News 06/05/1992

P92-16   Food and Drug Administration
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    The Food and Drug Administration today announced that Abbott
Laboratories of Abbott Park, Ill., is voluntarily recalling the
broad-spectrum anti-infective drug Omniflox (temafloxacin) tablets, and will
halt all further distribution of the drug.
    This action is being taken because of severe adverse events associated
with the use of the drug that have been reported to the company and to FDA
in the first three months of marketing.
    Temafloxacin was approved in late January 1992 and marketed in
mid-February. Since that time there have been approximately 50 reports of
serious adverse reactions, including three deaths. There were several cases
of severe low blood sugar, especially in very elderly patients with
decreased kidney function. Among the severe reactions there were a number
of cases of an unusual complex of adverse reactions consisting of hemolytic
anemia (destruction of red blood cells) and other blood cell abnormalities.
Also observed were patients with kidney dysfunction, about half of which
required renal dialysis. Other patients suffered liver dysfunction.
    There has also been a substantial number of reports of allergic
reactions, some of which have caused life-threatening respiratory distress.
    Temafloxacin is one of a newer class of synthetic oral fluoroquinolones
-- broad-spectrum antibiotics -- that are used to treat a variety of
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infections including lower respiratory tract infections, skin and skin
structure infections, infection of the prostate and urinary tract
infections. Similar antibiotics of its class have not been reported to be
associated with comparable numbers of serious adverse reactions.
    Consumers who have the medication are advised to consult their physician
and return any unused portions of the product to the place of purchase.
    FDA is one of the eight Public Health Service agencies within HHS.
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Temafloxacin Syndrome: Review of 95 Cases

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Four months after its approval in the United States, temafloxacin was withdrawn from the market worldwide because of frequent reports of serious hemolysis with or without other organ system dysfunction. We describe this "temafloxacin syndrome" on the basis of a review of 95 spontaneous reports of hemolysis sent to the Food and Drug Administration. Patients typically presented with fever, chills, and jaundice a mean of 6.4 days after starting therapy. A moderate degree of hemolysis was reflected by the mean drop in hemoglobin level (by 42 g/L) and by the mean lowest concentration of hemoglobin (97 g/L). New-onset renal dysfunction was noted in 54 cases (57%), and dialysis was required in 34 cases (63%). Coagulopathy was noted in 33 cases (35%), and 48 cases (51%) met the criteria for hepatic dysfunction. Four patients developed central nervous system complications, and two patients died. Prior quinolone use was more common among patients who developed hemolysis after only one dose as opposed to two or more doses ($P < .001$). These data suggest that temafloxacin causes immune hemolytic anemia, most likely secondary to immune complex formation.

Temafloxacin (Omniflox, Abbott Laboratories, Abbott Park, IL) was a broad-spectrum oral fluoroquinolone approved in the United States on 30 January 1992 for the treatment of infections of the urinary tract, lower respiratory tract, skin, and prostate. Because of a high frequency and unusual spectrum of serious adverse reactions reported to the Food and Drug Administration (FDA), the drug was voluntarily withdrawn from the market worldwide by its manufacturer on 5 June 1992. During the brief period of its use, an estimated 189,000 prescriptions were issued [1].

Spontaneous reporting of adverse events to the FDA [2] by physicians and other health professionals was critical to the prompt identification of the safety problems associated with temafloxacin. While reports frequently did not include complete laboratory or clinical data, sufficient information was available to signal an unusual and serious reaction. The purpose of this article is to describe the clinical elements of what we have chosen to call the temafloxacin syndrome.

Patients and Methods

We reviewed all adverse-event reports for temafloxacin submitted to the FDA by the manufacturer, physicians, other health-care providers, and consumers between 30 January and 31 August 1992. Cases were selected for analysis if evidence existed for hemolysis or hemolytic anemia without an alternative explanation or if at least two of the following

systems were involved in the absence of hemolysis: renal, hepatic, and coagulative.

