Systematic review of adverse drug reactions of ofloxacin

Amit S. Kamdi¹, Sarika D. Kokane⁎, Pankaj N. Bohra³, Suvarna M. Kalambe⁴

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.¹ Average incidence of ADRs from all drugs in India is 9.8%.² Skin is the most common organ system affected followed by Central Nervous System and Gastrointestinal Tract.³ 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. 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.

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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 C₁₈H₂₉FN₃O₄, it is approved by FDA in January 1997 to treat pelvic inflammatory disease (PID).³

Common side effects of ofloxacin are insomnia, nausea, vomiting, diarrhea, and headache. Incidence rate of adverse drug reactions (ADRs) to ofloxacin is 4.27%.⁴ About 11% experienced the side effects of ofloxacin use in clinical trials.⁵ Discontinuation of drug therapy because of side effects occurred in 4% patients.⁵ 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.⁶

**Gastrointestinal (GI) ADRs**

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

**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.⁹ However, these findings were not consistent as the post marketing surveillance in 1.5 million patient population showed that Nervous system ADRs ranked 1st followed by hypersensitivity reaction and GI disturbances in order of frequency.⁴ Sleep disturbances were common in children receiving ofloxacin treatment.¹⁰ The rare adverse reactions like hallucination, psychosis and shock also reported in Germany in post marketing experience.¹¹

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

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

Musculoskeletal ADRs

The complete rupture of Achilis tendon happened with elderly patients with concurrent administration of corticosteroid and ofloxacin.26 Myalgia, arthralgia and multiple tendonopathy noted in 53-year-old woman exposed to ofloxacin.27 Systematic review of observational cohort studies comparing different fluoroquinolones threw light on the relationship of tenosynovitis with ofloxacin use.28 The marked increase in serum myoglobin and presence of urine myoglobin confirmed the association of acute rhabdomyolysis with ofloxacin.29

Hepatobiliary ADRs

Asymptomatic hepatitis observed in resistant case of pulmonary tuberculosis, treated with the alternative therapy with Pyrazinamide and ofloxacin.30 Moderate increase in liver enzymes noted in patient with Wegener’s Granulomatosis treated with ofloxacin for the productive cough.30 A 70-year-old man having prostatic adenoma with urinary tract infection treated with ofloxacin developed fatal sub-fulminant hepatic failure.31 Acute severe hepatitis by ofloxacin described in 1991.32 Sensitized lymphocytes to trimethoprim/sulfamethoxazole and ofloxacin demonstrated in patient of cholestatic hepatitis, signifying strong relationship of ofloxacin with cholestatic hepatitis.33

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.34 Both syncope and tachycardia attributed to the cardiovascular side effects of ofloxacin induced dysrrhythmia.34

Renal ADRs

Acute renal failure due to ofloxacin reported in 1995.35 It induced nephrogenic diabetes insipidus in a young patient with bilateral lobar pneumonia-acquired secondary to influenza infection.36

Hematologic ADRs

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

Other ADRs

Ofloxacin inhibited the bacterial nitrite reduction.39 It induced the photo-onycholysis in the past.39

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REFERENCES