

**Systematic review of adverse drug reactions of ofloxacin****Amit S. Kamdi<sup>1</sup>, Sarika D. Kokane<sup>2\*</sup>, Pankaj N. Bohra<sup>3</sup>, Suvarna M. Kalambe<sup>4</sup>**<sup>1</sup>Department of Pharmacology,<sup>2</sup>Department of Biochemistry,  
Government Medical College,  
Chandrapur, Maharashtra, India<sup>3</sup>Department of Pediatrics,  
SNEH Foundation, Chinchwad,  
Pune, Maharashtra, India<sup>4</sup>Department of Research &  
Development, Sanjeevani  
Multipurpose Society, Mul,  
Chandrapur, Maharashtra, India**Received:** 18 September 2018**Accepted:** 22 September 2018**\*Correspondence to:**Dr. Sarika D. Kokane,  
Email: [sarikakokane@yahoo.com](mailto:sarikakokane@yahoo.com)**Copyright:** © the author(s),  
publisher and licensee Medip  
Academy. This is an open-  
access article distributed under  
the terms of the Creative  
Commons Attribution Non-  
Commercial License, which  
permits unrestricted non-  
commercial use, distribution,  
and reproduction in any  
medium, provided the original  
work is properly cited.**ABSTRACT**

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality in countries having limited healthcare resources. Of all the Adverse Drug Reactions, antimicrobials contribute 28% which is highest compared to the other drugs. Ofloxacin is an antimicrobial used for treating several bacterial infections. Incidence rate of adverse drug reactions (ADRs) to ofloxacin is 4.27%. Although these figures appear to be small, it is consumed for gastrointestinal infections along with ornidazole in India contributing significant burden of ADRs. However, there is no research done in past many years focusing on the adverse drug reactions of ofloxacin. This article bridges the gap of such a need. The objective of the present study was to review the adverse drug reactions related to ofloxacin in human and animal studies. Authors conducted Pubmed and Cochrane library search to review all the articles related to the adverse drug reaction of ofloxacin from 1980 to 2016. Authors got 84 articles pertaining to the adverse drug reactions of ofloxacin. Authors conclude that ofloxacin should be judiciously used as the side effect profile is increasing.

**Keywords:** Adverse drug reaction, Antibiotic, Human, Review, Side effects**INTRODUCTION**

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality in countries having limited healthcare resources. Global incidence of ADRs in hospitalized children is 9.53%, but hospitalization due to ADRs in the elder patients is 4 times greater than younger ones as they are receiving multiple medications for long term illnesses.<sup>1</sup> Average incidence of ADRs from all drugs

in India is 9.8%.<sup>2</sup> Skin is the most common organ system affected followed by Central Nervous System and Gastrointestinal Tract.<sup>2</sup> However, this may sound the tip of the iceberg as the ADR monitoring is still evolving in India.

Of all the Adverse Drug Reactions, antimicrobials contribute 28% which is highest compared to the other drugs.<sup>1</sup> Ofloxacin is an antimicrobial used for treating

several bacterial infections. Ofloxacin, belonging to quinolone group of drugs, is bactericidal and acts by inhibition of bacterial DNA gyrase. Having molecular weight 361.37g/mol and molecular formula C<sub>18</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>4</sub>, it is approved by FDA in January 1997 to treat pelvic inflammatory disease (PID).<sup>3</sup>

Common side effects of ofloxacin are insomnia, nausea, vomiting, diarrhea, and headache. Incidence rate of adverse drug reactions (ADRs) to ofloxacin is 4.27%.<sup>4</sup> About 11% experienced the side effects of ofloxacin use in clinical trials.<sup>5</sup> Discontinuation of drug therapy because of side effects occurred in 4% patients.<sup>5</sup> Although these figures appear to be small, it is consumed for gastrointestinal infections along with ornidazole in India contributing significant burden of ADRs. However, there is no research done in past many years focusing on the adverse drug reactions of ofloxacin. This article bridges the gap of such a need.

## REVIEW OF LITERATURE

### Search strategy

Authors searched the pertinent studies in PubMed. First authors searched the term “ofloxacin” in the Mesh database. Out of 7 search results, the term “Ofloxacin” having meaning “a synthetic fluoroquinolone antibacterial agent that inhibits the supercoiling activity of bacterial DNA GYRASE, halting DNA replication. Year introduced: 1989” selected and added to the Pubmed search builder. Later, authors searched the term “Adverse Drug Reaction” in the Mesh database.