A given case qualified for analysis if there was specific mention of the above disease processes in the adverse-event report. For reports not specifically describing these processes, a case was classified as hemolytic anemia if there was a decreased concentration of hemoglobin associated with an elevated level of bilirubin, an elevated concentration of lactate dehydrogenase (LDH), a decreased serum concentration of haptoglobin, hemoglobinuria, and/or free hemoglobin in plasma. Renal dysfunction was defined on the basis of an elevation of the serum creatinine level to at least 132 μmol/L (1.5 mg/dL). Hepatic dysfunction was defined by a serum level of aspartate aminotransferase (AST) of >120 U/L and/or a total bilirubin level of >68 μmol/L (4 mg/dL) [3]. A case was classified as coagulopathy if the platelet count was <100 × 10^9/L, the prothrombin time was prolonged by at least 1 second, or there was laboratory evidence of disseminated intravascular coagulation (DIC). We defined DIC as the presence of two or more of the following: prolonged prothrombin time, thrombocytopenia, a decreased serum concentration of fibrinogen, or an elevated level of fibrin-split products.

Cases meeting these criteria were analyzed with use of Epi Info Version 5, a statistical computer software package [4]. The significance of differences between groups was assessed by χ^2 or Fisher's exact test. One-way analysis of variance was used for the comparison of means. P values of <.05 were considered significant.

Results

One hundred fourteen cases met our criteria for analysis. Ninety-five patients (83%) had hemolysis, while 19 patients (17%) lacked hemolysis but otherwise met the criteria for
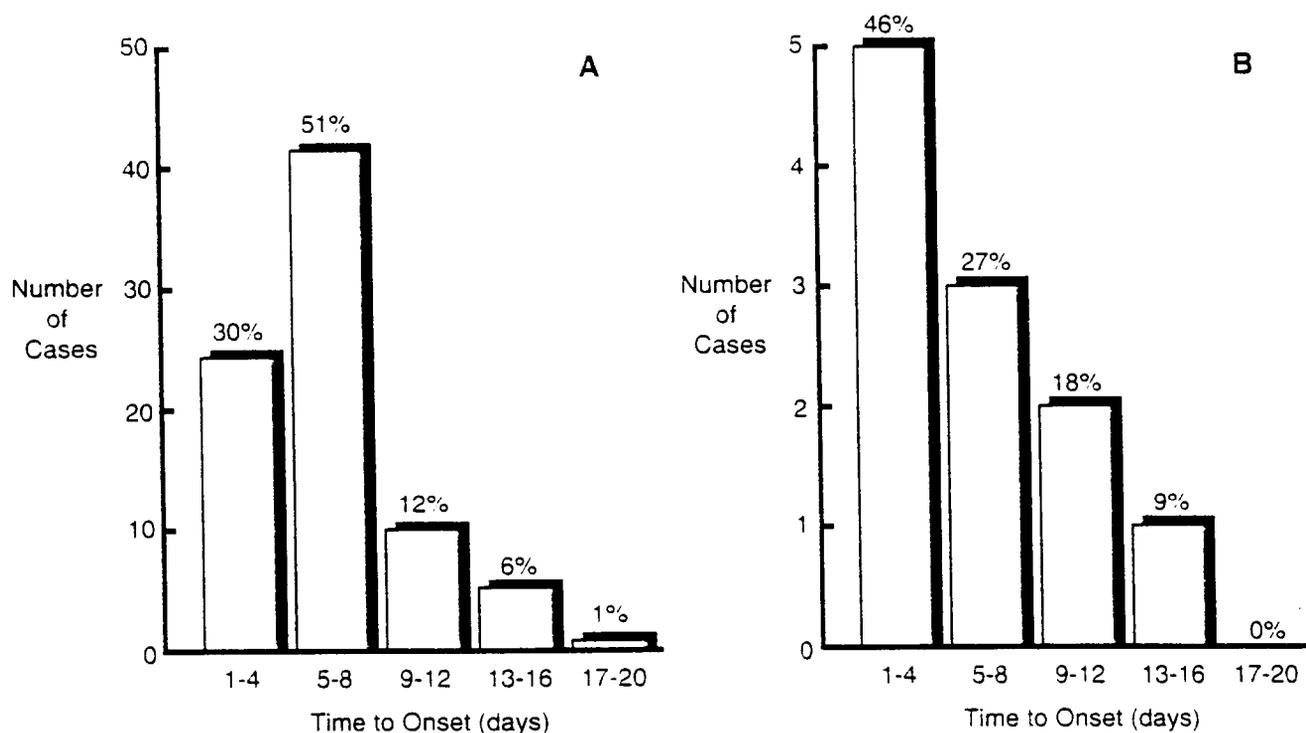
Figure 1. Time to onset of symptoms of an adverse reaction after initiation of treatment with temafloxacin in patients with hemolysis (*A*) \d patients without hemolysis but with dysfunction involving at least two body systems (*B*). The log-normal shape of the onset curve for _atients with hemolysis suggests a common-source exposure (i.e., to temafloxacin) as the cause of the disease process. The shape of the onset curve for patients without hemolysis suggests a reporting bias, with earlier-onset cases more frequently reported. Note the 10-fold difference in scale between *A* and *B*.

