



Research Article

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CIPROFLOXACIN INDUCED CUTANEOUS VASCULITIS: A CROSS REACTION TO NORFLOXACIN

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ABSTRACT

A 30 years old male patient was admitted to the dermatology department of Sagar Hospitals with chief complaints of lesions over the hands, lips and at the back of the body and also mild pedal edema noted on 2nd day after the patient had administered Tab paracetamol & Tab Ciprofloxacin for the treatment of febrile illness. The Patient had a history of the same reaction twice for the Tab Norfloxacin but never experienced this Adverse Drug Reaction (ADR) to Ciprofloxacin before using Norfloxacin. Upon general examination the patient was treated with Tab Hydralazine, Tab Prednisolone and Calamine lotion after the withdrawal of drug Ciprofloxacin. Dechallenge of Ciprofloxacin showed that there was an improvement in his symptoms indicating drug induced vasculitis. The causality assessment was done by using the Naranjo's adverse drug reaction probability scale and the score was 9 indicating highly probable relationship between the ADR and the drug, moderate in severity according to Hartwig severity assessment scale. From dechallenge and rechallenge information the patient was concluded to be allergic to Ciprofloxacin and Norfloxacin. In conclusion patient may need to avoid the class of fluoroquinolones since there is a cross reaction to Norfloxacin. Physicians and other healthcare professionals should maintain a high index of suspicion to closely monitor the cases of cutaneous vasculitis due to Ciprofloxacin and Norfloxacin since these drugs are commonly prescribed and well tolerated. Furthermore, this ADR can be prevented in future only by providing the awareness, counseling and also by issuing an ADR alert card to the patient.

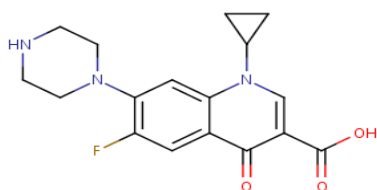
Keywords: Cutaneous Vasculitis, Ciprofloxacin, Norfloxacin, Cross Reaction

INTRODUCTION

Cross sensitivity is defined as sensitivity to one substance that renders an individual sensitive to other substances of similar chemical structure.¹ Fluoroquinolones have been used for more than 30 years to treat various illnesses such as urinary and respiratory tract infections and are well tolerated.² Recently, utilization of fluoroquinolones had led to severe allergic reactions and cross sensitivity reactions.³ In the last years, immediate reactions to quinolone antibiotics have been observed with increasing frequency, mainly urticaria, angioedema, and shock.⁴

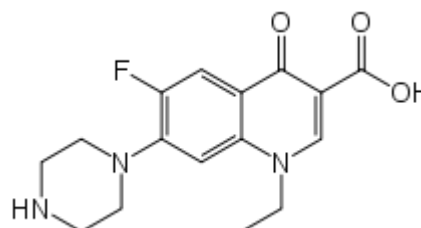
Fluoroquinolones are classified into two groups based on antimicrobial spectrum and pharmacology. Older group: Ciprofloxacin, Norfloxacin and ofloxacin. Newer group: delafloxacin, gemifloxacin, levofloxacin and moxifloxacin.⁵ Ciprofloxacin and Norfloxacin are the most common drugs causing hypersensitivity reactions, while levofloxacin is the least common with incidence of 1 per million population.⁶

Ciprofloxacin (C₁₇H₁₈FN₃O₃)



Ciprofloxacin is 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid. Ciprofloxacin is a member of the antibiotic class Quinolones. The presence of a fluorine group at position 6 of the molecule places it into a subclass called the

Fluoroquinolones. The bactericidal action of Ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV.⁷ It is a broad spectrum antibiotic that is widely used in clinical practice for many common afflictions including urinary tract and respiratory tract infections. It is effective against many aerobic Gram-negative organisms including several Streptococcus, Staphylococcus strains and several Gram-positive organisms including Escherichia coli.⁸ It is well absorbed from GIT with 70% bioavailability and follows hepatic metabolism. 40-50% of the drug is eliminated through urine with a half-life period of 4 hours and renal clearance of about 300ml/min.⁹ Ciprofloxacin is one of the most commonly used antibacterial agents with relatively few side effects. Serious adverse reactions reported with Ciprofloxacin are rare with an incidence of 0.6.¹⁰ A few cases of Ciprofloxacin-induced photosensitivity, hypersensitivity, anaphylaxis, vasculitis, erythema multiforme and Steven-Johnson syndrome or toxic epidermal necrolysis have been reported so far.¹¹ Frequently reported immediate hypersensitive reactions are urticaria, anaphylactic shock, rashes and erythema. Delayed type of reactions includes presumably IgE or T cell mediated reactions in about 2-3% of population.^{12, 13}



Structure of Norfloxacin

Norfloxacin is 1-ethyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3 quinolone carboxylic acid. It is a synthetic, broad-spectrum bactericidal agent which inhibits bacterial deoxyribonucleic acid synthesis. The fluorine atom at the 6 position provides increased potency against gram-negative organisms and the piperazine moiety at 7th position is responsible for antipseudomonal activity. It is widely used for the treatment of infections caused by micro-organisms susceptible to Norfloxacin, including urinary tract infections (uncomplicated and complicated) and gastrointestinal infections (e.g. shigellosis, traveler's diarrhea). Norfloxacin absorption is rapid and is eliminated through metabolism, biliary excretion, and renal excretion. Renal excretion occurs by both glomerular filtration and tubular secretion as evidenced by the high rate of renal clearance (approximately 275 ml/min).¹⁴ Frequently reported unwanted reactions were swelling or tearing of (rupture) a tendon, permanent nerve damage, headache with chest pain and severe dizziness, fainting, fast or pounding heartbeats, dark urine, clay-colored stools, muscle weakness, diarrhea depression, confusion, hallucination, seizure.¹⁵ Drug induced skin reactions are common, accounting for 30% for all reported adverse drug reactions. Some types of drug reaction can cause systemic as well as skin involvement, affecting the hepatic, hematological and lymphatic systems.¹⁶

