

**HEMOGLOBINUREA DUE TO OFLOXACIN  
IN A 9 YEAR OLD CHILD- A CASE REPORT**

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**Summary**

Ofloxacin is a commonly used antimicrobial agent. It is known to cause nausea, vomiting, diarrhea, dizziness, headache, restlessness and pruritis. Hemoglobinurea due to ofloxacin is not reported in the literature. We hereby report ofloxacin induced hemoglobinurea in 9 year old child who underwent treatment for enteric fever, giardiasis and amoebiasis. Patient's treatment was started with Tab. Ofloxacin 200 mg twice daily, Syrup (Paracetamol 125 mg + Ibuprofen 100 mg / 5ml )15ml four times daily, and Syrup (Metronidazole100 mg + diloxanide furate 125 mg / 5ml) 16 ml thrice daily. After 3 days of medication, patient complained dark colour urination following which hemoglobin 4+ was found in urine. A presumed diagnosis of ofloxacin induced hemoglobinuria was made in absence of other cause. Ofloxacin was changed to Inj. Ceftriaxone following which urine colour changed to normal and hemoglobinurea subsided. The causality assessment as per the Naranjo algorithm established a 'probable' association between the hemoglobinurea and ofloxacin (Naranjo Score 6).

**Keywords:** Hemoglobinuria, Ofloxacin, Typhoid

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### Introduction

Ofloxacin is a synthetic fluoroquinolone antimicrobial agent with an expanded spectrum of activity and increased antibacterial potency compared to non-fluoroquinolone quinolones [1]. It is indicated for urinary tract infections, proctitis, sexually transmitted diseases like gonorrhoea, trachomatis, gastrointestinal and abdominal infections like traveler's diarrhea, enteric fever, respiratory tract infections, soft tissue infections, prophylaxis of anthrax etc. Ofloxacin acts by inhibiting the A sub unit of DNA gyrase (topoisomerase), which is essential for bacterial DNA Synthesis [2,3]. Most common adverse effects includes nausea, vomiting, diarrhea, dizziness, headache, restlessness and rash, pruritis and rarely blood disorders like eosinophilia, leucopenia and thrombocytopenia [4]. Hemoglobineuria due to ofloxacin is not reported in the literature. We hereby report a case of Ofloxacin induced hemoglobineuria in 9 year old children underwent treatment for enteric fever with giardiasis and amoebiasis. We also carried out the causality assessment of the ADR (Adverse Drug Reaction) as per the Naranjo algorithm [5].

### Case report

A 9 old year female child presented in Emergency department of Dhulikhel hospital, Dhulikhel, Nepal on 27<sup>th</sup> July 2006 with complaints 3-4 episodes of diarrhea per day for the past 3-4 days, 3-4 episodes of vomiting in a day for 2 days and high grade fever with sweating since 3 days. On examination, patient was ill looking. Per abdominal examination showed, palpable liver (2 cm in right mid clavicular line), soft, non-tender abdomen and chest was clear bilateral. Patient did not have any anemic symptoms.

Stool examination showed cyst and trophozoites of *G. lamblia* and cyst of *E. histolytica*. The total leucocytes count was 9000 cells per cumm and the differential count showed neutrophils 88% and lymphocyte 12%. The random blood sugar 76 mg/dl, urea 21 mg/dl, serum creatinine 0.5 mg/ dl, sodium 134 and potassium 3.3. Urine examination revealed pH - acidic, transparency - clear, pus cell - 2-3, epithelial cell - 0-1, RBC - nil, crystal - nil and Cast - negative. *Salmonella para-typhi* "A" was isolated in blood culture after 168 hours.

Patient was admitted in the pediatric ward with the diagnoses of enteric fever, giardiasis and amoebiasis. Patient's treatment was started with Tab. Ofloxacin 200 mg twice daily, Syrup (Paracetamol 125 mg + Ibuprofen 100 mg / 5ml) 15ml four times daily, and Syrup (Metronidazole 100 mg + diloxanide furate 125 mg / 5ml) 16 ml thrice daily. After 3 days of medication, patient complained having of dark colour urination. So, hematology and urine sample were send to laboratory to find out the causative factors. The hematological finding revealed reticulocyte 1% and platelets 320000 cells per cumm. The glucose-6-phosphate Dehydrogenase (G6PD) deficiency status was not carried out. We also did not check the hemoglobin status of the patient as there was no features suggestive of anemia. Biochemical test showed serum creatinine-0.4 mg/dl, sodium-139 mmol/l and potassium-3.9 mmol/l and urine analysis found that colour-deep yellow, PH - acidic, transparency - clear, albumin - nil, pus cell - 2-4 / HPF, epithelial cell -nil, crystal - negative and in special test it was found that hemoglobin '4+' in urine.

