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ESOPHAGEAL MUCOSAL LESIONS AND DUODENAL ULCERS WITH LOW DOSE ENTERIC COATED ASPIRIN: A CASE REPORT

Pharmacology

KEYWORDS: esophageal lesion, low dose aspirin, enteric coated aspirin, duodenal ulcer, gastrointestinal hemorrhage

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ABSTRACT

In Type II diabetic patients, dual antiplatelet therapy is indicated for the primary prevention of cardiovascular and cerebrovascular events, which is commonly composed of low dose aspirin and other antiplatelet agents. This increases the risk of esophageal lesions, gastroduodenal ulcers and bleeding. Contrary to common belief enteric coated aspirin or buffered varieties are no more safer than the plain aspirin. We present a case of an elderly patient who developed adverse events that were associated with the low dose enteric coated aspirin. Patient's prognosis improved dramatically after the drug was withdrawn. Based on these findings, we argue for the need to assess the risk of gastrointestinal mucosal injury and hemorrhage in cases where LDA therapy is entailed.

INTRODUCTION:

Antiplatelet agents are commonly used to prevent the cardiovascular and cerebrovascular events. Low dose aspirin is most widely used, however, dual antiplatelet therapy has been proved to be more effective than the aspirin therapy alone. Using aspirin in the patients with no apparent cardiovascular disease is debatable. In lower risk group, the indication of aspirin therapy is contracted by its ability to increase the risk of bleeding, including intracranial and UGI hemorrhage.[1] However, in higher risk group, like Type II diabetic patients who have approximately 2-4 times greater risk of developing coronary heart diseases, aspirin provides promising benefits.[1,2]

One study has demonstrated that the diabetic patients have similar risk of CHD related death as that of the non-diabetic patients with a history Myocardial infarction.[3] Interestingly, in 18 year follow up of this study subjects, diabetics without any history of CHD presented even higher risk for CHD related death compared to the non diabetic subjects with prior objective evidence of CHD.[4] Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III) in the United States has declared diabetes to be 'CHD equivalent'.[5] American Diabetes Association recommends the daily administration of aspirin in the dose of 75-162 mg for diabetic patients with increased ASCVD risk. However, potential to bleed offsets the aspirin benefits.[6]

Contrary to the nominal believe of enteric coated aspirin being gastroprotective, one study has shown that low dose enteric coated and buffered aspirin varieties are no more safer than plain aspirin for the upper gastrointestinal mucosa.[7] Besides UGI bleeding, aspirin therapy also increases the risk of life threatening hemorrhage. Stomach and duodenum are one of the most pregnable organs that are exposed for the adverse events, however, recent studies has suggested, it also causes an elevated risk of esophageal lesions.[8-10]

Here we present a case of low dose enteric coated aspirin, given as primary prevention for the cardiovascular events which caused adverse drug events of esophageal lesions and duodenal ulcers.

CASE PRESENTATION:

A 75 year old male patient was brought to the tertiary care hospital after he had an episode of haematemesis (black colored) and had complaints of loss of power in lower limbs. After hospitalization, continuous hiccups were observed. He had diabetes mellitus type II and hypertension for more than 20 years and were receiving regular medications. He was alcoholic 20 years back and continues to be a chronic tobacco chewer. On physical examination his vitals were found to be stable including the blood sugar levels, except tenderness in the epigastric region and high blood pressure.

His Vitals during the hospital stay were as follows:

VITALS	Day 1	Day 2	Day 3	UNITS
BP	140/90	110/90	110/80	mmHg
PR	130	108	119	Beats/min
R/R	24	22	23	Breaths/min
CVS	S1+ S2+ S3-	S1+ S2+	S1+ S2+	-
GRBS	121	68	162	mg/dl
P/A	Mild epigastric tender	Soft, tender	Soft, tender	-
SPO2	98%	76%	97%	-

*BP=Blood pressure, PR=Pulse rate, R/R=Respiratory rate, CVS= Cardiovascular system, GRBS=General random blood sugar, SPO2=arterial oxygen saturation.

