INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

BILATERAL PEDAL EDEMA, HEPATOTOXICITY AND CUTANEOUS REACTIONS DUE TO OFLOXACIN-A CASE REPORT

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ARTICLE INFO

Article history

Received 28/08/2019

Available online 30/09/2019

Keywords

Ofloxacin, Edema, Hepatotoxicity, Cutaneous Reactions, Naranjo's Causality Assessment Scale.

ABSTRACT

Bilateral pedal edema is a common adr associated with many medications. If left untreated, it can pose various complications and interfere with the normal activities of daily living. To the best of our knowledge, there is no data yet published on bilateral pedal edema due to Ofloxacin. Hepatotoxicity and cutaneous reactions to drug therapy are the major health problems and identifying and omitting the offending drug at the earliest holds the keystone in management and prevention from a more severe form. We report a case of Ofloxacin induced bilateral pedal edema, hepatotoxicity and cutaneous reactions in a 72 year old Indian male that got resolved after withdrawal of the drug. The adverse reaction assessment was done using "Naranjo's causality assessment scale" which showed a 'probable' type of reaction with Ofloxacin in edema, cutaneous reactions and hepatotoxicity.Drug induced reactions are major threat for patient's quality of life and often go unnoticed.This case emphasizes that all clinicians should be aware of Ofloxacin induced adr's and it should be added to the list of drugs associated with the development of bilateral pedal edema.

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*Please cite this article in press as **Talha Jabeen** et al. Bilateral Pedal Edema, Hepatotoxicity and Cutaneous Reactions Due to Ofloxacin-A Case Report. Indo American Journal of Pharmaceutical Research.2019:9(08).*

INTRODUCTION

Ofloxacin, a fluorinated quinolone ,is a pyridine carboxylic acid derivative with rapid bactericidal activity against Gram-negative bacteria, many Gram positive bacteria and some anaerobes.[1]The drug was approved by FDA in December 1990 with good clinical efficacy in the treatment of urinary tract infections, respiratory tract infections, prostatitis, enteric fever and skin and soft tissue infections caused by susceptible organisms.[2] Because of its broader spectrum of activity, good safety profile and tolerability among the patients, It was the 299th most prescribed medication in the united states with more than a million prescriptions in the year 2016.[3] The primary target of Ofloxacin is DNA gyrase (topoisomerase 2) ,an essential bacterial enzyme that maintains the superhelical structure of DNA.DNA gyrase is required for replication, transcription, deactivation, and repair of bacterial DNA .[1]The common adverse effects involve the gastro intestinal system(<7%) , followed by central nervous system(<5%) and hypersensitivity reactions(2%).[4]

Pedal edema characterized by the accumulation of fluid in the feet and lower legs is an uncommon adverse effect from Ofloxacin therapy and could be overlooked by the physicians when compared to other side effects.Complications include painful swelling, infections, scarring and ulcerations of the infected area with interference in the normal activities of daily living.Immediate identification and withdrawal of the culprit agents are very much essential.

Hepatotoxicity due to drugs is the singlemost cause of US FDA non approval of drugs and withdrawal of drugs from market after approval.The hepatotoxicity due to fluoroquinolones as a class is 2-3%,usually in the form of transient elevation of transaminase levels, while cholestatic jaundice and hepatitis have been less common .[5], [6].If the underlying cause for toxic liver disease is not identified, it can go into more severe form or even death. Ofloxacin has been lesser known to cause livet toxicity.In our case, the amelioration of liver injury after the drug withdrawal indicates its prompt role in pathways leading to liver injury.

Drug induced cutaneous adverse effects are a major health problem and requires early detection and immediate withdrawal of the offending agent.

Here we describe a case of oral Ofloxacin induced bilateral pedal edema, mild hepatotoxicity with cutaneous involvement.

CASE REPORT

A 72-year-old man came to the hospital with complaint of bilateral pedal edema since 3 days and was admitted to intensive care unit. On Physical examination, the patient posed bilateral swelling of feet and lower leg with ulcer and blisters on left foot which was insidious in onset, gradually progressed and pitting in nature. His vitals include BP:160/80 mmHg , PR:88/min ,Temp:Afebrile. There was no erythema and organomegaly. The patient revealed he was taking Tab.Oflomac (Ofloxacin 200 mg) since 5 days which was prescribed by a local practitioner for typhoid. His cutaneous examination revealed rashes and blisters on his neck which were ignored by him as a complication of typhoid. His laboratory data (Table. 1) showed complete blood count with TLC:16,500/cumm, ESR:20mm/1stHR; abnormal hepatic profile with AST:56 IU/L, ALT:68 IU/L , ALP:130 IU/L, Direct Bilirubin:0.6 mg/dl and serum electrolytes with K^+:5.5mmol/L. The drug Ofloxacin was immediately withdrawn and he was given treatment with Ceftriaxone 1gm IV/BD , Metronidazole 500mg IV/BD, Pantoprazole 40 mg IV/OD with Tab. Montelukast +Levocetirizine 10/5 mg OD, Tab, Atorvastatin 10 mg OD, Tab. Hydrochlorothiazide+Telmisartan 12.5/80 mg OD and Tab.Metoprolol 50 mg OD and was advised lower limb elevation. He was a known hypertensive sine 10 years and was on medication: Tab. hydrochlorothiazide and telmisartan 12.5/80 mg OD and Tab.Metoprolol 50 mg .On 3rd day, Ceftriaxone was replaced by Piperacillin+Tazobactum 4/0.5 gm IV/TID . Following the cessation of Ofloxacin, his edema and skin rashes got resolved on the 3rd day. Further, the elevated liver enzymes was also noted to be normalize. On the 4th day, he was discharged home in a stable condition.