multisystem disease. The shapes of the time-to-onset curves for these two groups differed (figure 1); this finding suggested different etiologic mechanisms. The log-normal shape of the epidemic curve for patients with hemolysis suggested exposure to temafloxacin as the initiating event [5]. For this reason, we restricted subsequent analyses to hemolysis cases in order to better characterize the spectrum of illness associated with this drug.

Demographics. The patients' ages ranged from 29 to 86 years, with no clustering of cases in any age group (table 1). The numerical predominance of female patients appeared to reflect more use of temafloxacin by women rather than gender-related susceptibility [6]. No concomitant conditions or medications were common to a significant proportion of patients. The distribution of cases by oral dosage (with 58% of patients receiving 600 mg twice daily and 39% receiving 400 mg twice daily) was virtually identical to that for all persons treated with this drug in the United States (of whom 60% and 40% received 600 mg and 400 mg twice daily, respectively) [1]. The most common indications for treatment with temafloxacin among patients with reported adverse reactions were infections of the respiratory tract (50%), the genitourinary tract (28%), and the skin (7%). Approximately half of the 95 patients received the drug for indications not ap-

proved by the FDA. Respiratory tract infections were as frequent among nonhemolysis cases as among hemolysis cases; thus it is unlikely that respiratory pathogens played a role in the etiology of hemolysis.

Table 1. Demographic characteristics of 95 patients with temafloxacin-associated hemolysis.

Characteristic: unit of measure	Value
Age: y	
Mean	57.4
Range	29–86
Weight: lbs	
Mean	152
Range	102–224
Sex: %	
Male	39
Female	61
History of drug allergy: no. (%)	22 (23)
History of quinolone use: no. (%)	18 (19)
Time to onset: d	
Mean	6.4
Range	1–20
Hospitalized: no. (%)	79 (83)

Table 2. Parameters of hemolysis in 95 patients with "temafloxacin syndrome."

Parameter* (n†) unit of measure	Mean	Range
Decrease in hemoglobin level (31):		
g/L	42	4–88
Lowest hemoglobin value (66):		
g/L	97	40–137
LDH level (50): U/L	2,228	136–13,580
Total bilirubin level (62):		
µmol/L (mg/dL)	118 (6.9)	12–616 (0.7–36.0)

* Other parameters included the result of a direct Coombs' test (reported for 41 patients, positive in 14 cases and negative in 27 cases) and the need for RBC transfusion (16 patients).
† Number of patients with value reported.

Hemolysis. No information on symptoms was provided in 27% of the reports. In the remainder, the most commonly reported symptoms were discolored urine (52%), fever (42%), jaundice (41%), chills (38%), nausea and/or vomiting (30%), abdominal pain (25%), myalgia (16%), and back pain (14%). The mean time to onset of hemolysis was 6.4 days after the start of therapy. In patients who developed renal insufficiency, the serum creatinine level rose soon after the onset of symptoms. The majority of patients required hospitalization.

