Levofloxacin-Induced Autoimmune Hemolytic Anemia

Young R Oh, Sian M Carr-Lopez, James M Probasco, and Peter G Crawley

OBJECTIVE: To report a case of autoimmune hemolytic anemia (AIHA) secondary to levofloxacin.

CASE SUMMARY: An 82-year-old white man was treated with levofloxacin 500 mg/d for cellulitis. Three days following completion of levofloxacin therapy, the patient presented to the emergency department with severe jaundice, dizziness, and loss of vision. He received packed red blood cells (PRBCs) and was discharged home. Two days later at the follow-up visit, he was diagnosed with AIHA secondary to levofloxacin. The patient was hospitalized and treated with a tapering dose of prednisone and additional PRBC infusion. He was discharged from the hospital in stable condition after 3 days. Repeated hematologic laboratory studies following discharge demonstrated that the hemolytic anemia had resolved.

DISCUSSION: Hemolytic anemia due to levofloxacin is an extremely rare, but potentially fatal, adverse drug event. An objective causality assessment revealed that the adverse reaction was probable. To our knowledge, this is the first published case of levofloxacin-induced AIHA. However, there are published case reports of hemolytic anemia with other fluoroquinolones including ciprofloxacin (n = 12) and temafloxacin (n = 95). Temafloxacin was withdrawn from the market in 1992 due to this adverse effect. The mechanism by which levofloxacin triggers hemolytic anemia is unknown. We believe that an immune-mediated reaction is most likely.

CONCLUSIONS: Levofloxacin-induced AIHA is a rare but serious complication of therapy. Immediate discontinuation of the offending medication and treatment of the hemolytic anemia are essential. Until more information is available, levofloxacin should not be prescribed for patients with previous reactions to any fluoroquinolone.

KEY WORDS: hemolytic anemia, autoimmune; levofloxacin.

Ann Pharmacother 2003;37:1010-3.

Published Online, 10 Jun 2003, *www.theannals.com*, DOI 10.1345/aph.1C525

Autoimmune hemolytic anemia (AIHA) involves autoantibody production against red blood cell antigens that results in red blood cell death.[1] AIHA is a rare, but potentially fatal, disorder. Quinine and quinidine have chemical structures similar to the fluoroquinolone antibiotics, and all of these medications have been implicated in severe cases of hemolytic anemia.[2-4] We describe a case of AIHA due to levofloxacin. Using the Naranjo probability scale, we identified levofloxacin as the probable cause.[5]

Author information provided at the end of the text.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or reflecting the views of the US Air Force.

Case Report

An 82-year-old white man, weighing 54 kg and 168 cm in height, presented to the emergency department (ED) with symptoms of jaundice, fatigue, dizziness, loss of vision, and shortness of breath. Vital signs on admission revealed T 36.7 ˚C, HR 66 beats/min, and BP 96/46 mm Hg. The patient's calculated creatinine clearance was 48 mL/min. His chronic medical conditions included hypertension and coronary artery disease for which he was prescribed atenolol 50 mg once daily, aspirin 325 mg once daily, and furosemide 40 mg/d as needed. While in the ED, he stated that he was allergic to a "white pill," but could not be more specific.

The patient had fallen recently and sustained injuries to his left leg. He had been prescribed a 10-day course of levofloxacin for cellulitis subsequent to injuries to the leg. Approximately 4 days after levofloxacin initiation, the man noticed symptoms of fatigue and dizziness. By the end of the 10-day treatment with levofloxacin, the symptoms had progressed and included jaundice, severe fatigue, Coca-Cola–colored urine, loss of vision, and shortness of breath. On admission to the ED, blood work re-

vealed hemoglobin 7.0 g/dL, hematocrit 18.8%, lactate dehydrogenase (LDH) 1543 IU/L, and unconjugated (indirect) bilirubin 4.8 mg/dL. Electrolytes and liver enzyme tests were within normal limits.

Laboratory findings and clinical symptoms indicated medication-induced hemolytic anemia, with levofloxacin as the suspected cause (Table 1). The patient received 3 units of packed red blood cells (PRBCs) and was discharged from the ED, with a follow-up appointment scheduled with an internist in 2 days.

