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Norfloxacin

Updated: March 10, 2020.

OVERVIEW

Introduction

Norfloxacin is a first generation fluoroquinolone that is typically used to treated urinary tract infections and prostatitis. Norfloxacin has been linked to rare instances of acute hepatocellular injury.

Background

Norfloxacin (nor flox' a sin) is a first generation fluoroquinolone that has been available for treatment of bacterial infections for many years, but which now has limited indications and is not commonly used. Like other fluoroquinolones, norfloxacin is active against a wide range of aerobic gram-positive and gram-negative organisms and is believed to act by inhibition of bacterial DNA gyrase and topoisomerase IV that are required for synthesis of bacterial mRNAs (transcription) and DNA replication. In contrast, DNA gyrases are not present in human [and other eukarotic] cells and the equivalent topoisomerases are not sensitive to fluoroquinolone inhibition. Norfloxacin was first approved for use in the United States in 1986. Current indications are for urinary tract infections, sexually transmitted diseases and prostatitis due to sensitive organisms. Based upon studies from Europe, norfloxacin has also been used off-label as prophylaxis against spontaneous bacterial peritonitis in patients with cirrhosis and ascites. Norfloxacin is available as 400 mg tablets under the trade name Noroxin. Typical doses are 400 mg every 12 hours for 3 to 10 days, but chronic therapy has been used for antibacterial prophylaxis. Common side effects include gastrointestinal upset, headaches, skin rash and allergic reactions. Less common, but more severe side effects of norfloxacin include prolongation of the QT interval, seizures, hallucinations, tendon rupture, hypersensitivity reactions, angioedema, Stevens Johnson syndrome, photosensitivity and peripheral neuropathy.

Hepatotoxicity

Norfloxacin like other fluoroquinolones is associated with a low rate (1% to 3%) of serum enzyme elevations during therapy. These abnormalities are generally mild, asymptomatic and transient, resolving even with continuation of therapy. Norfloxacin has also been linked to rare but occasionally severe and even fatal cases of acute liver injury. While the numbers of cases have been few, the clinical pattern has been consistent with short latency period of 1 day to 3 weeks and abrupt onset of hepatocellular injury. The pattern of serum enzyme elevations can be either hepatocellular or cholestatic, cases with the shorter times to onset usually being more hepatocellular with markedly elevated ALT levels, and occasionally with rapid worsening of prothrombin time and signs of hepatic failure. The onset of illness may occur a few days after the medication is stopped. Many (but not all) cases have had allergic manifestations with fever, rash and eosinophilia. Autoantibodies are usually not present. Cholestatic and mixed patterns of injury have also been described particularly with delayed recognition

of the liver injury. These features are typical of all fluoroquinolone associated hepatotoxicity and the injury is believed to be class specific.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of hepatic injury is unknown, but appears to be hypersensitivity.

Outcome and Management

The severity of liver injury caused by norfloxacin ranges from mild and transient serum enzyme elevations to self-limited but severe hepatitis, to acute liver failure and death. Complete recovery is expected after stopping the drug and recovery is usually rapid (2 to 8 weeks). Cross reactivity of the hepatic injury between different fluoroquinolones has not been well documented, but is suspected based upon the similarity of clinical patterns of injury and latency. Thus, patients should be advised to avoid further exposure to the fluoroquinolones.

Drug Class: Antiinfective Agents

Other Drugs in the Subclass, Fluoroquinolones: Ciprofloxacin, Delafloxacin, Gemifloxacin, Levofloxacin, Moxifloxacin, Ofloxacin

CASE REPORT

Case 1. Cholestatic hepatitis in a patient with cirrhosis due to norfloxacin.(1)

A 58 year old man with alcoholic cirrhosis and acute variceal hemorrhage was treated with intravenous norfloxacin as prophylaxis against spontaneous bacterial peritonitis. After 4 days, he was switched to oral norfloxacin (400 mg twice daily). Five days later, he was noted to be jaundiced and laboratory testing showed increased levels of serum bilirubin (19.1 mg/dL), ALT (214 U/L), and alkaline phosphatase (1921 U/L) as compared to baseline (Table). Tests for hepatitis A, B, C and E were negative as were autoantibodies. Abdominal ultrasound showed no evidence of biliary obstruction. Norfloxacin was stopped and he improved without further intervention over the next several weeks. Six weeks later his blood test results had returned to baseline levels. He was later treated with intravenous ofloxacin without adverse events.