The extent of hemolysis in these patients was reflected by the mean drop in the hemoglobin level (by 42 g/L) and by the mean lowest concentration of hemoglobin (97 g/L) (table 2). Increases in LDH (mean, 2,228 U/L) correlated with decreases in hemoglobin and with lowest hemoglobin values ($P < .05$). Sixteen patients (17%) required red blood cell (RBC) transfusions. None of the measures of hemolysis correlated with age, sex, dose, or indication for treatment. The results of peripheral-blood smears were reported in only 13 cases and were usually normal. Glucose-6-phosphate dehydrogenase values were uniformly normal in the 8 cases tested. The direct antiglobulin (Coombs') test was positive in 14 (34%) of 41 reported cases. Three of these results were reported as positive only with the use of complement reagents.

Renal dysfunction. New-onset renal dysfunction was noted in 54 cases of hemolysis (57%), and dialysis was required in 34 cases (63%). Renal dysfunction was associated with the onset of hemolysis on the first day of temafloxacin use ($P < .05$) and with the presence of DIC ($P < .05$); it was not associated with age, sex, dose, indication for treatment, hepatic dysfunction, or degree of hemolysis. However, patients with renal failure who ultimately required dialysis had significantly higher LDH values than did patients with renal dysfunction who did not require dialysis ($P < .05$). The six reported renal biopsies all showed evidence of acute tubular necrosis. Associated findings on biopsy included "interstitial nephritis," "pigmented casts," "pigment," "hemolysis," and

"hemoglobin plugging." None of these patients was described as hypotensive.

Coagulopathy. Coagulopathy was noted in 33 cases of hemolysis (35%). This manifestation consisted of DIC in 13 cases, isolated thrombocytopenia in 17, and isolated prolongation of the prothrombin time in 3. One patient developed a "hemorrhagic diathesis"; the remainder of those with laboratory evidence of coagulopathy did not have significant clinical bleeding. Patients with DIC had higher mean levels of LDH and were at increased risk for RBC transfusion (in both instances, $P < .05$).

Hepatic dysfunction. Overall, 48 patients (51%) with hemolysis were classified as having hepatic dysfunction. Twenty-four patients were so classified on the basis of bilirubin level alone; five of these patients had AST levels of <120 U/L, while AST values were not reported in the remaining 19 instances. An additional 19 cases met both the AST and the bilirubin criteria. However, elevations in total bilirubin levels were well out of proportion to AST elevations. Sixteen patients had a total bilirubin level of >8 mg/dL (136 µmol/L), while two had an AST level of >500 U/L. It is possible that our selection criteria led to an overestimate of hepatic dysfunction by including patients with extreme elevations in bilirubin secondary to acute hemolysis alone. Unfortunately, markers of hepatic dysfunction other than AST and total bilirubin were reported less frequently. Concentrations of alanine aminotransferase and γ-glutamyl transpeptidase were more than three times the upper limit of normal in 5 of 23 cases and 6 of 13 cases in which they were reported, respectively. Information on fractionated bilirubin was reported in only 15 cases: direct bilirubin levels ranged from 0.2 to 8.3 mg/dL (3.4–141 µmol/L), with a mean of 2.3 mg/dL (39 µmol/L).

Sequelae. Four patients developed CNS complications, including seizures and neurological residua secondary to cerebrovascular accidents. All four of these patients had multisystem disease and required dialysis. Among all patients reported as having hemolysis, two died: one with renal failure and the other with ischemic colitis and DIC. Figure 2 indicates the associated clinical findings in patients who had hemolysis with or without other organ system dysfunction.