Since these symptoms developed after 3 days of Ofloxacin and in absence of other cause and there are also literature reports of hematuria due to fluoroquinolones, [6] a presumed diagnosis of Ofloxacin induced hemoglobineuria was made. Ofloxacin was changed to Inj. Ceftriaxone 1 gm IV twice daily. Three days after switching to Ceftriaxone the urine colour changed to normal and urine examination at the time of discharge revealed that colour-light yellow, pH-acidic, transparency-clear, sugar and albumin -nil, pus cells – up to 2, RBC-nil, cast-negative, crystal-nil and hemoglobin in urine was negative. At this time the patient was on all previous drugs except Ofloxacin. Since, the symptoms disappeared after stoppage Ofloxacin though the patient was on all previous medications; a confirmative diagnosis of Ofloxacin induced hemoglobineuria was made. We carried out the causality assessment of the ADR as per the Naranjo algorithm and was found to be “Probably” (Naranjo Score-6) associated with the use of Ofloxacin [5].

### **Discussion**

Drug induced hematologic disorders are very common. Frequently reported ones are agranulocytosis (Beta-lactam antibiotics, Carbamazepine, Chloramphenicol, Clomipramine etc.), Hemolytic anemia (Phenobarbitone, Phenytoin, Ciprofloxacin etc.), megaloblastic anemia (Chloramphenicol, Cyclophosphamide, Phenytoin etc.) and thrombocytopenia (Phenobarbitone, Chlorpromazine, Ethambutol etc) [7]. Drugs can also cause fatal blood toxicity like aplastic anemia (Carbamazepine, Diclofenac, Chloramphenicol etc). The severity of the hematological ADRs can range from mild symptom to life threatening aplastic anemia.

Hemoglobinuria is a condition in which free hemoglobin is found in urine which is characterized by cola- or tea-colored urine; it may also cause the urine that is dark red, maroon, or even bright cherry red. However, the abundant red cells finding by microscopical examination suggests hematuria which is different from hemoglobineuria [8,9]. The common causes of hemoglobineuria are infectious diseases, neoplasms, exposure to the cold etc. There are also reports of hemoglobinuria associated with typhoid fever [10, 11]. Our patient also had typhoid fever at the time of development of hemoglobinuria. However, we ruled out typhoid as the cause because the typhoid status of patient was diagnosed nearly after 7 days later and the ADR developed after 3 days of medications and subsided immediately after stopping Ofloxacin. Drug induced hemoglobinuria is very rare. The most common drugs causing hemoglobineuria are Chloroquine, Rifampicin, Primaquine etc [5.] Haemoglobinurea was also seen in a patient taking Suprofen [12] which is a drug similar to Ibuprofen. However, in our case though the patient was on Ibuprofen at the time of development of hemoglobineuria, we could not attribute this to Ibuprofen. The major reason being that hemoglobineuria vanished immediately after stopping Ofloxacin though the patient was on Ibuprofen. We could not find any report of hemoglobineuria due to Ofloxacin. In our case the hemoglobineuria subsided within a week. We could not locate the details regarding the usual time taken by the hemoglobineuria to stop when an offending agent is stopped. We also failed to test the G-6-PD deficiency status of the patient. In general, G6PD deficiency is the known causes for hemolysis by many drugs like Dapsone, Primaquine and Quinolones [13]. We also did not perform and tests to rule out the present hemolysis. However, the patient didn't exhibit symptoms such as icterus.

Usually hemoglobineuria is diagnosed by using lab studies like complete blood cell count (marked anemia), differential (high reticulocytes), review of the peripheral blood smear

(spherocytes), urine analysis (dark colour urine, presence of free hemoglobin), The D-L antibody test (the monospecific anti-C3 and IgG DAT, and the indirect antibody test are all useful in confirming a diagnosis), testing for underlying infectious diseases (tests for syphilis and various other viruses) [14]. In our patient, diagnosis was made based on special urine analysis which showed the presence of free hemoglobin. The special test which we used was rapid test card method where we used strips ('Combur Test' manufactured by Roche). The reliability of this method is considered very high and is the only method available at our hospital for checking the presence of hemoglobin in urine.

Management strategy for hemoglobineuria includes supportive care like strict avoidance of cold exposure and treatment of underlying cause like administer washed, warmed, packed RBC transfusions for life-threatening hemolysis and symptomatic anemia, treatment of infections, such as syphilis, treatment of neoplasms. Immunosuppressive drugs have been effective but should be restricted to progressive or idiopathic cases [15]. However, in our patient the hemoglobinuria subsided when the suspected drug was withdrawn and hence did not need any treatment. Avoiding chilling of exposed body parts or the extremities is essential to prevent recurrent episodes and patients should avoid activities that would increase their likelihood of being chilled, such as jogging outside in cold weather or at high altitudes [14].

### **Conclusion**

Ofloxacin is a broader spectrum antimicrobial used frequently in the treatment of many conditions. Although hematological adverse effects are rare with Ofloxacin, one should monitor the patients who are being prescribed with this drug. Many times Ofloxacin is used in management of typhoid fever and typhoid fever is a known cause of hemoglobinuria, this ADR gains importance. We also recommend that patient prescribed with Ofloxacin should be monitored for dark colorization of urine and upon occurrence the possible chance of hemoglobinuria should be ruled out. This ADR also reminds us that we should be extra cautious while prescribing fluoroquinolones in children, which is not approved by many authorities.

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