Upper gastrointestinal bleed in a post menopausal woman due to combination of high first dose aspirin and clopidogrel prescribed for acute coronary syndrome

Vishal R. Tandon, Rubeena Maqbool, Iram Kahkashan, Rashmi Sharma, Vijay Khajuria, Zahid Gillani
Department of Pharmacology and Therapeutics, Government Medical College, Jammu, Jammu and Kashmir, India

ABSTRACT
Combination of aspirin, clopidogrel and enoxaparin remains the standard treatment for acute coronary syndrome (ACS) but is known to increase the incidence of upper gastrointestinal bleed (UGIB). We hereby report an unusual case of gastrointestinal bleed (GIB) as it resulted inspite of proton pump inhibitor (PPI) prophylaxis within the second day of treatment in a post-menopausal woman (PMW) with high first dose of aspirin clopidogrel dual combination in a patient of ACS.

Key Words: Acute coronary syndrome, aspirin, clopidogrel, enoxaparin, gastrointestinal bleed

INTRODUCTION
Anti-thrombotic and anti-platelet therapy is increasingly used world wide for prevention and treatment of primary and recurrent thrombotic events.[1] Advancing age women with established cardiovascular disease (CVD) and with an estimated risk of 10 years CVD are likely to benefit from preventive anti-platelet treatment.[2] Anti-platelet therapy is well-established to significantly lower all cases mortality specifically CVD related mortality among post menopausal women (PMW).[3]

Combination of aspirin, clopidogrel and enoxaparin remains the standard treatment for acute coronary syndrome (ACS) but is known to increase the incidence of upper gastrointestinal bleed (UGIB) probably due to cumulative toxicity.[4,5]

Thus, most of the recommendations advise to use co-prescription of proton pump inhibitors along with anti-platelet and anti-thrombotic activity.[1,4]

Since acute upper gastrointestinal bleed due to combination of aspirin, clopidogrel and enoxaparin is potentially life threatening condition and is reported in past,[4,5] the current case is unusual as it resulted in gastrointestinal bleeding (GIB) in spite of proton pump inhibitor prophylaxis within second day of treatment in a PMW being prescribed relatively high first dose of aspirin and clopidogrel dual combination presenting with ACS. Hence, the case is worth reporting.

CASE REPORT
A 59-year-old postmenopausal women (PMW) attained since 3 years with 50 kg weight was admitted as a patient of ACS on 23-6-2014 in a tertiary care teaching hospital. She had no previous history of hypertension, diabetes mellitus, smoking or alcohol intake. The patient had no

Address for Correspondence: Dr. Vishal R. Tandon, Department of Pharmacology and Therapeutics, Government Medical College, Jammu - 180 001, Jammu and Kashmir, India. E-mail: dr_vishaltandon@yahoo.com

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history of any regular or long term use of non-steroidal anti-inflammatory drugs/corticosteroid in the past. There was no past history of peptic ulcer or GIB, anti-platelet drugs, anti-coagulant drug use.

Patient presented with left-sided chest pain radiating to back and left arm with diaphoresis and intermittent episodes of syncope and was brought to emergency where blood pressure was recorded 130/90 mmHg, pulse rate was 126 beats/min. Chest and per abdomen examination was normal. Echocardiogram was done which showed recent anterior wall myocardial infarction. Troponin test was positive. Hemoglobin was 9.8 gm%, total leukocyte count 8400/cumm, platelet count 2.1 lac/cumm, blood urea 29 mg/dl, serum creatinine 0.9 mg/dl, blood sugar 88 mg%, serum cholesterol 200 mg%, triglycerides 165 mg%, clotting and bleeding time was normal, international normalized ratio within normal limit, serum uric acid 4.6 mg/dl, bilirubin 1 mg/dl, SGOT 35 U/L and SGPT 46U/L. Echocardiography showed mild left ventricular dysfunction with an ejection fraction of 40%. Ultrasonography (USG) was normal. The patient was started treatment immediately in the form of oxygen, injection enoxaparin 0.6 ml subcutaneously twice daily. Morphine, beta blockers and angiotensin converting enzyme inhibitors as a standard treatment practice was started. Tablet aspirin in the single loading dose of 325 mg was started followed by 75 mg once daily; tablet clopidogrel 300 mg stat followed by 75 mg, tablet sorbitrate 10 mg sublingual and tablet glyceryltrinitrate thrice daily was given. Tablet atorvastatin 80 mg followed by 40 mg once daily, tablet pantoprazole 40 mg once daily, tablet alprazolam 0.25 mg once daily was started to the patient on 23-6-2014.

After 2 days of treatment patient complained of acute severe epigastric pain, tenderness and minor hematemesis. The gastroenterologist advise was sought and USG and video endoscopy was advised which revealed drug induced erosive enteral gastritis [Figure 1].