Out of 3 search results, we selected the term “Drug-Related Side Effects and Adverse Reactions” having meaning “Disorders that result from the intended use of pharmaceutical preparations. Included in this heading are a broad variety of chemically-induced adverse conditions due to toxicity, drug interactions, and metabolic effects of pharmaceuticals. Year introduced: 2014” and added to the Pubmed Search Builder. Authors searched [“Ofloxacin”[Mesh]] AND “Drug-Related Side Effects and Adverse Reactions”[Mesh]] together in Pubmed search builder without language barrier.

Articles not in English translated into English language using Google translation service. Same search strategy was utilized while searching through Copernicus database. Authors searched the Cochrane library using the term “ofloxacin” without language limit and executed advanced search between the years 1990 to 2016.

### Inclusion criteria

Authors included all randomized trials, comparative studies, controlled clinical trials, observational studies, case reports with or without free full text, without language barrier in writing the review.

### Exclusion criteria

Authors excluded the studies that did not show the ADRs related to ofloxacin. These included ADRs related to Levofloxacin and similar drugs. Authors excluded other studies that just assessed ofloxacin antibacterial activity

### Data extraction

Authors discarded irrelevant studies after screening all titles and abstracts and evaluated the full texts of the remaining studies to determine the inclusion criteria. Authors used the standard prepared forms for data extraction.

## DISCUSSION

Authors divided the ADRs related with ofloxacin into different systems like fatal, gastrointestinal, nervous system, cutaneous, musculoskeletal, hepatobiliary, cardiovascular, renal, hematological, ocular and others.

### Fatal ADR

Anaphylactic shock described in a boy after taking oral ofloxacin.<sup>6</sup>

### Gastrointestinal (GI) ADRs

GI disturbances such as nausea, vomiting and gastric pain were the most common ADRs followed by Central nervous system.<sup>7</sup> Pseudomembranous colitis associated with clostridium difficile attributed to ofloxacin treatment.<sup>8</sup>

### Nervous system ADRs

Among the Central Nervous System adverse drug reactions, headache and insomnia were the major ones compared to the hallucinations, nightmares, confusion and depression as the minor ones.<sup>9</sup> However, these findings were not consistent as the post marketing surveillance in 1.5 million patient population showed that Nervous system ADRs ranked 1<sup>st</sup> followed by hypersensitivity reaction and GI disturbances in order of frequency.<sup>4</sup> Sleep disturbances were common in children receiving ofloxacin treatment.<sup>10</sup> The rare adverse reactions like hallucination, psychosis and shock also reported in Germany in post marketing experience.<sup>11</sup>

Generalized tonic clonic seizures prompted by ofloxacin cannot be ruled out in patient with compromised renal function secondary to drug accumulation.<sup>12</sup> Status epilepticus described with ofloxacin use.<sup>13</sup> It provoked delirium too.<sup>14</sup> It caused Idiopathic intracranial hypertension in a 25-year-old man treated with 400mg/day for 16 months.<sup>15</sup> It triggered Tourette-like syndrome in elderly patient admitted in community hospital for management of pneumonia.<sup>16</sup>

### **Cutaneous ADRs**

Angioedema developed in a 24-year-old male patient who received ofloxacin-ornidazole combination for loose motions.<sup>17</sup> Cutaneous vasculitis occurred in a diabetic foot infected patient, and another patient of urinary tract infection treated with ofloxacin.<sup>18</sup> The patient treated with ofloxacin for bronchitis and pharyngitis, got intense erythemas followed by sub- corneal pustulation associated with fever and neutrophil leukocytosis, diagnosed as toxic pustuloderma.<sup>19</sup> Fixed drug eruption reported with ciprofloxacin, amoxicillin, and independently as well.<sup>20</sup> It caused the toxic epidermal necrosis.<sup>21</sup> Erythema multiforme like rash ascribed to ofloxacin use.<sup>22</sup> A rare variant of erythema nodosum leprosum of type 2 Lepra reaction testified in ofloxacin aided multi drug therapy.<sup>23</sup> The type1 Lepra reaction occurred in single lesion paucibacillary leprosy treated with single dose rifampin, ofloxacin, and minocycline.<sup>24</sup> It triggered Sweet's syndrome (acute febrile neutrophilic dermatosis) in a patient with Crohn's disease.<sup>25</sup>

### **Musculoskeletal ADRs**

The complete rupture of Achilles tendon happened with elderly patients with concurrent administration of corticosteroid and ofloxacin.<sup>26</sup> Myalgia, arthralgia and multiple tendonopathy noted in 53- year-old woman exposed to ofloxacin.<sup>27</sup> Systematic review of observational cohort studies comparing different fluoroquinolones threw light on the relationship of tenosynovitis with ofloxacin use.<sup>7</sup> The marked increase in serum myoglobin and presence of urine myoglobin confirmed the association of acute rhabdomyolysis with ofloxacin.<sup>28</sup>