The follow-up laboratory testing at that visit revealed hemoglobin 7.2 g/dL and hematocrit 19.0%. The patient was admitted to the hospital. Additional laboratory test results revealed: LDH 596 IU/L, white blood cell count $17 \times 10^3/mm^3$ with 22.2% eosinophils, unconjugated bilirubin 9.7 mg/dL, and urine urobilinogen 1.0 EU/dL. Haptoglobin level was <6 mg/dL. A direct Coomb's test was positive. Physical examination was significant for scleral and tympanic icterus and diffuse skin jaundice. A peripheral blood smear performed at the time of admission showed spherocytosis and no schistocytes. Autoantibody test revealed warm antibodies. During his hospitalization, an interview with the patient's daughter revealed that he had had an allergic reaction, reported as hives, to ciprofloxacin approximately 5 years earlier. The rash had generalized to his trunk and extremities without facial involvement, and had resolved with drug discontinuation and treatment with topical calamine lotion. His daughter verified that he was not allergic to any other medication.

The patient was diagnosed with AIHA secondary to levofloxacin, and treatment was initiated promptly. The patient received 3 units of PRBCs on day 1 of hospitalization, and oral prednisone 60 mg/d was initiated. Over the next 2 days, the patient's hemoglobin and hematocrit concentrations increased to 9.9 g/dL and 28.0%, respectively. Clinical symptoms resolved within 3 days. He was discharged from the hospital in stable condition on hospital day 3 with a hemoglobin level of 9.8 g/dL. Upon discharge, oral prednisone was prescribed to complete the steroid taper as follows: prednisone 60 mg/d for an additional 4 days, 40 mg/d for 5 days, 20 mg/d for 5 days, and then stopped. This probable adverse drug event was reported to the Food and Drug Administration (FDA).

Table 1. Laboratory Test Results

Test (normal range)	Clinical Course: Day 1 (ED)	Day 3 (hospital day 1)	Day 4 (hospital day 2)	Day 5 (hospital day 3)	Day 7 (outpatient)	Day 50 follow-up)
Hemoglobin (13.1–17.7 g/dL)	7.0	7.2	9.9	9.8	11.6	11.4
Hematocrit (39.7–52.1%)	18.8	19.0	28.0	27.6	35.0	34.1
LDH (98–192 IU/L)	1543	596	601		454	201
Unconjugated bilirubin (0.3–1.5 mg/dL)	4.8	9.7	6.7		2.1	0.5
Urine urobilinogen (0.2 EU/dL)	1.0	1.0				
Urine bilirubin (negative)	negative	small				
Haptoglobin (16–200 mg/dL)		<6				
Direct antiglobulin test (direct Coombs')		positive				
Spherocytes	noted	noted		2+		
Eosinophils (1.0–4.0%)	16.5	22.2	2.0	0.4	0.1	2.7
SCr (0.9–1.3 mg/dL)	1.1	1.2	1.1		1.1	0.8
Autoantibodies		warm				
RBC antigen profile (eluate)		IgG positive				

IgG = immunoglobulin G; LDH = lactate dehydrogenase; RBC = red blood cell; SCr = serum creatinine.

Discussion

We believe that our patient developed AIHA secondary to levofloxacin use. The time course and clinical presentation indicated medication-induced hemolysis. Diagnosis of AIHA requires both serologic evidence, such as positive direct antiglobulin test (direct Coombs' test) and identification of an autoantibody, as well as clinical or laboratory evidence of hemolysis.[6,7] This case met the diagnostic criteria for AIHA.

