



## Ofloxacin

Updated: March 10, 2020.

## OVERVIEW

### Introduction

Ofloxacin is a second generation fluoroquinolone that was previously used widely for therapy of mild-to-moderate bacterial infections, but which has been replaced by more potent and less toxic fluoroquinolones and is now used largely topically as eye and ear drops. Ofloxacin has been linked to rare instances of acute hepatocellular injury.

### Background

Ofloxacin (oh flox' a sin) is an oral, second generation fluoroquinolone that was previously widely used to treat mild-to-moderate urinary and respiratory tract infections caused by susceptible organisms. Ofloxacin is a semisynthetic antibiotic and a racemic mixture; its l-enantiomer is available as levofloxacin which continues to be a widely used antibiotic. Like other fluoroquinolones, ofloxacin 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. Ofloxacin was approved for use in the United States in 1990, but was discontinued by its initial sponsor in 2009, partially because of the frequency of adverse side effects. Nevertheless, ofloxacin remains available several in generic forms as 200, 300 and 400 mg tablets. Current indications are acute bronchitis, community acquired pneumonia, skin, infections, cystitis, pelvic inflammatory disease, prostatitis, urethritis and gonorrhea. Typical doses are 200 to 400 mg every 12 hours for 3 to 10 days, but longer courses are sometimes used for complicated or recurrent infections. Common side effects include gastrointestinal upset, headaches, skin rash and allergic reactions. Less common but more severe side effects of fluoroquinolones include prolongation of the QT interval, seizures, hallucinations, tendon rupture, hypersensitivity reactions and photosensitivity.

### Hepatotoxicity

Mild elevations in ALT and alkaline phosphatase levels occur in 1 to 2% of patients on ofloxacin. These abnormalities are generally mild, asymptomatic and transient, resolving even with continuation of therapy. Ofloxacin has also been linked to rare but occasionally severe and even fatal cases of acute liver injury. The time to onset is typically short (2 days to 2 weeks) and the presentation is often abrupt with nausea, fatigue, abdominal pain and jaundice. 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. Cases with a cholestatic pattern of enzymes may run a prolonged course but are usually self-limiting. Many (but not all) cases have had allergic manifestations with fever, rash and eosinophilia. Autoantibodies are usually not present. The hepatotoxicity of ofloxacin is similar to that of other fluoroquinolones and appears to represent a class effect.

Likelihood score: A (well established but 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 ofloxacin induced liver injury ranges from mild and transient serum enzyme elevations to self-limited jaundice to acute liver failure. Recovery is usually rapid (2 to 8 weeks) after stopping the medication. Cross reactivity of the hepatic injury between different fluoroquinolones has not been well defined, 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, particularly levofloxacin which is the levorotatory isomer of ofloxacin.

Drug Class: [Antiinfective Agents](#)

Other Drugs in the Subclass, [Fluoroquinolones](#): [Ciprofloxacin](#), [Delafloxacin](#), [Gemifloxacin](#), [Levofloxacin](#), [Moxifloxacin](#), [Norfloxacin](#)

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Ofloxacin – Generic, Floxin®

### DRUG CLASS

Antiinfective Agents

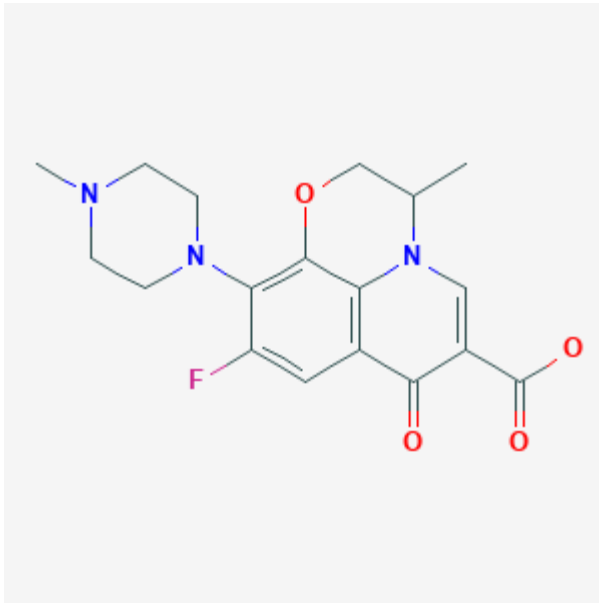
### COMPLETE LABELING

Product labeling at [DailyMed](#), National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE

Table continued from previous page.