### **Hepatobiliary ADRs**

Asymptomatic hepatitis observed in resistant case of pulmonary tuberculosis, treated with the alternative therapy with Pyrazinamide and ofloxacin.<sup>29</sup> Moderate increase in liver enzymes noted in patient with Wegener's Granulomatosis treated with ofloxacin for the productive cough.<sup>30</sup> A 70-year-old man having prostatic adenoma with urinary tract infection treated with ofloxacin developed fatal sub-fulminant hepatic failure.<sup>31</sup> Acute severe hepatitis by ofloxacin described in 1991.<sup>32</sup> Sensitized lymphocytes to trimethoprim/sulfamethoxazole and ofloxacin demonstrated in patient of cholestatic hepatitis, signifying strong relationship of ofloxacin with cholestatic hepatitis.<sup>33</sup>

### **Cardiovascular ADRs**

Although the low rate of torsades-de-pointes reported for ofloxacin compared to other fluoroquinolones, its use in patients with prolonged QT interval cautioned.<sup>34</sup> Both syncope and tachycardia attributed to the cardiovascular side effects of ofloxacin induced dysarrhythmia.<sup>34</sup>

### **Renal ADRs**

Acute renal failure due to ofloxacin reported in 1995.<sup>35</sup> It induced nephrogenic diabetes insipidus in a young patient with bilateral lobar pneumonia-acquired secondary to influenza infection.<sup>36</sup>

### **Hematologic ADRs**

A 9-year-old girl reported hemoglobinuria due to ofloxacin.<sup>37</sup> It induced leucopenia in Malaria patient when given for acute gastroenteritis with *E. coli*.<sup>38</sup>

### **Other ADRs**

Ofloxacin inhibited the bacterial nitrite reduction.<sup>39</sup> It induced the photo-onycholysis in the past.<sup>39</sup>

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

### **REFERENCES**

1. Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *Br J Clin Pharmacol.* 2001 Jul;52(1):77-83.
2. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *Br J Clin Pharmacol.* 2008 Feb 1;65(2):210-6.
3. Center Watch. Floxin Tablets New FDA Drug. Available at: <http://www.centerwatch.com/drug-information/fda-approved-drugs/drug/212/floxin-tablets-ofloxacin-tablets>. Accessed on 2018 May 25.
4. Jüngst G, Mohr R. Side effects of ofloxacin in clinical trials and in post marketing surveillance. *Drugs.* 1987 Oct 1;34(1):144-9.
5. Guay DR, Opsahl JA, McMahon FG, Vargas R, Matzke GR, Flor S. Safety and pharmacokinetics of multiple doses of intravenous ofloxacin in healthy volunteers. *Antimicrob Agents Chemotherap.* 1992 Feb 1;36(2):308-12.
6. Gu YM, Chen XY, Wang YQ. Anaphylactic shock in a boy after taking oral ofloxacin. *Chi J Pediatr.* 2005 Aug;43(8):607.
7. Wilton LV, Pearce GL, Mann RD. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. *Br J Clin Pharmacol.* 1996 Apr 1;41(4):277-84.
8. Dan M, Samra Z. Clostridium difficile colitis associated with ofloxacin therapy. *Am J Med.* 1989 Oct 1;87(4):479.
9. Blomer R, Bruch K, Krauss H, Wacheck W. Safety of ofloxacin-adverse drug reactions reported during phase-II studies in europe and in Japan. *Infection.* 1986 Jul 1;14(4):S332-4.