Some drugs have the ability to alter the skin and its associated structures (hair and nails) function among which vasculitis is the most commonly characterized skin inflammation in vessel walls and clinically palpable purpuric lesions most commonly found on the lower limbs. Cutaneous vasculitis without other organ involvement is the rule, but systemic involvement, such as renal, can occasionally occur. Drugs are the cause of approximately 10% of cutaneous vasculitis cases and should be considered in any patient with small vessel vasculitis.¹⁷

Here there is a case of cutaneous vasculitis associated with Ciprofloxacin administration which was a cross sensitivity reaction to Norfloxacin.

CASE REPORT

A 30 years old male patient was admitted to the Dermatology Department of Sagar Hospitals with chief complaints of lesions over the hands, lips and at the back of the body and also mild pedal edema on 2nd day (Figure 1 & Figure 2) after the patient had administered Tab paracetamol & Tab Ciprofloxacin for the treatment of febrile illness and generalized weakness. Upon physical and general examination, patient was conscious & oriented; febrile; with mild pedal edema; RR-22cpm; Pulse Rate-85 bpm; B.P.-125/80mmHg; Hb-11.5gm/dl; WBC-12500cell/cumm; ESR-30mm/hr. On systemic examination, CVS-S1 & S2 (+), RS-NVBS. The patient was treated with Tab Cetrizine 10mg, Tab Prednisolone 20mg and Calamine lotion after the withdrawal of the drug Ciprofloxacin. Patient had a history of the same reaction, twice for Tab Norfloxacin but never experienced this Adverse Drug Reaction (ADR) to Ciprofloxacin before using Norfloxacin. Based on the above information here we have suspected it as a possible cross sensitivity reaction/ADR of Ciprofloxacin as shown in Fig (3 and 4). Patient was further referred to General Medicine to confirm the ADR/Cross sensitivity reaction. Upon analysis it is found that the patient had suffered from cutaneous vasculitis due to the administration of Ciprofloxacin. Certain literature also supports that 2% chances of

hypersensitivity reactions are associated with this drug. In order to confirm the relation between the drug and the following event De challenge (withdrawal of the drug) was performed after which the reaction was subsided.

Causality and severity Assessment: The causality assessment was done using the Naranjo's adverse drug reaction probability scale and the score was 9 indicating highly probable relationship between the ADR and drug. The reaction was moderate in severity according to Hart-wig severity assessment scale.

RESULTS AND DISCUSSION

In medicine, a case report is a detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of an individual patient. Case reports may contain a socio demographic profile of the patient, but usually describe an unusual or novel occurrence. Here case report was discussed on cross sensitivity between Ciprofloxacin and Norfloxacin.

Patient had a history of first hypersensitivity reaction (within 8 hours) to Norfloxacin and was not allergic to Ciprofloxacin. In this case report, patient had experienced immediate hypersensitivity reaction (within 2 hours) to Ciprofloxacin after exposure to Norfloxacin, only which proved the cross sensitivity between Ciprofloxacin and Norfloxacin.

All fluoroquinolones have similar core structure (4-oxo-1, 4-dihydroquinoline ring) with fluorine atom attached at position 6 except, first generation fluoroquinolones-quinolone and nalidixic acid. Norfloxacin, a second generation fluoroquinolone, is the result of replacement at C-7 methyl side chain with piperazine group, while replacement of N-1 ethyl group of Norfloxacin with cyclopropyl group generates Ciprofloxacin. Ciprofloxacin and Norfloxacin have similar core structure this is may be the reason for cross-sensitivity in this reaction. This patient may have similar hypersensitivity reactions to other fluoroquinolones. In such case it is advisable to avoid fluoroquinolones and shift to other class of antimicrobials to treat infectious conditions.¹⁸ Detection of IgE antibodies in blood and skin tests were helpful to identify such cross reactions and prevent the same.¹⁹ 54.5% immediate type of reactions to fluoroquinolones are IgE mediated and occurs due to binding of IgE to 7th position of core structure of fluoroquinolones.²⁰

Additionally, the results of previous In vitro study showed that Ciprofloxacin and Norfloxacin could stimulate histamine release.²¹ To our knowledge, there was only one case report on cross sensitivity between Ciprofloxacin and Norfloxacin.²² But there were many case reports on cross immediate hypersensitivity reaction between Ciprofloxacin and levofloxacin.^{23,24}

CONCLUSION

Subsequently the patient was diagnosed to have Cutaneous Vasculitis and further confirmed to have been allergic to Ciprofloxacin and Norfloxacin (probably most Fluoroquinolones). These drugs are commonly prescribed and well tolerated. Furthermore, this ADR can be prevented in future, only by providing the awareness, counseling and also by issuing an ADR alert card to the patient. Physicians and other healthcare professionals should maintain a high index of suspicion to closely monitor the cases of cutaneous vasculitis due to Ciprofloxacin and Norfloxacin.



Figure: 1 Rashes over legs



Figure 2 Lesions over hands

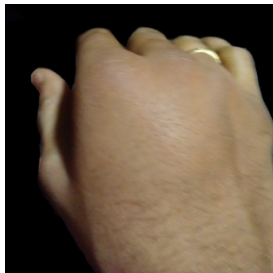


Figure 3 Non pitting edema on the wrist



Figure 4 Redness and swelling on the feet

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