Anaphylactoid Reactions Reported after Treatment with Ciprofloxacin

Harold Davis, MD; Ermona McGoodwin, BS; and T. Greene Reed, MD, MPH

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Ciprofloxacin (Cipro, Miles Inc., West Haven, Connecticut) is a fluorinated quinolone that is a broad-spectrum antibacterial agent. It is recommended for the treatment of infections caused by susceptible bacteria in lower respiratory infections, skin and skin-structure infections, bone and joint infections, urinary-tract infections, and infectious diarrhea. Recommended adult dosages range from 250 mg every 12 hours (for mild urinary-tract infections) to 750 mg every 12 hours (for more severe or complicated infections). Ciprofloxacin oral tablets have been approved for marketing in the United States since October 1987; the drug should not be used in children or pregnant women. Like other members of this drug class, the most frequent adverse reactions have involved the gastrointestinal system (nausea, vomiting, diarrhea) or, importantly, the central nervous system (including seizures) (1, 2). We report here a possible association between ciprofloxacin and anaphylactoid reactions.

The Spontaneous Reporting System of the Food and Drug Administration (FDA) receives reports of suspected adverse drug reactions directly from health professionals, consumers, and drug manufacturers (3). In this study, a case of an anaphylactoid reaction was defined as a reaction in a patient described in an adverse drug-reaction report as having "anaphylaxis" or an "anaphylactoid reaction"; or the acute onset of symptoms or signs, unaccounted for by another disease process, from at least two of the following groups: circulatory (hypotension, shock), respiratory (asthma, apnea, dyspnea, laryngeal edema, hypoventilation, laryngismus, stridor), and cutaneous (urticaria, angioedema). In November 1988, a review of all reactions that were reported in association with ciprofloxacin and had occurred from October 1987 through June 1988 identified 15 reactions that met the case definition (Table 1). These 15 reactions comprised 5.7% of the 262 reports received for ciprofloxacin.

Twelve reports were from the United States, two from West Germany, and one from Japan. Six persons were reported hospitalized; no deaths were reported. Eleven patients were female and four male and the mean reported age was 34.2 years (range, 7 to 52 years). Fourteen reactions occurred after patients previously unexposed to ciprofloxacin took their first dose of the drug. For the 13 patients with available data, the interval between ingestion of the dose and reaction onset ranged from 5 minutes to 1 hour. Nine patients had taken 500-mg tablets; two patients, 250-mg tablets; one patient, a 750-mg tablet; one patient, a 200-mg tablet; and two patients, unknown doses. When the reactions occurred, 11 of the 15 patients were not taking other drugs concomitantly.

To estimate the rate of reporting relative to exposure, we used estimates of annual drug use from the National Prescription Audit, a data base purchased by the FDA from IMS America Ltd., Ambler, Pennsylvania. This data base has information on prescriptions dispensed by chain and independent pharmacies in the contiguous United States, but does not reflect the use of ciprofloxacin in hospitals, which purchase approximately 20% of the ciprofloxacin distributed in the United States. The estimated number of prescriptions dispensed in the United States for ciprofloxacin from October 1987 through June 1988 was 972 000. This figure overestimates the number of persons exposed as outpatients because some persons will have more than one prescription dispensed for ciprofloxacin in a calendar year. Using these data and excluding the three foreign cases, we calculated an estimated reporting rate of anaphylactoid reactions in the United States after ciprofloxacin to be 1.2 per 100 000 prescriptions.

A summary of adverse reactions to ciprofloxacin in 8861 patients treated during clinical trials worldwide reported that skin rashes or pruritis occurred in about 1% of patients (1). No episodes of anaphylactoid reactions were described. In addition, no episodes of anaphylactoid reactions were described in reports to the FDA of 2868 courses of ciprofloxacin given to 2799 patients participating in clinical pre-marketing trials (FDA. Unpublished data). A report (4) described three men with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex who developed anaphylactoid reactions after receiving the drug for the second time after 10 to 14 days without treatment. At least two of these patients had stopped taking the drug during the first course because of a possible adverse reaction.

Our finding that 14 patients developed anaphylactoid reactions after taking their first dose of ciprofloxacin suggests that cross-reacting antibodies might have initiated these reactions. Anaphylactoid reactions have been reported after use of nalidixic acid (5) and cinoxacin (6), which are nonfluorinated quinolones, and after norfloxacin (7), which, like ciprofloxacin, is a fluoroquinolone. It is not known whether any of the patients we report here had previously taken other quinolone antibacterial agents.