Our patient's clinical signs and symptoms, as well as the laboratory results, are consistent with the presentation of hemolysis (i.e., significant decreases in hemoglobin and hematocrit levels, large increases in LDH, elevated unconjugated bilirubin and urine urobilinogen levels but negative urine bilirubin, hemoglobinuria as evidenced by dark urine, spherocytosis, reduced haptoglobin).[7] The combination of elevated serum LDH and decreased haptoglobin is 90% specific for diagnosing hemolysis.[8,9] AIHA can be subclassified on the basis of the characteristic temperature reactivity of the red blood cell autoantibody.[1,6,7] There are 6 categories of AIHA: warm, cold, warm and cold, paroxysmal cold, drug-induced, and AIHA associated with bone marrow transplantation. Among these classes, up to 80% of cases are warm autoimmune hemolytic anemia (WAIHA).[10]

The treatment of AIHA varies depending on which type of autoimmune hemolytic antibodies are present.[10] Laboratory analysis determined the precise subtype for this case to be warm autoantibody. Treatment of WAIHA includes glucocorticoids, such as prednisone, at conventional doses of 1–2 mg/kg/d orally as first-line therapy.[6,7,10] Recommended duration of therapy is 1–3 weeks. The onset of the response is usually rapid. Significant hematologic improvement is often evident within a few days, and most patients show improvement within 2 weeks. Nearly one-third of patients achieve a lasting remission with prednisone therapy, while >50% continue to require some form of low-dose maintenance therapy with prednisone for months.[10] Splenectomy and immunosuppressive agents are indicated in patients with partial or no response to corticosteroids.[6] Splenectomy removes the primary site of extravascular hemolysis. Cytotoxic drugs are another treatment option for patients who have failed glucocorticoids and/or splenectomy.[10] The commonly used drugs are cyclophosphamide and azathioprine, generally in combination with a corticosteroid. Cyclosporine, danazol, rituximab, or intravenous immunoglobulin may be indicated in refractory cases.[6] Our patient was treated with prednisone 1 mg/kg/d, and responded well to tapering the dose.

Changes to the chemical structure of individual fluoroquinolones have resulted in a variety of serious adverse drug reactions.[2,11-13] Thus, there is considerable interest in clarify-

ing the structure–adverse effect relationships of the fluoroquinolones. To date, the relationship of fluoroquinolone structure and drug-induced immune hemolytic anemia has not been defined. The basic ring structure of fluoroquinolones is similar to that of quinine and quinidine — both of those agents have been reported to cause immune hemolytic anemia.[4] Quinine, quinidine, and fluoroquinolones have a very similar dual ring structure with a nitrogen in position 1.[2] However, the side chains differ. Hemolytic adverse effects may be related not only to the core ring structure, but also to the side chain modifications. For example, temafloxacin has a highly lipophilic side chain compared with other fluoroquinolones. In 1992, temafloxacin was withdrawn from the market because of frequent reports of serious hemolysis, including 3 deaths. This was termed "temafloxacin syndrome." The mean time to onset of hemolysis was 6.4 days after the start of therapy. This is similar to the onset of symptoms seen in our patient. Hemolytic anemia has also been reported with ciprofloxacin.[3,14,15] A MEDLINE search (1966–February 2003) for levofloxacin and ofloxacin (levo-isomer of levofloxacin)-induced hemolytic anemia produced no published cases. During postmarketing surveillance of ofloxacin in approximately 1.5 million patients, 18 cases of blood dyscrasias were reported.[16] Unfortunately, further details about the types of blood dyscrasias are not available. On the other hand, hemolytic anemia is listed in the levofloxacin package insert as a result of worldwide postmarketing surveillance. The exact incidence of levofloxacin-induced hemolytic anemia has not been reported by the manufacturer or the FDA. It may be inaccurate to conclude that temafloxacin, ciprofloxacin, and levofloxacin are the only fluoroquinolones responsible for hemolytic anemia. It is possible that other quinolones may also cause hemolytic anemia, although reports of such reactions have not been submitted to the FDA.

The exact mechanism responsible for the hemolytic syndrome associated with temafloxacin and ciprofloxacin is unknown.[4] Interestingly, data suggest the strong association between prior use of a quinolone and the onset of hemolysis after the first dose of temafloxacin. Patients with no history of quinolone use developed hemolytic events slower (mean 7.3 d) than those with prior quinolone use.[4] This difference may be explained by the time required to initiate a primary immune response in AIHA. Our patient had previous exposure to ciprofloxacin. Data from the reports suggest that the hemolytic events associated with fluoroquinones are immune mediated. Further studies should elucidate the exact mechanism of fluoroquinolone-induced hemolytic anemia.

