Anaphylactoid Reaction to Diflunisal

Timothy E. Poe, PharmD, George H. Limpert, MD, and Guyton J. Winker, MD
Winston-Salem, North Carolina

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 cardiopulmonary 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[1] reviewed adverse reactions to NSAIDs, which revealed anaphylactoid reactions to most of these agents. A similar reaction (acute anaphylactic reaction with

Submitted, revised, June 9, 1988.

From the Department of Family and Community Medicine, Bowman Gray School of Medicine, of Wake Forest University, Winston-Salem, North Carolina. Requests for reprints should be addressed to Dr. Timothy E. Poe, Department of Family and Community Medicine, Bowman Gray School of Medicine of Wake Forest University, 300 S. Hawthorne Rd., Winston-Salem, NC 27103.

bronchospasm) is reported by the manufacturer (Dolobid, Merck Sharp & Dohme) in the package circular,[2] 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).[3] The reduction of prostaglandin synthesis may also result in mast cell instability with resultant release of vasoactive amines.[4] 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.[5] Another proposed mechanism is a true type I hypersensitivity (anaphylactic) reaction,[4] 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.

Acknowledgment

This publication is prepared in association with the University of North Carolina Area Health Education Center Program.

References

1. Rossi AC, Knapp DE: Tolmetin-induced anaphylactoid reactions. N Engl J Med 1982; 307:499–500
2. Product information insert. West Point, Penn, Merck Sharp & Dohme, October 1985
3. Patterson R, Anderson J: Allergic reactions to drugs and biologic agents. JAMA 1982; 248:2637–2645
4. Haines DE, Witte GN, Graman HB, et al: Case report: Zomepirac-induced anaphylactic shock: An under-reported phenomenon. Am J Med Sci 1985; 290:165–166
5. Schlumberger HD: Pseudo-allergic reactions to drugs and chemicals. Ann Allergy 1983; 51:317–324