Table 1:Laboratory parameters of the patient on Day 1 and Day 3 after admission.

Parameters	Values on Day 1	Values on Day 3	Normal Values
TLC (/cumm)	16,500	9,200	4,000-11,000
ESR (MM/1st HR)	20	13	5-10
AST (IU/L)	56	36	5-34
ALT (IU/L)	68	38	0-40
ALP (IU/L)	130	110	15-112
Direct Bilirubin(mg/dl)	0.6	0.1	0-0.2

TLC: Total Leucocyte Count, ESR: Erythrocyte Sedimentation Rate, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP : Alkaline Phosphatase

DISCUSSION

Pedal edema has been reported as an adverse effect from many medications including antihypertensive drugs, non steroidal anti-inflammatory drugs, antidepressants, anticancer agents, alpha adrenergic antagonists and others.[7] Among Fluoroquinolone antimicrobials, bilateral pedal edema has been reported with Levofloxacin. [8] We report the first case of bilateral pedal edema due to Ofloxacin.

Edema is an accumulation of fluid in the extracellular compartment, which results in increase in the volume of interstitial fluid. Although there are many pathological mechanisms underlying edema, in patients over 50 years of age the most common cause is venous insufficiency[9] in which blood does not return to the heart efficiently from the peripheral areas of the body. As reported by Gosnell A et al and Hyman DA et al, Stasis could also be the main pathomechanism.[10],[11] Further, due to differential susceptibility of individuals, development of Fluoroquinolones induced ADR'S are highly unpredictable. In our case, the presence of peripheral edema could be attributed to the use of Ofloxacin since edema disappeared when the drug was withdrawn.

The patient LFT showed a mild elevation in the levels of AST, ALT, ALP and Direct Bilirubin.AST and ALT activities are widely used as key biochemical indicators for severity of liver injury. Though in our case there is a mild risk for hepatotoxicity, considering the previous published reports by Jones SE, et al "Quinolones may induce hepatitis" [6] and Gonzalez Carro P,et al "Fatal subfulminant hepatic failure with ofloxacin",[12] we thought hepatotoxic profile of Ofloxacin should also be mention. Oxidative stress is thought to play a key role in fluoroquinolones induced hepatotoxicity. Oxidative stress represent an imbalance between oxidants and antioxidants therby causing damage to macromolecules such as DNA and mitochondrial depletion in the liver.[13]

Further, in our patient development of rashes and blisters on neck got subsided after the drug withdrawal. Ramani YR et al has reported "Ofloxacin Induced Cutaneous Reactions In Children" where he reported three different variants of reactions associated with oral Ofloxacin in children. In all the three cases, resolution of symptoms after the withdrawal of drug is seen. Genetic association of HLA alleles and a deficient hydroxylase enzyme are responsible for immune reactions and hypersensitivity. [4]

In our case, the patients adverse effects got resolved after drug discontinuation. Treatment was done using broader spectrum antibiotics-Ceftriaxone, Metronidazole and Piperacillin to treat infected ulcer and prevent complications. Antihistanine i.e. Levocetirizine and leukotriene receptor antagonist i.e, Monteleukast are given to relieve itching and allergy.The high potassium levels during serum electrolytes estimation are contributed to his previous medications which include angiotensin receptor blocker and beta blocker.

The adverse drug reaction assessment was done using "Naranjo's casualty assessment scale" which showed a 'probable' type of reaction with ofloxacin in causing pedal edema,cutaneous reactions and hepatotoxicity.

CONCLUSION

As antimicrobial therapy involving Ofloxacin is highly in practice in developed as well as developing countries, therefore it is imperative to report Ofloxacin-induced ADRs for the advancement of medical knowledge on prevalence, diagnosis, susceptibility and treatment outcomes which ultimately improves quality of care provided to the patient's .Further, the drug therapy should be essentially monitored in geriatrics and pediatrics where there is much more likelihood of development of edema and cutaneous reactions.The area of Ofloxacin safety requires a high volume of research to be done and should also focus on the alternative better treatment options.

ACKNOWLEDGEMENT

The author is grateful to the faculty of Bhaskar Pharmacy College and Bhaskar General Hospital, Moinabad, Hyderabad for their support.

ABBREVIATIONS

adr/ADR	:adverse drug reaction
FDA	:food and drug administration
DNA	:deoxyribose nucleic acid
BP	:blood pressure
PR	:pulse rate
Temp	:temperature
K^+	:potassium
TID	:thrice a day
BD	:twice daily
OD	:once daily
LFT	:liver function test
HLA	:human leukocyte antigen
TLC	:Total Leucocyte Count,
ESR	: Erythrocyte Sedimentation Rate
AST	:Aspartate Aminotransferase,
ALT	: AlanineAminotransferase,
ALP	:Alkaline Phosphatase

CONFLICT OF INTEREST

There is no conflict of interest.

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