Several factors indicate that levofloxacin was the most likely cause of autoimmune hemolysis in our patient. First, there are previous reports of hemolytic syndrome with other quinolones. Second, the time course, clinical presentation, and laboratory test results are similar to those in other cases, although our patient did not have renal sequelae as was reported in some of the other fluoroquinolone cases.[3,4] Third, the patient did not have a history of concurrent autoimmune disease, lymphoproliferative disorder, or immunodeficiency disorder, which should be part of the differential diagnosis of AIHA.

Summary

In our case, severe AIHA following exposure to levofloxacin was successfully treated with the combination of PRBCs and prednisone. Our case is of particular interest because the patient had a history of allergic reaction to ciprofloxacin, suggesting the possibility of cross-sensitivity. This adverse effect is a rare but serious complication of levofloxacin use. Until further information is obtained, levofloxacin should not be used in a patient with a sensitivity reaction to other fluoroquinolone antibiotics and/or quinine and quinidine. Clinicians should be aware of this potential adverse reaction with levofloxacin use. Immediate discontinuation of the offending medication and optimal treatment of the anemia is critical.

Young R Oh PharmD, Major, USAF, BSC, Pharmacy Practice Resident, Department of Clinical Pharmacy Services, David Grant USAF Medical Center, Travis Air Force Base, CA

Sian M Carr-Lopez PharmD, Professor and Vice-Chair, Thomas J Long School of Pharmacy and Health Sciences, University of the Pacific at Stockton; Regional Coordinator and Pharmacy Residency Program Director, David Grant USAF Medical Center

James M Probasco MD, Captain, USAF, MC, Family Practice Resident, Department of Family Practice, David Grant USAF Medical Center

Peter G Crawley MD PhD, Captain, USAF, MC, Internal Medicine Resident, Department of Internal Medicine, David Grant USAF Medical Center

Reprints: Young R Oh PharmD, Major, USAF, BSC, David Grant USAF Medical Center, 101 Bodin Circle, Travis Air Force Base, CA 94535-1800, FAX 707/423-7994, E-mail young.oh@60mdg.travis.af.mil

References

1. Hashimoto C. Autoimmune hemolytic anemia. Clin Rev Aller Immunol 1998;16:285-95.
2. Rubinstein E. History of quinolones and their side effects. Chemotherapy 2001;47(suppl 3):3-8.
3. Allan DS, Thompson CM, Barr RM, Clark WF, Chin-Yee IH. Ciprofloxacin-associated hemolytic-uremic syndrome. Ann Pharmacother 2002;36:1000-2. DOI 10.1345/aph.1A350
4. Blum MD, Graham DJ, McCloskey CA. Temafloxacin syndrome: review of 95 cases. Clin J Infect Dis 1994;18:946-50.
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
6. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002;69:258-71.
7. Winkelstein A, Kiss JE. Immunohematologic disorders. JAMA 1997; 278:1982-92.
8. Marchand A, Galen RS, Van Lente F. The predictive value of serum haptoglobin in hemolytic disease. JAMA 1980;243:1909-11.
9. Galen RS. Application of the predictive value model in the analysis of test effectiveness. Clin Lab Med 1982;2:685-99.
10. Petz LD. Treatment of autoimmune hemolytic anemias. Curr Opin Hematol 2001;8:411-6.
11. Wood ML, Schlessinger S. Levaquin induced acute tubulointerstitial nephritis — two case reports. J Miss State Med Assoc 2002;43:116-7.
12. Owens RC, Ambrose PG. Torsades de pointes associated with fluoroquinolones. Pharmacotherapy 2002;22:663-72.
13. Bertino J, Fish D. The safety profile of the fluoroquinolones. Clin Ther 2000;22:798-817.

14. Maguire RB, Stroncek DF, Gale E, Yearlsey M. Hemolytic and acute renal failure associated with temafloxacin-dependent antibodies. Am J Hematol 1994;46:363-6.
15. Norrby SR, Lietman PS. Safety and tolerability of fluoroquinolones. Drugs 1993;45:59-64.
16. Monk JP, Campoli-Richards DM. Ofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs 1987;33: 346-91.

EXTRACTO

OBJETIVO: Informar un caso de anemia hemolítica autoinmune secundaria a levofloxacina.