Ofloxacin	82419-36-1	C18-H20-F-N3-O4	 <p>The image shows the chemical structure of Ofloxacin, a fluoroquinolone antibiotic. It features a central quinolone ring system with a fluorine atom at the 6-position, a piperazine ring at the 7-position, and a propyl side chain at the 8-position. The side chain is substituted with a methyl group and an oxygen atom, forming a cyclic ether structure. The quinolone ring also has a carbonyl group at the 4-position and a carboxylic acid group at the 3-position.</p>
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## 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).

Jüngst G, Mohr R. Side effects of ofloxacin in clinical trials and in postmarketing surveillance. *Drugs*. 1987;34 Suppl 1:144-9. PubMed PMID: 3325257.

(In postmarketing surveillance of 1.5 million patients treated with ofloxacin in Germany, 18 liver related adverse events were reported, 15 serum enzyme elevations and 3 cases of "cholestasis").

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).

- Blum A. Ofloxacin-induced acute severe hepatitis. *South Med J*. 1991;84:1158. PubMed PMID: 1891746.
- (86 year old woman with heart disease developed nausea and vomiting 10 days after completing a 14 day course of ofloxacin [bilirubin not mentioned, ALT 4160 U/L, LDH 5510 U/L, Alk P 403 U/L], with accompanying renal failure and rapid resolution; suggestive of ischemic liver injury).
- Hautekeete ML, Kockx MM, Naegels S, Holvoet JK, Hubens H, Kloppel G. Cholestatic hepatitis related to quinolones: a report of two cases. *J Hepatol*. 1995;23:759–60. PubMed PMID: 8750178.
- (82 year old woman developed jaundice after 12 days of oral ofloxacin [bilirubin 4.5 rising to 6.5 mg/dL, ALT 65 U/L, Alk P 352 U/L, eosinophils 11%], jaundice lasting 4 weeks and then resolving; a second case was due to ciprofloxacin).
- Ball P, Tillotson G. Tolerability of fluoroquinolone antibiotics. Past, present and future. *Drug Saf*. 1995;13:343–58. PubMed PMID: 8652079.
- (Review of the nature and frequency of adverse reactions to the fluoroquinolones mentions that clinically apparent liver injury is rare, but that severe and occasional fatal cases have been reported with ciprofloxacin, levofloxacin, norfloxacin and ofloxacin, and from postmarketing surveillance has estimated the frequency of clinically apparent liver injury to be 0.8 per 100,000 recipients).
- Jones SE, Smith RH. Quinolones may induce hepatitis. *BMJ*. 1997;314:869. PubMed PMID: 9093098.
- (21 year old man developed jaundice 5 days after starting ofloxacin and 1 day after starting ciprofloxacin [peak bilirubin 8.2 mg/dL, AST 557 U/L, Alk P 530 U/L], resolving within 4 weeks of stopping).
- González Carro P, Huidobro ML, Zabala AP, Vicente EM. Fatal subfulminant hepatic failure with ofloxacin. *Am J Gastroenterol*. 2000;95:1606. PubMed PMID: 10894622.
- (70 year old man developed jaundice 5 weeks after a 5 day course of ofloxacin [bilirubin 13.5 mg/dL, ALT 1382 U/L, Alk P 392 U/L], with gradual worsening and hepatic failure resulting in death 16 weeks after onset).
- Stahlmann R. Clinical toxicological aspects of fluoroquinolones. *Toxicol Lett*. 2002;127:269–77. PubMed PMID: 12052667.
- (Review of the serious toxicities of the fluoroquinolones, their frequency and possible mechanisms; the hepatotoxicity of trovafloxacin became evident only after approval and over 2.5 million prescriptions worldwide with 140 reported cases of "severe hepatic reactions" despite no serious hepatotoxicity in clinical trials in several thousand patients).
- 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 none to ofloxacin; average time to onset 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).
- 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).

Patel TK, Barvaliya MJ, Sharma D, Tripathi C. A systematic review of the drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Indian population. *Indian J Dermatol Venereol Leprol*. 2013;79:389–98. PubMed PMID: 23619444.

(Systematic review of 10 case series of SJS/TEN from India identified 352 cases, among which 342 implicated a medication with most common being antimicrobials [37%], anticonvulsants [16%] and NSAIDs [16%]; fluoroquinolones accounted for 33 cases [10%], 4 of which were due to ciprofloxacin, 1 to ofloxacin and 1 to ciprofloxacin).

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]).

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 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).

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).

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

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

Kuula LSM, Viljema 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).