wjpmr, 2021,7(8), 259 – 262.

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Case Study

ISSN 2455-3301

WJPMR

FOSFOMYCIN INDUCED THROMBOCYTOPENIA: A CASE REPORT

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Article Received on 06/05/2021 **Article Revised on 27/05/2021** **Article Accepted on 17/06/2021**

ABSTRACT

This is a rare case presentation of fosfomycin induced thrombocytopenia. A 36-year-old patient with urosepsis having history of diabetes, hypertension, pancreatitis, renal failure and old CVA was presented with decline in thrombocytes count after administration of fosfomycin. The platelet counts were regained to normal after discontinuing the drug. Naranjo scale exhibits the reaction asa probable adverse effect.

KEYWORDS: Fosfomycin, Platelet Count, Thrombocytopenia, Adverse effects.

INTRODUCTION

Thrombocytopenia is a condition where the platelet count decreases than the normal range (150,000- 400,000 per microliter (or 150 - 400 x 109 per liter), and considered as mild if ≤ 50 lakhs/L, moderate if 30 to 50 lakhs /L, and severe if ≤ 30 lakhs /L.

Reduced platelets can lead to abate clotting after an injury, bruising and bleeding inside the tissues, manifested by petechial rashes, hematuria and melena, epistaxis, ecchymosis, fatigue and splenomegaly.

Drug induced immunologic thrombocytopenia is a common and serious condition caused by various drugs including heparin, sulfonamides, penicillin's, NSAID's, anticonvulsants, antidiabetic drugs, quinine, gold salts etc.

The major mechanism involved is the destruction of platelets, due to the binding of drug dependentantibodies to the glycoproteins on the cell membranes of thrombocytes.

Fosfomycin is a broad spectrum antibiotic used for uncomplicated urinary tract infection.

Some common adverse effects of the drug include diarrhea, nausea, pain, pharyngitis, headache, rhinitis. No previous clinically significant data about the drug suggests drug induced thrombocytopenia. This is a rare case of Fosfomycin induced thrombocytopenia.

CASE REPORT

A 36-year-old male patient was hospitalized with generalized weakness and reduced urine output in a secondary care hospital having history of hypertension, diabetes mellitus with pancreatitis, renal failure and old CVA. Patient is a chronic smoker as well as an alcoholic for 20 years. On theday of admission BP was 90/60mm Hg and PR was 102bpm and was hypotensive all over the duration of hospital stay. The laboratory investigations on admission are mentioned in table 1. Peripheral smear showed normocytic normochromic anemia, neutrophilic leukocytosis with toxicgranules. His urine routine exhibited numerous PUS cells with few RBC's and few epithelial cells,urine culture revealed the presence of Klebsiella spp.

Based on the subjective and objective data the patient was diagnosed with urosepsis. Inj. Amoxiclav 1.2g IV BD (amoxicillin+ potassium clavulanate) was started empirically along with corticosteroids, antidiabetic drugs, analgesics, gastro protective agents and hepatoprotective agents. On antibiogram, he was found resistant to all antibiotics except colistin. Since colistin is ahigher antibiotic being contraindicated in renal patients, Fosfomycin 3g sachets in 50ml of water once daily, simultaneously Inj. meropenem 1g stat followed by 500mg q12h was given.

On day 4 the platelet count was 1.44L/cumm and on 5th day after administration of Fosfomycin, it became 0.64L/cumm. Fosfomycin was given for 5 days and on 6th day of Fosfomycin his platelet count became 0.17L/cumm and was presented with 1 episode of melena (blood in stools). His hemoglobin, RBC, WBC and

PT/INR levels did not show any drastic variations, peripheral smear showed normocytic normochromic anemia with thrombocytopenia, with few giant platelets. Fosfomycin was withheld and meropenem alone was continued and from next day platelet count began to incline. It increased to 0.20L/cumm, 0.26L/cumm, 0.34L/cumm, 0.45L/cumm in the respective days. Within a couple of weeks his platelets were regained to normal range. A positive dechallenge was observed on withdrawal of the drug. Since the patient had other comorbidities, reexposure of drug can put the patient at risk, hence rechallenge was not done.

The Naranjo ADR assessment scale gives a score of 7 which indicates a probable reaction.

Table 1: Laboratory data on the day of admission and after giving Fosfomycin.

Investigations	Data on day of admission	Data after administering Fosfomycin
HEMOGLOBIN	7.9g%	6.4g%
RBC	2.77millioncells/mcl	2.19millioncells/mcl
PLATELETS	2.54L/cumm	0.64 L/cumm
WBC	21750/microL	33880/microL
ESR	140mm/hr	50mm/hr
SODIUM	106mEq/L	113.9mEq/L
POTASSIUM	3.9mEq/L	2.7mEq/L
UREA	105mg/dl	100mg/dl
CREATININE	5.2mg/dl	4.8mg/dl
CRP	73.67mg/L	70.48mg/dl
FBS	235mg/dl	203mg/dl

Table 2: Platelet counts during the hospital stay.