The patient was receiving antiplatelet therapy, aspirin + clopidogrel (tab. Clopitab-A, 150 mg aspirin & 75 mg clopidogrel) and enteric coated aspirin (tab. Ecosprin, 75 mg aspirin) once daily as primary prevention from cardiovascular events.

Physician ordered following laboratory tests for the objective evidence which revealed following results:

LAB INVESTIGATIONS	TEST VALUES	NORMAL VALUES	UNITS
Prothrombin Time	18	13	Sec
COMPLETE BLOOD PICTURE: • Neutrophils	87%	40-75%	-
SERUM ELECTROLYTES: • Sodium • Chloride	123 93	135-145 95-105	mmol/L mmol/L
Blood Urea	73	10-45	mg/dl
Serum creatinine	4.3	0.6-1.5	mg/dl

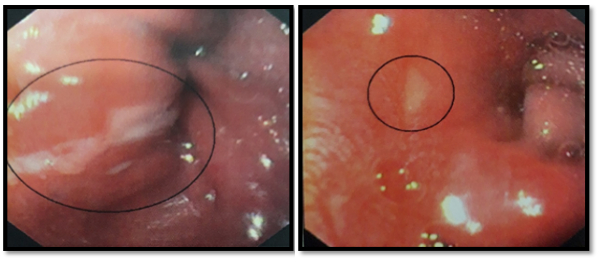
Laboratory investigations showed that prothrombin time, blood urea and serum creatinine levels were beyond the normal range, suggesting LDA related adverse event. Hyponatremia, hypochloremia and neutrophilia was also present.

On day 1, the patient was taken off from the dual antiplatelet therapy

since he developed hypoprothrombinemia and tranexamic acid (500 mg IV BD), an antifibrinolytic agent was given. Furosemide (Inj. Lasix 20 mg IV stat) was also administered for renal insufficiency. In addition, injection pantoprazole (80 mg in normal saline), Ondansetron (8 mg IV TID), Rosuvastatin (tab. Rosuvas 20 mg BD), buscopan (IV stat) was administered. To prevent cerebrovascular events, head end elevation was recommended.

Salbutamol, ipratropium bromide (Neb. Duolin) and Formoterol, budesonide (Neb. Foracet) beta adrenergic blockers were also given, because basal crackles were heard on respiration.

Endoscopic and ultrasonographic examination was performed on day 2 which reported:



a. Discreet esophageal ulcers seen in esophagus **b.** Deformed duodenal cap with ulcers seen D1

His endoscopic diagnosis was concluded as:
- Chronic duodenal ulcer
- Multiple esophageal ulcers

Sonographic Examination showed:
Bilateral increase in renal parenchymal echotexture
Mild splenomegaly

On day 2, the endoscopic and ultrasonographic impressions strongly indicated LDA toxicity. He was given sucralfate (syrup Sucrafil O 15 ml QID/ RT). The patient also developed pulmonary aspiration and was given cold saline lavage and metoclopramide (inj. Perinorm IV BD). Since the patient's GRBS dropped to 68 mg/dl on 2nd day, anti diabetic drugs were stopped and 5% dextrose at 40 ml/hr IV was administered. Inj. Human actrapid insulin was indicated if glucose levels escalated above 220 mg/dl. GRBS was aimed to be maintained between 150-200 mg/dl.

On day 3, patient had no fresh complaints and same treatment was continued. The patient was clinically improving and thus was discharged after a week. The discharge summary included Furosemide, ondansetron, rosuvastatin, Inj HAI and metformin.