Because many episodes of adverse drug reactions are not reported to the FDA, the actual number of anaphylactoid reactions after ciprofloxacin use is probably underestimated. In addition, we cannot accurately estimate the actual number of persons exposed to the drug. The reactions reported to the Spontaneous Reporting System are those temporally associated with a drug and are not proved to be causally related to use of the drug. The close temporal association between drug ingestion and reaction onset, however, and the finding of 11 cases in which no other concomitant drugs had been ingested, suggest that ciprofloxacin exposure may result in anaphylactoid reactions. Clinicians should be aware of the possibility of anaphylactoid reactions when treating patients with ciprofloxacin.

From the Food and Drug Administration, Rockville, Maryland. For current author addresses, see end of text.

Table 1. *Characteristics of 15 Patients with Anaphylactoid Reactions after Use of Ciprofloxacin, 1987-1988*

Patient	Sex, Age (y)	Location	Dose and Duration before Reaction	Reaction Reported	Concomitant Drugs	Medical History	Outcome
1	F, 16	United States	500 mg; onset 20-30 minutes after first dose	Anaphylactoid reaction; hypotension; urticaria; hoarseness	None	Pneumonia	Hospitalized
2	F, 30	United States	500 mg; took ciprofloxacin 1 month earlier for 9 days. Had reaction after first dose of second course	Anaphylaxis; hypotension; rash; fever	None	Upper respiratory infection	Hospitalized
3	F, 52	United States	500 mg; onset 15 minutes after first dose	Anaphylactoid reaction; shock; pruritis; urticaria	None	Bronchitis; diabetes; stroke	Recovered
4	F, 40	United States	500 mg; onset 15 minutes after first dose	Anaphylaxis	amantadine	Sinusitis; bronchitis	Recovered
5	M, 30	United States	500 mg; onset 5 minutes after first dose	Anaphylaxis; facial edema; dyspnea; urticaria	None	Skin infection; codeine allergy	Recovered
6	F, 35	United States	500 mg; onset after first dose	Anaphylaxis	None	Urinary-tract infection	Treated in emergency department; recovered
7	F, 36	United States	500 mg; onset 10 minutes after first dose	Anaphylactoid reaction; dyspnea; hypotension; vaginal bleeding	None	Gum infection	Hospitalized
8	F, 38	United States	500 mg; onset 15 minutes after first dose	Anaphylactoid reaction; syncope	None	Respiratory-tract infection	Hospitalized
9	M, 50	Japan	200 mg; onset within 20 minutes after first dose	Anaphylactoid reaction; larnygeal edema; urticaria; conjunctivitis	None	Infected atheroma	Recovered
10	M, 24	West Germany	Unknown dose; onset 30 minutes after first dose	Anaphylaxis; urticaria; asthma	None	Urethritis; asthma; eczema	Recovered
11	M, 29	United States	750 mg; onset 10 minutes after first dose	Dyspnea; facial edema; pruritis; pharyngeal edema	None	Infected pilonidal cyst	Recovered
12	F, 43	West Germany	250 mg; onset immediately after first dose	Anaphylactoid reaction; urticaria; dyspnea; blood pressure decrease	fenoterol; cortisone	Asthma	Recovered
13	F, unknown	United States	Unknown dose; onset within 1 hour of first dose	Anaphylactoid reaction; urticaria; dyspnea	Unknown	Bronchitis	Hospitalized; recovered
14	F, 7	United States	250 mg; onset within 30 minutes of first dose	Anaphylactoid reaction; urticaria; wheezing	None	Urinary-tract infection; ragweed allergy	Recovered
15	F, 49	United States	500 mg; onset within minutes of first dose	Dyspnea; rash; facial edema	cefoxitin	Unknown	Hospitalized; recovered

All suspected drug reactions should be reported to the drug's manufacturer or directly to the Food and Drug Administration, Division of Epidemiology and Surveillance (HFD-730), 5600 Fishers Lane, Rockville, MD 20857. A reporting form is available as the last page in most copies of the 1989 *Physician's Desk Reference* (7).

The use of trade names is for purposes of product identification only and is not intended as product endorsement by the Food and Drug Administration or the Department of Health and Human Services. The opinions in this paper are those of the authors and not necessarily those of the Food and Drug Administration.

Requests for Reprints: Harold Davis, MD, Office of Epidemiology and Biostatistics, Food and Drug Administration, 5600 Fishers Lane, HFD-730, Rockville, MD 20857.

Current Author Addresses: Dr. Davis: National Center for Health Statistics, Division of Health Examination Statistics, Center Building, Room 2-58 3700 East-West Highway, Hyattsville, MD 20782.
Ms. McGoodwin: Office of Epidemiology and Biostatistics, Food and Drug Administration, 5600 Fishers Lane, HFD-730, Rockville, MD 20857.
Dr. Reed: Division of Anti-Infective Drug Products, Food and Drug Administration, 5600 Fishers Lane, HFD-520, Rockville, MD 20857.

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