Platelet counts before administering Fosfomycin			Platelet counts during Fosfomycin administration					Platelet counts after stopping the drug				
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13
2.54	-	1.44	-	0.64	0.30	0.20	0.22	0.17	0.20	0.26	0.34	0.45

DISCUSSION

Identifying thrombocytopenia mechanism in this patient is a crucial task as the patient had several comorbidities and was treated with several drugs simultaneously. Even though the conclusion of fosfomycin induced thrombocytopenia can be confirmed based on the probable reaction result of Naranjo scale for ADR assessment as well as the pattern of change in platelet counts across the duration of therapy. On the basis of evaluation of drug induced thrombocytopenia.[1] (table 3), the reaction can be considered probable. Resolving thrombocytopenia after ceasing the drug supports the confirmation of the causative drug.

In a review literature study Angela S Loo.et.al explains about various mechanisms of antimicrobial drug induced thrombocytopenia. Since the prothrombin time was normal and there was no evidence of bone marrow suppression or autoantibody presence and the reaction subsided on discontinuation of drug, the probable mechanism in case of fosfomycin would be the quinine type antibody production, were the drug produces antibodies which have higher affinity towards the platelet antigens causing its destruction.[9] Exposure of antibodies to the antigens can exhibit systemic symptoms like giddiness, chills, syncope, nausea. Some of them may also have immune mediated hemolytic anemia and neutropenia in addition to thrombocytopenia.[5] As the platelet count declines the risk for bleeding becomes high, occasionally some of them may be asymptomatic.

In consideration to the platelet count (≤1000/μL) interventions must be initiated. Discontinuation of the suspected drug can mostly increase the platelet count as well as relieve the symptoms of bleeding (hematuria, GI varices, purpuric lesions).[5] In severely ill patients blood or FFP transfusions may be required.

Fosfomycin is an old bactericidal broad spectrum antibiotic developed before 45 years.[12]

It inhibits the bacterial cell wall synthesis by inactivating the enol pyruvyl transferase enzyme which irreversibly blocks the condensation of uridine Diphosphate-N-acetyl glucosamine with p- enol pyruvate, which results in bactericidal activity in the urine. Also, the adhesion of bacteria to uroepithelial cells is reduced. Fosfomycin has an oral Tmax of 4 hours with 37% rapid oral bioavailability. 38% of the drug is excreted unchanged in urine and 18% by fecal excretion. The elimination half-life of the drug is 5.7 hours.[15]

Table 3: Criteria used to evaluate causative relationships indrug-induced thrombocytopenia.

Criterion	Description
1	Therapy with the candidate drug preceded thrombocytopenia
2	Improvement from thrombocytopenia was observed and sustained after the drug therapy was discontinued
2	The suspected drug was the only drug used before the onset of thrombocytopenia or hold on to other drugs or reintroduced after ceasing of therapy with the candidate drug with preserved normal platelet count
3	Other elements for thrombocytopenia were excluded
4	Re-exposure of the suspected drug resulted in recurrence of thrombocytopenia
Level of evidence	
I definite	Criteria 1, 2, 3 and 4 are met
II probable	Criteria 1, 2 and 3 are met
III possible	Criterion 1 met Criterion 1 not met
IV unlikely	

Source: Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology.[1]

Antibiotic induced colitis has been reported in reference to fosfomycin, therefore, it is important to look into this diagnosis in patients who have got serious diarrhea during or after the use of Fosfomycin. Also, drugs inhibiting peristalsis are contraindicated in this situation.[15]

In a study on adverse events of fosfomycin use based on FDA adverse event reporting system, theadverse effects identified with parentral fosfomycin were phlebitis, rashes, hypokalemia and gastrointestinal disorders. Oral administration exhibited gastrointestinal disturbances. All these adverse effects were accordant to its safety profile.[14]

The product monograph gives the data of causing variations in laboratory counts in US study population, however the incidence of thrombocytopenia is not well defined.[18]

CONCLUSION

Drug induced thrombocytopenia is a prime case to be considered inspite of all other etiologies of thrombocytopenia. It can be caused by several drugs including antimicrobials. The case report gives a rare presentation of thrombocytopenia induced by oral fosfomycin. The platelet count was regained to normal on discontinuation of the drug and bleeding risk was cut out. Since a single case report doesn't determine the frequency of fosfomycin induced thrombocytopenia, advanced study must be taken up.

ACKNOWLEDGEMENT

We express our sincere gratitude to KLE College of Pharmacy, Hubballi for all the assistance.

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