Single-dose onset. Ten patients developed hemolysis after only one dose of temafloxacin. Prior use of a quinolone was reported for 7 (70%) of these patients as opposed to only 11 (13%) of the 85 whose illness developed after the first day of treatment ($P < .001$). The single-dose group tended to have more multisystem involvement, especially renal disease ($P < .05$). Nevertheless, the outcome was no worse in these cases than in those of later onset. Four patients had received a previous course of temafloxacin 3–5 weeks before the exposure resulting in their illness. All four developed renal failure, and three required dialysis. One patient had developed mild hemolysis on day 6 of the prior course of temafloxacin;
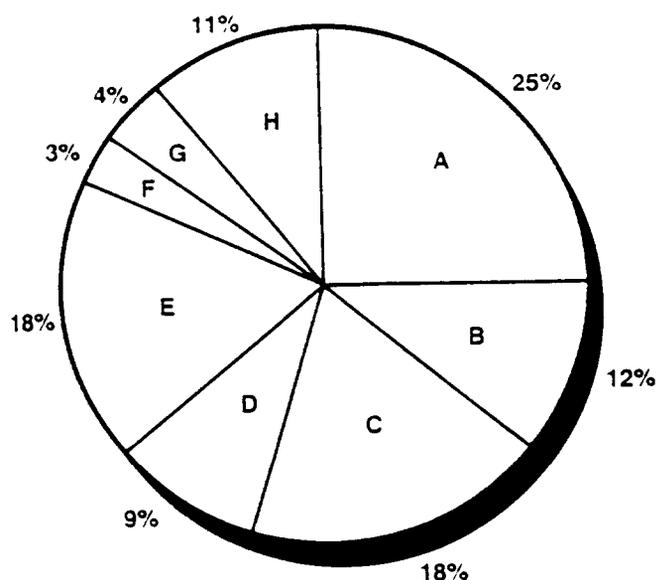
Figure 2. Distribution of hemolysis cases by body system involvement. A = hemolysis alone. B through H = hemolysis plus the following conditions: renal involvement (B); renal and hepatic involvement (C); renal and coagulative involvement (D); renal, hepatic, and coagulative involvement (E); coagulative involvement (F); coagulative and hepatic involvement (G); and hepatic involvement (H).

ingestion of a single tablet 5 weeks later resulted in disease requiring dialysis and RBC transfusion.

Discussion

We describe 95 cases of hemolysis—often accompanied by renal failure, coagulopathy, and hyperbilirubinemia—associated with the use of temafloxacin. The data available to us did not permit an estimate of the incidence rate for this event. Although we had an estimate of the number of prescriptions issued, we did not have reliable information about samples dispensed from physicians' offices and thus could not accurately estimate the denominator for patients exposed to temafloxacin. More important, we were uncertain about the numerator for temafloxacin-associated hemolysis events. Underreporting is a widely recognized problem in the field of drug surveillance. Many studies have documented that only 10%–15% of serious adverse reactions are reported [2, 7].

The reported spectrum of adverse events involved patients with few or no complicating illnesses. Patients typically presented with discolored urine, fever, jaundice, chills, nausea, vomiting, abdominal pain, myalgia, and/or back pain. The log-normal shape of the onset curve suggested exposure to temafloxacin as the initiating event [5]. In most cases, this "temafloxacin syndrome" resolved without sequelae several days to several weeks after discontinuation of treatment.

Since a drop in hemoglobin level was assessed in only a

minority of cases (n = 31), we looked at the available data for other indicators of the extent of hemolysis. Elevated levels of bilirubin have been suggested as appropriate indicators by some researchers; however, the interpretation of high bilirubin levels is confounded by the results of studies of individuals with chronic hemolysis and by expert opinion suggesting that concentrations of >68 μmol/L (4 mg/dL) indicate impaired hepatic function [3, 8]. In our series of cases, increases in serum levels of LDH appeared to be the best marker of the degree of hemolysis. Our analysis demonstrated that elevated serum levels of LDH correlated with renal failure, dialysis, DIC, and transfusion in the cases reported.

Drug-induced hemolytic anemia generally results from either direct toxicity or immune-mediated destruction of erythrocytes. Direct toxic effects in patients with normal erythrocytes are usually dose related, slow in onset, and frequent in occurrence [9]. These reactions develop sooner in patients with defects in erythrocyte enzymes or unstable hemoglobin levels. Several characteristics of the patients we described argue against direct toxicity as the mechanism for temafloxacin-induced hemolytic anemia. Hemolysis did not appear to be dose related and was reported for only a small percentage of patients who received the drug. None of the patients affected was reported as having an underlying erythrocyte enzyme defect or hemoglobinopathy. The onset of hemolysis occurred sooner than would be expected for a drug with direct toxicity to normal erythrocytes.

