately 24 hours after the initial anaphylactoid reaction, she was discharged from the hospital in no apparent distress and without further complications. She was instructed to avoid aspirin and nonsteroidal anti-inflammatory drugs, in both prescription and over-the-counter forms. Treatment of the muscle strain was continued with heat and rest. Two weeks after discharge she was doing well with a blood pressure of 130/70 mmHg, her pulse regular at 68 beats per minute, and her lungs clear to auscultation. Her white cell count at that time was  $5.3 \times 10^9/L$  ( $5,300/mm^3$ ) with 0.77 neutrophils, 0.22 lymphocytes, and 0.01 eosinophils. She has continued to avoid other NSAIDs including aspirin.

## COMMENT

A computer search of the literature revealed several reports of anaphylactoid reactions to NSAIDs but not to diflunisal. Rossi and Knapp<sup>1</sup> reviewed adverse reactions to NSAIDs, which revealed anaphylactoid reactions to most of these agents. A similar reaction (acute anaphylactic reaction with

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**TEMOVATE®**

(clobetasol propionate)

**Cream, 0.05% Ointment, 0.05%****(potency expressed as clobetasol propionate)****For Dermatologic Use Only — Not for Ophthalmic Use.****BRIEF SUMMARY**

The following is a brief summary only. Before prescribing, see complete prescribing information in TEMOVATE® Cream and Ointment product labeling.

**CONTRAINDICATIONS:** TEMOVATE® Cream and Ointment are contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in these preparations.

**PRECAUTIONS: General:** TEMOVATE® is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 g per day. Systemic absorption of topical corticosteroids has resulted in reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include the application of the more potent corticosteroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS: Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatologic infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Certain areas of the body, such as the face, groin, and axillae, are more prone to atrophic changes than other areas of the body following treatment with corticosteroids. Frequent observation of the patient is important if these areas are to be treated.

As with other potent topical corticosteroids, TEMOVATE Cream and Ointment should not be used in the treatment of rosacea and perioral dermatitis. Topical corticosteroids in general should not be used in the treatment of acne.

**Information for Patients:** Patients using TEMOVATE should receive the following information and instructions:

1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive.

4. Patients should report any signs of local adverse reactions to the physician.

**Laboratory Tests:** The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone have revealed negative results.

**Pregnancy: Teratogenic Effects: Pregnancy Category C:** Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic in animals after dermal application. Clobetasol propionate has not been tested for teratogenicity by this route; however, it appears to be fairly well absorbed percutaneously, and when administered subcutaneously it proved to be a relatively potent teratogen in both the rabbit and mouse.

There are no adequate and well-controlled studies of the teratogenic effects of topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

**Nursing Mothers:** It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are prescribed for a nursing woman.

**Pediatric Use:** Use of TEMOVATE Cream and Ointment in children under 12 years of age is not recommended.

**Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a large skin surface area to body weight ratio.**

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilloedema.

**ADVERSE REACTIONS:** TEMOVATE® Cream and Ointment are generally well tolerated when used for two-week treatment periods.

The most frequent adverse reactions reported for TEMOVATE Cream have been local and have included burning sensation (4 of 421 patients) and stinging sensation (3 of 421). Less frequent adverse reactions were itching, skin atrophy, and cracking and fissuring of the skin (1 of 421).

The most frequent adverse events reported for TEMOVATE Ointment have been local and have included burning sensation, irritation, and itching (2 of 366 patients). Less frequent adverse reactions were stinging, cracking, erythema, folliculitis, numbness of fingers, skin atrophy, and telangiectasia (1 of 366).

The following local adverse reactions are reported infrequently when topical corticosteroids are used as recommended. These reactions are listed in an approximately decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. Systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. In rare instances, treatment (or withdrawal of treatment) of psoriasis with corticosteroids is thought to have provoked the pustular form of the disease.

**OVERDOSAGE:** Topically applied TEMOVATE® can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

**DOSAGE AND ADMINISTRATION:** A thin layer of cream or ointment should be applied with gentle rubbing to the affected skin areas once in the morning and once at night. TEMOVATE® Cream and Ointment are potent; therefore, treatment must be limited to 14 days, and amounts greater than 50 g per week should not be used. TEMOVATE Cream and Ointment are not to be used with occlusive dressings.

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bronchospasm) is reported by the manufacturer (Dolobid, Merck Sharp & Dohme) in the package circular,<sup>2</sup> and a review of other of their reports reveals experiences similar to the experience with the 47-year-old patient described above. The majority of anaphylactoid reactions to NSAIDs in the published literature, however, have been reported with tolmetin and zomepirac.

The mechanism(s) by which the NSAIDs cause anaphylactoid reactions is still poorly understood. One explanation for the reaction is the reduction of prostaglandin synthesis resulting in the increase of leukotrienes (slow-reacting substances of anaphylaxis).<sup>3</sup> The reduction of prostaglandin synthesis may also result in mast cell instability with resultant release of vasoactive amines.<sup>4</sup> Thus these mechanisms may be related to the pharmacologic effects of the drug on the immune system. These effects have been termed a pseudo-allergic (anaphylactoid) reaction.<sup>5</sup> Another proposed mechanism is a true type I hypersensitivity (anaphylactic) reaction,<sup>4</sup> which is mediated by antigen interacting with immunoglobulin E antibody, causing basophils and mast cells to release pharmacologically active mediators.

The incidence of anaphylactoid reactions with any of the NSAIDs is difficult to determine. It appears to be an underreported adverse effect. Although the true mechanism for this reaction continues to be debated, physicians should be aware of possible anaphylactoid reactions to diflunisal and all other NSAIDs. Patients who have had a reaction to any of the NSAIDs (including aspirin) may be cross-sensitive to other agents. This case illustrates that physicians cannot assume that a history of ingestion of one or more NSAIDs without incident assures no complications with another. Since it is almost impossible to predict cross-sensitivity, patients should be advised to avoid other NSAIDs (and aspirin), a point that has taken on greater significance with the over-the-counter availability of ibuprofen.

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