10. Upton C. Sleep disturbance in children treated with ofloxacin. *BMJ*. 1994;309(6966):1411.
11. Jüngst G, Mohr R. Overview of postmarketing experience with ofloxacin in Germany. *J Antimicrob Chemotherap*. 1988 Jul 1;22(Supplement\_C):167-75.
12. Walton GD, Hon JK, Mulpur TG. Ofloxacin-induced seizure. *Ann Pharmacotherap*. 1997 Dec;31(12):1475-7.
13. Jeandel C, Laurain MC, Jouanny P, Penin F, Vespignani H. Status epilepticus induced by ofloxacin. *Internal Medicine J*. 1994 Mar;15(3):218-9.
14. Fennig S, Mauas L. Ofloxacin-induced delirium. *J Clin Psychia*. 1992; 53(4):137-8.
15. Getenet JC, Croisile B, Vighetto A, Grochowicki M, Goudable B, Aimard G, et al. Idiopathic intracranial hypertension after ofloxacin treatment. *Acta Neurol Scand*. 1993 Jun;87(6):503-4.
16. Thomas RJ, Reagan DR. Association of a tourette-like syndrome with ofloxacin. *Ann Pharmacother*. 1996;30(2):138-40.
17. Fredy IC, Krishnaveni YA, Lohith KB PP. Case report: ofloxacin induced - angioedema. *World J Pharm Pharm Sci*. 2015;5(1):1217-20.
18. Huminer D, Cohen JD, Majadla R, Dux S. Hypersensitivity vasculitis due to ofloxacin. *BMJ*. 1989 Jul 29;299(6694):303.
19. Tsuda S, Kato K, Karashima T, Inou Y, Sasai Y. Toxic pustuloderma induced by ofloxacin. *Acta Dermatovenereol*. 1993 Oct;73(5):382-4.
20. Kawada A, Himura M, Noguchi H, Banba K, Ishbashi A, Banba H, et al. Fixed drug eruption induced by ofloxacin. *Contact Dermatitis*. 1996 Jun;34(6):427-38.
21. Melde SL. Ofloxacin: a probable cause of toxic epidermal necrolysis. *Ann Pharmacotherap*. 2001 Nov;35(11):1388-90.
22. Nettis E, Giordano D, Pierluigi T, Ferrannini A, Tursi A. Erythema multiforme-like rash in a patient sensitive to ofloxacin. *Acta Derm Venereol*. 2002;82(5):395-6.
23. Dave S, Thappa DM, Nori AV, Jayanthi S. A rare variant of erythema nodosum leprosum: a case report. *Dermatol Online J*. 2003 Jan 1;9(5).
24. Sousa AL, Stefani MM, Pereira GA, Costa MB, Rebello PF, Gomes MK, et al. Mycobacterium leprae DNA associated with type 1 reactions in single lesion paucibacillary leprosy treated with single dose rifampin, ofloxacin, and minocycline. *Am J Tropical Med Hygiene*. 2007 Nov 1;77(5):829-33.
25. Özdemir D, Korkmaz U, Şahin İ, Şencan İ, Kavak A, Küçükbayrak A, et al. Ofloxacin induced Sweet's syndrome in a patient with Crohn's disease. *J Infection*. 2006 May 1;52(5):e155-7.
26. van der Linden PD, Sturkenboom MC, Herings RM, Leufkens HM, Rowlands S, Stricker BH. Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Internal Med*. 2003 Aug 11;163(15):1801-7.
27. Schwald N, Debray-Meignan S. Suspected role of ofloxacin in a case of arthralgia, myalgia, and multiple tendinopathy. *Rev Rheumatism*. 1999;66(7-9):419-21.
28. Hsiao SH, Chang CM, Tsao CJ, Lee YY, Hsu MY, Wu TJ. Acute rhabdomyolysis associated with ofloxacin/levofloxacin therapy. *Ann Pharmacotherap*. 2005 Jan;39(1):146-9.
29. Ridzon R, Meador J, Maxwell R, Higgins K, Weismuller P, Onorato IM. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. *Clin Infectious Dis*. 1997 Jun 1;24(6):1264-5.
30. Jones SF, Smith RH. Quinolones may induce hepatitis. *Br Med J*. 1997 Mar 22;314(7084):869.
31. Carro PG, Huidobro ML, Zabala AP, Vicente EM. Fatal subfulminant hepatic failure with ofloxacin. *Am J Gastroenterol*. 2000 Jun;95(6):1606.
32. Blum A. Ofloxacin-induced acute severe hepatitis. *South Med J*. 199;84(9):1158.
33. 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(6):759-60.
34. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy. J Human Pharmacol Drug Therapy*. 2001 Dec 1;21(12):1468-72.
35. Espiritu J, Walton T. Acute renal failure due to ofloxacin. *West Virginia Med J*. 1995 Jan;91(1):16.
36. Bharani A, Kumar H. Diabetes insipidus induced by ofloxacin. *BMJ*. 2001 Sep 8;323(7312):547.
37. Nepali N, Kalam A, Subish P, Khan GM. Hemoglobinuria due to ofloxacin in a 9 year old child- a case report. *Pharmacol Online*. 2007;1:1-5.
38. Tripathy S, Adhya A. Ofloxacin induced leucopenia in complicated falciparum malaria: a case report. *Cases J*. 2009 Dec;2(1):7097.
39. Dokianakis SN, Kornaros ME, Lyberatos G. On the effect of pharmaceuticals on bacterial nitrite oxidation. *Water Sci Technol*. 2004 Sep 1;50(5):341-6.

**Cite this article as:** Kamdi AS, Kokane SD, Bohra PN, Kalambe SM. Systematic review of adverse drug reactions of ofloxacin. *Int J Basic Clin Pharmacol* 2018;7:2277-80.