Case Report

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Cefoperazone Induced Gastrointestinal Bleeding

Internal Medicine Section

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ABSTRACT

Cefoperazone is a beta-lactam antibiotic which is frequently used in treating a variety of gram positive and gram negative infections. The chemical structure of cefoperazone contains a side chain of N-methylthiotetrazole which can inhibit vitamin K metabolism resulting in hypoprothombinemia. We report a case of cefoperazone induced coagulopathy manifesting as gastrointestinal bleeding. A Naranjo assessment score of 5 was obtained, indicating a probable relationship between the patient's coagulation function disorder and her use of the suspect drug.

Keywords: Cefoperazone, Coagulopathy, Vitamin K

CASE REPORT

A 73-year-old elderly female reported to was seen in the outpatient department of our hospital. She was suffering from high grade fever, dysuria and multiple episodes of vomiting which started three days prior to presentation. She denied history of oliguria, haematuria, pedal oedema, pain abdomen, haemetemesis or melena. Patient was a known diabetic for the past 15 years and she was on long acting insulin for the last three years. She had underwent surgery for cataract in both eyes 10 years ago. The patient denied history of microvascular complications of diabetes like retinopathy, neuropathy or nephropathy. Examination of the patient at admission was unremarkable except for pallor. Patient was provisionally diagnosed as a case of urinary tract infection.

Baseline blood investigations revealed neutrophilic leukocytosis with deranged renal parameters (eGFR of 37ml/min). There was microcytic hypochromic anaemia. Serum electrolytes, liver function tests and coagulation parameters were within normal limits. Patient's urine microscopy showed numerous White Blood Cells (WBC) but no Red Blood Cells (RBC). Urine dipstick was positive for sugar but negative for protein. Ultrasonography of abdomen and pelvis was unremarkable. Blood and urine sample were sent for culture and patient was started on third generation cephalosporin (ceftriaxone) empirically. The blood and urine cultures grew-multi drug resistant *E.coli*. Based on the sensitivity pattern, patient was started on cefoperazone-sulbactam after dose modification (2 grams of cefoperazone plus 0.5 gram of sulbactam 12th hourly) based on estimated Glomerular Filtration Rate (eGFR). Patient was also on Intra-venous (IV) fluids (isotonic normal saline), insulin, paracetamol and Proton Pump Inhibitors (PPI). Patient improved clinically and repeat investigations showed improvement of leukocytosis and renal parameters.

On day 5 of admission, patient complained of pain abdomen and passage of dark coloured stools. Patient had pallor which worsened since admission and mild tenderness of abdomen. Ryles tube insertion was done with suspicion of upper Gastrointestinal (GI) bleeding. It showed brown coloured aspirate suggestive of upper GI bleed. blood investigations showed a drop in hemoglobin and elevated prothrombin time with International Normalized Ratio (INR) of 6.0. Platelet counts, activated partial thromboplastin time and liver function tests were within normal limts. Cefoperazone was thought to be the cause of coagulopathy and stopped immediately and vitamin K was administered. Vitamin K 10milligrams was given intravenous, eighth hourly for one day. Oral feeds were withheld and pantoprazole infusion was started. Blood parameters on the next day showed normalisation of prothrombin time and INR. Ryle's Tube aspiration showed no fresh Upper gostro intestinal (UGI) bleed. Patient had pain abdomen and melena for two more days. Patient was started on alternative antibiotic (Meropenem) for her urinary tract infection. Coagulation parameters were monitored daily but no further derangement was noted. A Naranjo assessment score of 5 was obtained, indicating a probable relationship between the patient's coagulation function disorder and her use of the suspect drug.

Patient recovered completely at discharge with no pyuria and renal parameters were normalised. Patient was followed up after 1 month and she was clinically stable and Laboratory Investigations were within normal limits albeit mild anaemia as depicted in [Table/Fig-1].

Lab prameters	DAY 1	DAY 5	DAY 6	DAY 8	Day of Discharge	Day of Follow Up
Hemoglobin	9.8g/dl	5.6g/dl	Test not done	8.1g/dl	8.3g/dl	8.9 g/dl
Total leucocyte count	14,500/ microliter	12,200/ microliter	Test not done	Test not done	8,400 / microliter	9,400/ microliter
Prothrombin time	14.7 seconds	76.3 seconds	15.9 seconds	15.4 seconds	15.6 seconds	15.3 seconds
International normalized ratio (INR)	1.06	6.7	1.09	1.05	1.06	1.04
Blood urea	55 mg/dl	40 mg/dl	42 mg/dl	38 mg/dl	36 mg/dl	38 mg/dl
Serum Creatinine	2.3 mg/dl	1.9 mg/dl	1.8 mg/dl	1.7 mg/dl	1.2mg/dl	1.3mg/dl

[Table/Fig-1]: Laboratory Investigations.

DISCUSSION

Vitamin K deficiency impairs the carboxylation and activation of factors II, VII, IX, and X, causing functional deficiencies of these factors. The use of various antibiotics may cause hypoprothrombinemia because they could eradicate the intestinal bacterial source of vitamin K [1].

Cefoperazone is a third generation cephalosporin which is prescribed for a wide variety of respiratory, skin, and urinary tract infections. Ceftazidime and cefoperazone are the only third-generation drugs that provide antipseudomonal coverage. The third-generation cephalosporins except for cefoperazone penetrate cerebrospinal fluid and are indicated for the treatment of bacterial meningitis

[2]. Cefoperazone acts by inhibiting bacterial wall synthesis and it is given usually with a combination of sulbactam which is a beta-lactamase inhibitor. Cefoperazone has a methy thiotetrazole side chain which on metabolism produces free N-methylthiotetrazole. (NMTT) [3]. NMTT can cause hypoprothrombinemia by inhibiting vitamin K epoxide reductase [4]. Patients with normal vitamin K concentrations do not manifest with coagulopathy where as vitamin K deficient patients are at high risk of coagulopathy secondary to the drug administration probably due to any of the above mentioned reasons. Isolated prolongation of prothrombin time following Cefoperazone administration and rapid correction following vitamin K supplementation is suggestive of Cefoperazone induced coagulopathy.

Very few cases are reported regarding coagulopathy secondary to Cefoperazone administration [5-7]. A recent article by Z Cai et al., has reviewed the literature (Pubmed) and found that only about 30 articles mentioning cefoperazone-induced hypoprothrombinemia and hemorrhage have been published [8]. A study by Strom et al., has noted the frequency of bleed at various sites secondary to cefoperazone administration. The most frequent site of bleeding was from the urinary tract, and more than 75% of cases of bleeding were microscopic. The second most frequent site was the integument, then bleeding from the nose, mouth, or pharynx, then the digestive system [9].

Mueller et al., reported significant number of patients who developed this complication [10]. Vitamin K supplementation as a preventive measure has been suggested by Mueller et al., but a study done by Rock off et al., did not recommend routine use of vitamin K [11]. Indian literarure regarding cefoperazone induced coagulopathy is limited [12].

CONCLUSION

Cefoperazone induced coagulopathy is a known but rare manifestation, especially in patients with vitamin K deficiency. The manifestation of this coagulopathy resulting in life threatening complications, like the one seen in our patient is potentially preventable by serial monitoring of coagulation parameters and vitamin K supplementation. However, more studies are required to look for the incidence of coagulopathy and bleeding following cefoperazone administration, in an Indian context and role of vitamin K as a preventive measure.

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