RESUMEN DEL CASO: Un hombre de raza blanca de 82 años recibió levofloxacina 500 mg diarios para tratar su celulitis. Tres días luego de terminar el tratamiento con el antibiótico, el paciente se presentó en la sala de emergencia con ictericia severa, vértigo, y pérdida de visión. Allí recibió una transfusión de concentrado de glóbulos rojos y fue dado de alta. Dos días más tarde, en la visita de seguimiento, se le diagnosticó anemia hemolítica autoinmune inducida por levofloxacina. El paciente fue hospitalizado y recibió tratamiento con prednisona y una transfusión adicional de glóbulos rojos. Luego de 3 dias de hospitalización fue dado de alta en condición estable. Las pruebas de seguimiento hematológicas demostraron que la anemia hemolítica resolvió.

DISCUSIÓN: La anemia hemolítica secundaria a levofloxacina es un evento adverso extremadamente raro pero potencialmente letal. La evaluación objetiva de causabilidad que se utilizó indicó que este evento adverso era probable. Según los autores, este es el primer caso publicado en el cual se asocia a levofloxacina con este evento adverso. Sin embargo, en la literatura se han informado casos de anemia hemolítica inducida por otras quinolonas como ciprofloxacina (n = 12) y temafloxacina (n = 95). Temafloxacina se retiró del mercado en 1992 debido a este efecto adverso. El mecanismo por el cual levofloxacina induce la anemia hemolítica no se conoce. Los autores entienden que esta reacción está posiblemente mediada por el sistema inmune.

CONCLUSIONES: La anemia hemolítica inducida por levofloxacina es una complicación rara pero severa de este medicamento. Se requiere descontinuar el medicamento inmediatamente. También es esencial manejar adecuadamente la anemia hemolítica. Mientras no haya más información disponible sobre este evento adverso, los autores recomiendan que no se prescriba levofloxacina a pacientes que hayan presentado previamente algún tipo de reacción a otra fluoroquinolona.

Mirza D Martínez

RÉSUMÉ

OBJECTIF: Décrire un cas d'anémie hémolytique autoimmune secondaire à la lévofloxacine.

RÉSUMÉ DE CAS: Un homme de race blanche de 82 ans était traité pour une cellulite avec de la lévofloxacine 500 mg par jour. Trois jours après la fin de son traitement antibiotique, le patient s'est présenté à l'urgence pour ictère sévère, étourdissement, et perte de vision. A l'urgence, on lui administra des culots globulaires et il retourna chez lui. Deux jours plus tard, lors d'une visite de contrôle, le médecin diagnostiqua une anémie hémolytique autoimmune secondaire à la lévofloxacine. Le patient fut hospitalisé et traité avec des doses décroissantes de prednisone et il reçut d'autres culots globulaires. Après une hospitalisation de 3 jours, le patient est retourné chez lui dans un état stable. Les analyses sanguines effectuées après la sortie du patient de l'hôpital confirment la disparition de l'anémie hémolytique.

DISCUSSION: L'anémie hémolytique secondaire à la lévofloxacine est un effet indésirable extrêmement rare mais potentiellement fatal. Le lien de causalité de l'événement a révélé une réaction probable. A notre connaissance, ce cas est le premier cas publié. Cependant, il existe d'autres cas d'anémie hémolytique secondaire à d'autres fluoroquinolones dont la ciprofloxacine (n = 12) et la témafloxacine (n = 95). D'ailleurs, la témafloxacine a été retirée du marché en 1992 en raison de cet effet secondaire. Le mécanisme d'action par lequel la lévofloxacine occasionne l'anémie hémolytique est inconnu. La cause la plus probable serait une réaction immunologique.

CONCLUSIONS: L'anémie hémolytique induite par la lévofloxacine est une complication rare mais sérieuse de la thérapie. La médication doit être cessée immédiatement et le patient doit absolument recevoir un traitement pour son anémie hémolytique. Jusqu'à ce que plus d'informations soient disponibles, la lévofloxacine ne devrait pas être prescrite à des patients ayant déjà présenté de telles réactions aux fluoroquinolones.

Louise Gagnon