There was no history of any other major or minor bleeding in the form of echymosis, epistaxis or hematuria. The blood pressure dropped to 90/60 mmHg and pulse rate was 126 beats/min. The patient was given injection pantoprazole 6 hourly daily along with sucralfate gel twice daily. Injection diazepam 10 mg was given stat. Rest all treatment was allowed to continue but all anticoagulants and anti-platelets were stopped on 27-6-2014. The patient improved as was evident from subsequent endoscopy after 7 days of continuous treatment for the adverse event and de-challenge of anti-platelet and anticoagulant drugs. Patient however required prolonged hospitalization and was discharged on 13-7-2014 and is on regular follow-up.

Subsequent investigations revealed that all the biochemical parameters were within normal limit. HIT’s induced antibodies were not done due to lack of facility. While reviewing the literature the patient was labeled as aspirin, clopidogrel and enoxaparin combination therapy induced upper gastrointestinal bleed, inspite of preventive co-prescription of proton pump inhibitors possibly within one day of treatment. Incidentally there was no other drug, chemical or disease other than possible combination of aspirin, clopidogrel and enoxaparin which could explain or be co-related with this adverse event. De-challenge along with supportive treatment in the form of pantoprazole and sucralfate ameliorated the condition. The re-challenge could not be done due to ethical and clinical constraint. No dose related study was done in the current case. The Narango’s score was 7 and WHO causality assessment showed probable correlation with the current adverse event.\textsuperscript{6,7} The severity of reaction was assessed by Hartwig Adverse drug reaction assessment scale\textsuperscript{8} which classified the adverse drug reaction as serious and potentially life threatening; whereas the preventive assessment scale was done by using Schumock and Thornton scale\textsuperscript{9} which classified the said adverse drug reaction as preventive.

**DISCUSSION**

European society of cardiology recommends in patients of ACS a loading dose of aspirin 300 mg followed by daily maintenance dose of 75-100 mg daily along with 300 mg of loading dose of clopidogrel followed by 75 mg daily dose for 9-12 months in patients of ACS.\textsuperscript{10} The current case report raises the concern for loading dose of anti-platelet dual combination as a standard treatment practice in view of GIB resulting in current case.

The current case is in agreement with Huang KW et al., 2013\textsuperscript{11} who reported that the dual therapy increases the severity of gastritis.
risk of upper GI bleed in patients of ACS. Whereas, current case report disagrees with the finding of Heer T et al., 2009,[8] who reported that there is no increased incidence of bleeding with combination of two anti-platelet drugs. They while comparing aspirin and aspirin plus clopidogrel therapy recorded no significant difference in major GIB between two groups (1.5% vs 0.9%) P = 0.35.

However, it is partially in accordance to the findings of Ng FH et al., 2008,[9] as they documented that the incidence of GIB associated with combination of aspirin, clopidogrel and enoxaparin to be 2.7%. Furthermore, they reported that previous peptic ulcer disease or cardiogenic shock are significant independent risk factor for such GIB and co-prescription with PPI can significantly decrease this risk unlike our case as there was no risk factor in the form of previous peptic ulcer disease, cardiogenic shock and proton pump inhibitors failed to provide any protection. Similar preventive role of PPI have been reported by Huang KW et al., 2013[10] unlike noticed in present case.

The mechanism of current adverse event is uncertain. However, low dose aspirin is known to cause cumulative gastrointestinal toxicity whereas clopidogrel binds to and irreversibly blocks the platelet ADP receptor, thereby inhibiting ADP induced platelet activation and aggregation for the lifespan of platelets and enoxaparin by its non selective anticoagulant action is known to increase the incidence of major and minor bleeding including upper gastrointestinal bleeding.

The fluctuation in ovarian hormone during peri-menopausal and post-menopausal period have also shown to affect gastrointestinal tract symptoms which include increased incidence of bowel discomfort, abdominal pain, bloating, increase incidence of acid peptic disease, gastro esophageal reflux disease and altered bowel pattern.[11] Thus, making PMW, a special high risk patient for the use of high first dose dual combination of anti-platelet drugs in ACS.

Since CVD affects more men than females until 55 years of age, but there after women supersede men due to metabolic or hormonal changes. Thus, anti-platelet drug are going to be prescribed increasingly in women due increase in life expectancy.

Hence, the current case report highlights and tries to draw attention and create awareness among prescribers that in advancing age, PMW before such combination is given, a thorough screening for various risk factors like any previous gastro intestinal complaint, any long term use of non steroidal anti-inflammatory drugs, corticosteroids, may be screened. Moreover, it leaves behind a very important research question about use of dual high dose anti-platelet therapy in PMW because such adverse events can be potentially life threatening.

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Conflicts of interest
There are no conflicts of interest.

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