DISCUSSION:
Low dose aspirin in the dose of 75-325 mg is prevalently used for the purpose of primary and secondary prevention of cardiovascular and cerebrovascular thrombotic events. Gastrointestinal complications such as peptic ulcers and UGI bleeding are considered to be the major ADR of low dose aspirin therapy.[11-13] Earlier studies have concluded the relationship between the risk of UGI blood loss and aspirin dose, to be with an odds ratio of 2, 3 and 4 for 75, 150 and 300 mg respectively. The damage to gastrointestinal mucosa can be reduced for a short term by enteric coated aspirin, however, it does not decreases the UGI hemorrhage risk.[13,14]

Gastrointestinal hemorrhage can be life threatening, which is commonly provoked by the ulcers or varices. In geriatric patients, particularly with a history of cardio or cerebral diseases, aspirin and NSAIDs has proven to be the potential cause. According to a meta-analysis which included about 24 randomized controlled trials, gastrointestinal hemorrhage was recorded in 2.47% of subjects receiving aspirin, in contrast to 1.42% in the placebo group with an odds ratio of 1.68. Furthermore, there was no relationship documented between hemorrhage and the drug dosing[15]

In another study, endoscopic findings and clinical details of 647 subjects presented with melena and hematemesis were analyzed. Erosive esophagitis in aspirin users showed an odds ratio of 2 with 95% confidence interval. In contrast, subjects taking other thrombotic agents like warfarin, clopidogrel and dipyridamole showed an odds ratio of 3. NSAIDs and aspirin related esophageal damage was reported in a number of studies. A more recent study has shown that subjects who was not presented with the hematemesis but receiving LDA had more severe esophageal scores than the patients receiving other analgesics or neither.[16]

Aspirin not only irritates the gastric mucosa but also inhibits prostaglandins synthesis in the gastric mucosa by irreversibly blocking the COX-1 enzyme, ergo enteric coated tablets were developed.[17] Dammann et al showed that enteric coated low dose aspirin(100 mg/day) markedly reduced the gastroduodenal damage in comparison to the plain aspirin at an equal dose[18] This result was contradicted by other studies that has shown no considerable difference in the risk associated with the enteric coated and plain aspirin. Thus, it's advisable for the patients with risk for developing ulceration to receive gastroprotective agents like co therapy with the proton pump inhibitors.[7]

The proper use of aspirin remains tricky. The patient had type II diabetes and hypertension, which qualifies him to be at higher risk for both cardiovascular and cerebrovascular events. Thus, using dual antiplatelet therapy as the primary prevention strategy seems to be rational. On top of that, enteric coated aspirin has been widely accepted as gastroprotective which is in contrary to many studies and the present case as well.

Naranjo's causality assessment scale was used to evaluate the adverse drug reaction, a score of 7 was calculated and enteric coated low dose aspirin therapy was concluded to be the probable cause for the esophageal lesions and duodenal ulcers. American diabetes association has recommended to avoid the use of low dose aspirin as antiplatelet therapy if the potential risks for bleeding and other adverse drug reactions offsets the modest benefit.

NARANJO'S CAUSALITY ASSESSMENT SCALE:

QUESTION	YES	NO	DON'T KNOW	SCORE
1. Are there previous *conclusive* reports on this reaction?	+1			+1
2. Did the adverse event appear after the suspected drug was administered?	+2			+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1			+1
4. Did the adverse event reappear when the drug was re-administered?			0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?		+2		+2
6. Did the reaction reappear when a placebo was given?			0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?			0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?			0	0

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9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?		0		0
10. Was the adverse event confirmed by any objective evidence?	+1			+1
TOTAL SCORE				+7

CONCLUSION:

Some studies has shown that enteric coated low dose aspirin and plain aspirin has similar UGI bleeding and ulceration risk. Therefore, it is highly recommended to weigh the risks and benefits of aspirin therapy before consideration. This case report of esophageal lesion and duodenal ulcer induced by the low dose enteric coated aspirin highlights the need to assess the gastrointestinal risk if LDA therapy is indicated. It also underlines the need to tailor the individualized drug therapy for better therapeutic outcomes.

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CONFLICT OF INTEREST:

The authors has no conflict of interest.

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