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"UNRAVELING THE INTERPLAY: WARFARIN AND METRONIDAZOLE DRUG INTERACTION DYNAMICS"

General Medicine

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ABSTRACT

A 65 year old male patient was admitted in our hospital with complaints of breathlessness on exertion, haematemesis, history of malaena. Patient had history of loose stools 10 days back and was on tab metronidazole 400mg tid for 5 days. On general examination, there was pallor and laboratory investigations showed PT (test) more than 100, peripheral smear showed normocytic normochromic RBCs admixed with microcytic and macrocytic RBCs with anisopoikilocytosis showing occasional tear drop cells. Patient was on Tab Acitrom 2mg 0-0-2. Tab acitrom was stopped and patient was given Vit K, Fresh frozen plasma and Packed red blood cells transfusion. Patient's Haemoglobin started improving and PT came within normal limits. Patient improved symptomatically.

KEYWORDS

Vitamin K antagonists (VKA), PT (prothrombin time), Drug interactions, Anemia.

INTRODUCTION:

VKAs block the function of the enzyme vitamin K epoxide reductase (VKOR), which is needed to 'recycle' vitamin K epoxide—the biological inactive form of vitamin K—back to active vitamin K. Vitamin K serves as an essential cofactor for the activation of several proteins, including the coagulation factors II, VII, IX and X and protein C and S[2]. Thus, through the selective inhibition of VKOR, administration of VKA results in a deficiency of vitamin K and thereby depletion of coagulation proteins. The anticoagulant effects of VKA are delayed until the already present coagulation factors are sufficiently depleted. The therapeutic effect can be seen when the clotting factors synthesis is reduced by 40-50%. Since factor VII has the shortest half-life (4–6 hours), coagulopathy can be expected 12–16 hours after ingestion of a VKA. The usual indications of VKAs are prophylaxis of deep vein thrombosis; treatment of deep vein thrombosis, pulmonary embolism, transient ischemic attack; arterial disease (myocardial infarction), prosthetic heart valves[1].

In this case report we present a case of interaction between VKA (acenocoumarol) and metronidazole resulting in bleeding manifestations.

Case Presentation:

65 year old male patient came with complaints of breathlessness on exertion since four days, vomiting and headache. Patient was apparently asymptomatic four days back, following which he developed breathlessness on exertion, MMRC grade 3, not associated with decreased urine output. Headache in the occipital region, increased on lying in supine position, not associated with blurring of vision, photophobia. History of vomiting two days back, blood stained , non bile stained, non projectile. History of melaena 2 days back. History of loose stools was present 2 weeks back for which patient didn't consult any doctor but took tab metronidazole 400mg tid for 5 days.Patient has no known comorbidities. Patient diagnosed with deep vein thrombosis in left leg one month back. Started on tab acitrom 2mg 0-0-2. The patients family history was nonexistent. The patient was conscious, oriented and afebrile. On general examination, pallor was present. No signs of icterus, clubbing, cyanosis, and lymphadenopathy noted. No abnormalities were found in the heart, lungs, abdomen and central nervous system during the systemic examination.

Complete blood picture showed low hemoglobin (hb- 4.3), total count was raised (16.74). Renal function test showed urea – 113, creatinine – 2.6. Bleeding time was within normal range (2min 10sec), clotting time was within normal range (4min 25sec). PT (test) was more than 100. 2D ECHO showed mild concentric LVH, no regional wall motion abnormalties at rest, normal LV systolic function (LVEF – 60%).

Tab acitrom was stopped. Patient was intubated in view of low saturation. Fresh frozen plasma and packed red blood cells transfusion was done. Patient was given Vit K.

Serial monitoring of Hb and PT-INR was done. Patient started maintaining saturation at room air. Patient improved symptomatically.

DISCUSSION:

Tab Acitrom (acenocoumarol) which is a vitamin K antagonist (oral anticoagulant) acts by competitively antagonising the vitamin K and thus lowering the plasma levels of clotting factors (II, VII, IX, X). The t1/2 is about 18-24 hours. Its duration of action is for 2-3 days. It is available as 0.5, 1, 2, 4mg tablets. Usually a loading dose of 8-12mg is given and then a maintenance dose of 2-8mg is given. The dose must be individualised by monitoring the prothrombin time. The recommended INR is 2-2.5 for prophylaxis of DVT; 2-3 for treatment of thrombosis/embolism; 3-3.5 for recurrent thromboembolism, MI. When there is no proper monitoring and if INR exceeds 4, bleeding is the most likely complication[5]. There can be epistaxis, haematemesis, melaena, hematuria, intracranial bleed. In such cases, the anticoagulant should be withheld immediately. Vit K to be given which is the specific antidote, and its effect can be seen after 6-24 hours. Fresh frozen plasma which is a source of clotting factors can be transfused. Packed red blood cells transfusion can be given to correct the anemia. Apart from bleeding the other adverse effects could be ulcers in the oral cavity, dermatitis, urticaria, alopecia[4]. Factors which enhance the effect of VKAs could be malnutrion, liver diseases, hyperthyroidism,

drugs like broad spectrum antibiotics(cephalosporins, doxycycline, fluoroquinolones, macrolides, metronidazole, penicillins), aspirin,phenytoin,liquid paraffin[8]. Factors which decrease the effect of VKAs could be pregnancy, nephrotic syndrome, genetic warfarin resistance, drugs like barbiturates,oral contraceptives[6]. Foods that affect warfarin green leafy vegetables, including broccoli, spinach and lettuce, chickpeas, liver, egg yolks, mature cheese and blue cheese, avocado, olive oil[3]. Contraindications for VKA use are bleeding disorders, severe hypertension, ocular and neurosurgery, chronic alcoholic, cirrhosis of liver, renal failure.

In this case, as the patient was not aware about the drug interactions, he took metronidazole. Metronidazole inhibits CYP2C9 which is responsible for metabolism of acenocoumarol and so the anticoagulant effect of acenocoumarol was enhanced resulting in bleeding manifestations[9]. Metronidazole increases the INR and thus when patient is advised to take metronidazole, the dose of acenocoumarol should be reduced by 25-40% and regular monitoring of INR should be done[7]. Though acenocoumarol is considered to be one of the safe drugs, as it is a commonly used drug, it is always essential to explain the patient about the common drug interactions and also to consult a doctor before taking any medicine to avoid complications

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