Key Points

Medication:	Norfloxacin, 500 mg daily for 6 days
Pattern:	Cholestatic (R=0.2)
Severity:	3+ (jaundice and hospitalization prolonged)
Latency:	9 days
Recovery:	Approximately 6 weeks
Other medications:	Propofol, somatostatin, propranolol, lactitol.

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	18	126	2.8	Variceal hemorrhage
9 days	0	121	1921	14.9	Norfloxacin stopped

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
3 weeks	2 weeks	44	749	2.1	
8 weeks	6 weeks	18	227	1.4	
Normal Values		**<41**	**<279**	**<1.2**	

Comment

The abrupt and rapid onset after starting and the rapid resolution on stopping the agent are typical of fluoroquinolone hepatotoxicity. Cases that are cholestatic are less likely to be severe and result in fatalities, but even cholestatic hepatitis has serious implications in patients with cirrhosis. The lack of recurrence with subsequent use of ofloxacin is striking, but it is probably prudent to avoid use of fluoroquinolones in patients with clinically apparent liver injury caused by any agent in that class.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Norfloxacin – Noroxin®

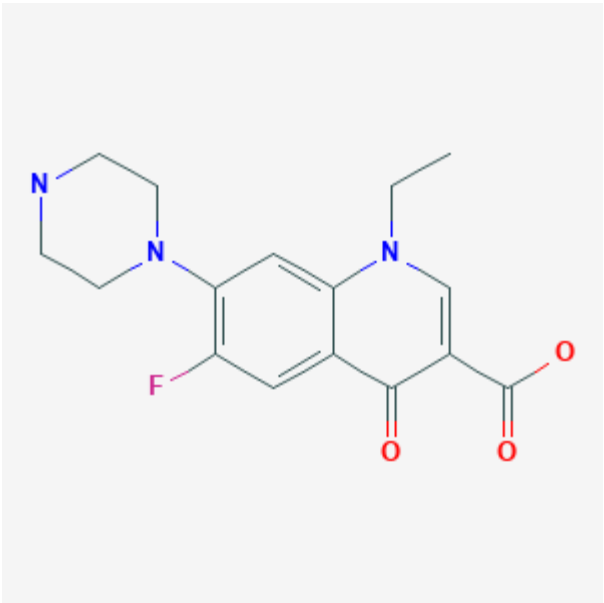
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Norfloxacin	70458-96-7	C16-H18-F-N3-O3	

CITED REFERENCE

1. Romero-Gómez M, Suárez García E, Fernández MC. Norfloxacin-induced acute cholestatic hepatitis in a patient with alcoholic liver cirrhosis. Am J Gastroenterol. 1999;94:2324–5. PubMed PMID: 10445586.

ANNOTATED BIBLIOGRAPHY

References updated: 10 March 2020

Zimmerman HJ. Quinolones. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999. p 603.

(Expert review of hepatotoxicity published in 1999; mentions that cinoxacin, nalidixic acid, ciprofloxacin, norfloxacin, enoxacin, and ofloxacin are associated with minor serum enzyme elevations during therapy and with rare instances of clinically apparent liver injury).

Moseley RH. Fluoroquinolones. Hepatotoxicity of antimicrobial and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. p. 468-9.

(Review of hepatotoxicity of antibiotics mentions that hepatocellular and cholestatic forms of injury have been reported due to the quinolones, including cases of ductopenia, acute liver failure and death).

MacDougall C. The quinolones. Sulfonamides, trimethoprim-sulfamethoxazole, quinolones, and agents for urinary tract infections. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1015-8.

(Textbook of pharmacology and therapeutics).

Corrado ML, Struble WE, Peter C, Hoagland V, Sabbaj J. Norfloxacin: a review of safety studies. Am J Med. 1987;82 Suppl 6B:22–6. PubMed PMID: 3605158.

(Early report on safety of norfloxacin from the sponsor; states that adverse events are uncommon and usually mild and that ALT elevations are rare [0.1%]).

Halkin H. Adverse effects of the fluoroquinolones. Rev Infect Dis. 1988;10 Suppl 1:S258–61. PubMed PMID: 3279499.

(Combined analysis of databases provided by manufacturers on adverse events of fluoroquinolones in approximately 30,000 persons receiving ciprofloxacin, ofloxacin, pefloxacin, norfloxacin and enoxacin found similar types and rates of adverse events among the agents, overall in 4-8%, elevated liver enzymes in 1.8-2.5%, but eosinophilia in 2.4% with ciprofloxacin and 5-19% with ofloxacin).

López-Navidad A, Domingo P, Cadafalch J, Farrerons J. Norfloxacin-induced hepatotoxicity. J Hepatol. 1990;11:277–8. PubMed PMID: 2254636.