We believe that these data suggest an immunologic mechanism for the reported adverse events. The strong association between prior use of a quinolone and the onset of hemolysis after the first dose of temafloxacin suggests an immune-mediated hypersensitivity phenomenon (Gell and Coombs type II or III) [10]. Seventy percent of patients with no reported history of quinolone use developed hemolysis more than 5 days after the start of therapy with temafloxacin (mean, 7.3 days). This interval is consistent with the time required to mount a primary immune response in drug-induced immune hemolytic anemia [11].

Drug-induced immune hemolytic anemia occurs by one of three possible mechanisms: hapten-cell, autoimmune, or immune complex [9]. The hapten-cell and autoimmune mechanisms usually result in mild to moderate hemolysis in the absence of significant intravascular destruction of RBCs (i.e., hemoglobinemia or hemoglobinuria). In both cases, the direct antiglobulin test is positive with anti-IgG reagents and negative with anti-C3 reagents. The immune complex mechanism more often results in severe intravascular hemolysis because the terminal complement components (those constituting the C5b through C9 complex) are activated. In almost all cases of hemolysis due to complement-activating, drug-dependent antibodies, the direct antiglobulin test is negative unless anti-C3 reagents are used [11].

The direct antiglobulin test was positive in only 14 of 41

cases in which it was reported. While the reagents used were not specified in most instances. three patients had a positive test only with the use of complement reagents. We believe that the patients reported here most likely developed drug-induced immune hemolytic anemia secondary to immune complex formation. Most had signs of significant intravascular hemolysis (i.e.. rapid decreases in hemoglobin and haptoglobin levels. large increases in LDH and total bilirubin levels. and hemoglobinuria). and several had positive antiglobulin tests when complement reagents were used. It is possible that anti-C3 reagents were not used in those cases with negative direct antiglobulin tests.

The core structure of fluoroquinolone agents closely resembles that of quinine and quinidine. both of which are known to cause immune hemolytic anemia and thrombocytopenia by an immune complex mechanism [12]. Quinine-induced DIC [13. 14] and hemolytic uremic syndrome (HUS) [15. 16] have been reported after rechallenge with a single dose. The cases of HUS share many of the clinical features we have described. Endothelial cell damage appears to play a significant role in the pathogenesis of HUS. Pfueller et al. demonstrated a quinine-dependent antibody that reacted with both platelet membrane GPIIIa and endothelial cells [17]. In contrast. Stroncek et al. were unable to detect specific reactivity to cultured endothelial cells despite the presence of multiple quinine-dependent antibodies to different epitopes on platelets. erythrocytes. and neutrophils [16]. These authors speculated that quinine-dependent antibodies caused complement-mediated adhesion of neutrophils to endothelial cells. which resulted in neutrophil-mediated vascular damage and an HUS-like picture.

To date. the mechanism responsible for the temafloxacin syndrome remains largely unknown. Our analysis suggests that temafloxacin induced the immune hemolytic anemia. most likely secondary to immune complex formation. We are unable to determine whether hemolysis triggered the involvement of other body systems or whether a common underlying process initiated hemolysis and multisystem disease. The former mechanism is supported by the presence of acute tubular necrosis with hemoglobin casts in four of the six renal biopsy samples described. Similar findings on renal biopsy have been reported for a patient who developed immune complex–mediated hemolytic anemia and renal failure associated with tolmetin and suprofen [18]. In contrast. the presence of common epitopes on differing cell types (e.g.. GPIIIa on platelets and endothelial cells [19]) raises the possibility of a common underlying process triggering the temafloxacin syndrome.

Whether hemolysis alone. multiple temafloxacin-dependent antibodies. or cross-reacting antibodies precipitated multisystem disease remains speculative. While the similarities to quinine-induced disease are intriguing. other marketed fluoroquinolones with the same core structure have

caused neither a comparable number nor a comparable spectrum of adverse reactions. Future studies must confirm an immunologic mechanism. characterize temafloxacin-dependent antibodies (if they are present). and delineate the unique qualities of temafloxacin that resulted in this syndrome.

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