(72 year old woman developed abdominal pain 7 days after starting norfloxacin [peak bilirubin 1.0 mg/dL, ALT 310 U/L, Alk P 271 U/L], resolving within a few weeks upon stopping).

Wolfson JS, Hooper DC. Overview of fluoroquinolone safety. Am J Med. 1991;91 Suppl 6A:153S–61S. PubMed PMID: 1767803.

(Review of side effects reported in 22 clinical trials of fluoroquinolones; elevations in ALT and/or Alk P levels occurred in 1.8-2.7% of patients on cipro-, nor-, or ofloxacin).

Davoren P, Mainstone K. Norfloxacin-induced hepatitis. Med J Aust 1993; 159: 423, 426.

(25 year old woman developed abdominal pain, fever and jaundice within 2 days of starting norfloxacin [bilirubin 3.7 mg/dL, ALT 2726 U/L, Alk P 168 U/L], resolving within 3 weeks of stopping).

Lucena MI, Andrade RJ, Sanchez-Martinez H, Perez-Serrano JM, Gomez-Outes A. Norfloxacin-induced cholestatic jaundice. Am J Gastroenterol. 1998;93:2309–11. PubMed PMID: 9820434.

(70 year old man developed jaundice and pruritus 12 days after starting norfloxacin [bilirubin 10 mg/dL, ALT 178 U/L, Alk P 443 U/L], resolving within 4 weeks of stopping).

Romero-Gómez M, Suárez García E, Fernández MC. Norfloxacin-induced acute cholestatic hepatitis in a patient with alcoholic liver cirrhosis. Am J Gastroenterol. 1999;94:2324–5. PubMed PMID: 10445586.

(58 year old man with alcoholic cirrhosis but normal liver tests developed jaundice 5 days after starting oral norfloxacin for prophylaxis against spontaneous bacterial peritonitis [bilirubin 14.9 mg/dL, ALT 214 U/L, AST 121 U/L, Alk P 1921 U/L], with return to baseline within 1 month of stopping).

Björnsson E, Olsson R, Remotti H. Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. Am J Gastroenterol. 2000;95:3662–4. PubMed PMID: 11151924.

(71 year old woman developed fever and eosinophilia [61%] after a week of therapy with norfloxacin and at 2 weeks had liver test abnormalities [bilirubin normal, ALT 69 Alk P 960 U/L], which returned to normal with stopping; recurrence of fever, eosinophilia [55%] and ALT elevations [102 U/L] within a day of reexposure).

Orman ES, Conjeevaram HS, Vuppalanchi R, Freston JW, Rochon J, Kleiner DE, Hayashi PH; DILIN Research Group. Clinical and histopathologic features of fluoroquinolone-induced liver injury. Clin Gastroenterol Hepatol. 2011;9:517–23.e3. PubMed PMID: 21356330.

(Among 679 cases of drug induced liver injury presenting between 2004 and 2010 at 8 US medical centers, 12 [1.8%] were attributed to fluoroquinolones including 6 cipro-, 4 moxi-, 1 levo-, and 1 gatifloxacin, but not from norfloxacin; average time to onset was 4 days [range 1-39], with both hepatocellular and cholestatic enzyme patterns, seven with rash or fever, mortality limited to those with hepatocellular injury and jaundice; hepatic injury appeared to be class specific).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, including one due to ciprofloxacin, but none to norfloxacin).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, none of which were attributed to a fluoroquinolone).

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, et al. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci. 2012;27:268–73. PubMed PMID: 22379337.

(Summary of 2 years of adverse event reporting in Korea; of 9360 reports, 567 were liver related, including 29 [5.1%] attributed to quinolones).

Harr T, French LE. Stevens-Johnson syndrome and toxic epidermal necrolysis. Chem Immunol Allergy. 2012;97:149–66. PubMed PMID: 22613860.

(Review of the clinical features, epidemiology, genetics and pathogenesis of SJS and TEN).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, one due to trovafloxacin [acute liver failure], but none attributed to ciprofloxacin or other fluoroquinolones).

Alshammari TM, Larrat EP, Morrill HJ, Caffrey AR, Quilliam BJ, LaPlante KL. Risk of hepatotoxicity associated with fluoroquinolones: a national case-control safety study. Am J Health Syst Pharm. 2014;71:37–43. PubMed PMID: 24352180.

(Retrospective analysis of Veterans Affairs patients receiving a fluoroquinolone [n=7862] found a higher relative risk of developing acute liver injury after receipt of ciprofloxacin compared to matched controls [adjusted odds ratio: OR=1.29], but not after receipt of levofloxacin [OR=1.16) or moxifloxacin [OR=0.98]).

Lontos S, Shelton E, Angus PW, Vaughan R, Roberts SK, Gordon A, Gow PJ. A randomized controlled study of trimethoprim-sulfamethoxazole versus norfloxacin for the prevention of infection in cirrhotic patients. J Dig Dis. 2014;15:260–7. PubMed PMID: 24612987.

(Among 80 patients with advanced cirrhosis given oral prophylaxis with daily trimethoprim-sulfamethoxazole or norfloxacin, infection rates were similar in the two groups as were rates of death and liver transplantation as well as adverse event rates; no instances of drug induced liver injury).

Goldberg DS, Forde KA, Carbonari DM, Lewis JD, Leidl KB, Reddy KR, Haynes K, et al. Population-representative incidence of drug-induced acute liver failure based on an analysis of an integrated health care system. Gastroenterology 2015; 148: 1353-61. e3.

(Analysis of Kaiser Permanente health care database from 2004 to 2011 identified 62 patients with suspected acute liver failure, 32 [52%] of whom had a presumed drug etiology, the most common being acetaminophen [18: 56%] and various herbal products [5: 16%], with single instances attributed to imatinib, simvastatin, leflunomide, isoniazid and valproate, but none to ciprofloxacin or other fluoroquinolones).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. e7.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 38 cases [4%] were attributed to fluoroquinolones, including 16 due to ciprofloxacin [the 8th most common prescription drug cause], 13 due to levofloxacin and 8 to moxifloxacin).

Elliott TR, Symes T, Kannourakis G, Angus P. Resolution of norfloxacin-induced acute liver failure after N-acetylcysteine therapy: further support for the use of NAC in drug-induced ALF? BMJ Case Rep. 2016;2016:bcr2015213189. pii. PubMed PMID: 26740270.

(77 year old woman developed jaundice 2 weeks after a 3 day course of norfloxacin [bilirubin 8.5 mg/dL, ALT 248 U/L, Alk P 256 U/L], with progression to hepatic failure [INR 2.7], but dramatic clinical improvement after a 2 day infusion of N-acetylcysteine, liver tests normalizing 3 months later).

Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, Fontana RJ, Ghabril MS, et al; U.S. Drug Induced Liver Injury Network Investigators. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology. 2017;65:1267–77. PubMed PMID: 27981596.

(Among 363 patients with drug induced liver injury who underwent liver biopsy, 26 [7%] had bile duct loss of whom 94% developed evidence of chronic liver injury suggestive of vanishing bile duct syndrome, 2 of which were due to fluoroquinolones, 1 to moxifloxacin and 1 levofloxacin).

Yim HJ, Suh SJ, Jung YK, Yim SY, Seo YS, Lee YR, Park SY, Jang JY, Kim YS, Kim HS, Kim BI, Um SH. Daily norfloxacin vs. weekly ciprofloxacin to prevent spontaneous bacterial peritonitis: a randomized controlled trial. Am J Gastroenterol. 2018;113:1167–76. PubMed PMID: 29946179.

(Among 124 patients with cirrhosis and ascites given prophylaxis with daily norfloxacin [400 mg] or weekly oral ciprofloxacin [750 mg], subsequent rates of bacterial peritonitis were similar [7% vs 5%] as were rates of liver transplantation and death).

Moreau R, Elkrief L, Bureau C, Perarnau JM, Thévenot T, Saliba F, Louvet A, et al; NORFLOCIR Trial Investigators. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology. 2018;155:1816–27.e9. PubMed PMID: 30144431.

(Among 291 patients with advanced cirrhosis treated for 6 to 12 months with daily oral norfloxacin or placebo, 6-month mortality rate was less with norfloxacin [15% vs 19%] as were gram-negative bacterial infections and no norfloxacin related severe adverse events were identified).

Comparison table: some systemic fluoroquinolones. Med Lett Drugs Ther. 2018;60:e57–e58. PubMed PMID: 29635268.

(Table comparing 4 fluoroquinolones [cipro-, levo-, dela- and moxifloxacin] mentions that ALT and AST elevations are a class adverse event).

Kuula LSM, Viljemaa KM, Backman JT, Blom M. Fluoroquinolone-related adverse events resulting in health service use and costs: A systematic review. PLoS One. 2019;14:e0216029. PubMed PMID: 31026286.

(Systematic review of observational studies on safety of fluoroquinolones concluded that due to lack of published literature, health service and costs could not be evaluated).