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A pharmaceutical case of NSAID-induced ulcer with gastrointestinal bleeding

Bassey Ukeme Michael[*1], Idongesit Akpan Inyang[2], Akpanama Sunday Paul[3], Sunday Olajide Awofisayo[3]

1. Seamed Pharmacy - Calabar Itu Highway, Uyo.
2. Department of Clinical Pharmacy, University of Uyo, Uyo, Nigeria

Primrose Pharmacy, Osisioma Aba, Abia State, Nigeria

Correspondence:
Bassey Ukeme Michael
Seamed Pharmacy - Calabar Itu Highway, Uyo
Email: bassuk@gmail.com Phone: +234-8037947338

ABSTRACT

Non-steroidal anti-inflammatory drugs are widely prescribed and have known adverse effects on the renal and gastric mucosa. This case study presents NSAID-induced ulcer with gastrointestinal bleeding. Pharmaceutical care approaches were applied to evaluate drug use in the client. Pharmaceutical care protocols were deployed to manage the ulcer symptoms while and the presenting bleeding. Pharmaceutical counselling bothering on removal of exposure to over-the-counter OTC non-steroidal anti-inflammatory drugs (NSAIDs) was emphasized alongside abstinence from foods that provoke gastric acid secretion. Recommending medications to ameliorate the bleeding condition and managing the lesion produced a positive outcome.

KEYWORDS: NSAID, Ulcer, Gastrointestinal Bleeding, Pharmaceutical Care, Pharmaceutical care

INTRODUCTION

Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are widely used for pain management but their association with gastrointestinal ulcers and bleeding is a recognized concern [1]. Most often prescriptions of NSAIDs precede the prescriber's knowledge of a latent gastrointestinal lesion [2]. Symptoms of peptic ulcer disease are variable and may include abdominal pain, nausea, vomiting, weight loss and bleeding or perforation with complicated disease [3]. This case outlines the challenges faced in managing a client with NSAIDs-induced ulcer.

NSAIDs probably damage the small bowel through cyclo-oxygenase (COX)-dependent and COX-independent pathways. COX-dependent pathway is mediated through inhibition of prostaglandin synthesis, leading to disruption of the small bowel mucosal barrier [4, 5].

Non-steroidal anti-inflammatory drugs (NSAIDs) account for 8% of prescriptions worldwide and are used most commonly in age over 65 years [6, 7]. Symptomatic upper gastrointestinal (GI) peptic ulcer disease and bleeding are the most recognised adverse events related to NSAIDs [8].

Misoprostol is effective against duodenal and gastric ulcer and bleeding. Furthermore, omeprazole will prevent both gastric and duodenal ulcers. Histamine-2-receptor antagonists will prevent duodenal but not gastric ulcers, and may reduce ulcer bleeding. The case study presents the pharmaceutical care approach to the case.

METHODOLOGY/OBSERVATIONS

Nature of Encounter

A multiple-encounter case study of JC, a 45-year-old female that presented with recurrent ulcer with bleeding

Medical History

The client, a history of recurrent peptic ulcer disease diagnosed about five years ago, now exacerbated very recently, by NSAIDs use prescribed for chronic back pain.

Medication History

Client had a significant record of drug use which included corticosteroids for weight gain in her teens. She also took high doses of multivitamins for the same purpose. After the first diagnosis of peptic ulcer, she had continued self-medication and followed recommendations from a couple of drug dealers in her community.

History of Present Illness

The client reported worsening abdominal pain, dark stools, and light headedness, indicating possible gastrointestinal bleeding.

Current Complaint and Presentation

Presenting with abdominal, lower back pain, dizziness, numbness/tingling in hands, tiredness, loss of appetite and irritability.

Further complaint included shortness of breath and fast heart beat.

Other Diseases/Co-Morbidity

The client denies other noticeable symptoms of diseases or co-morbidities.

Familial and HEAD-SU

JC has no familial history of hypertension and epilepsy. The maternal uncle died of complications of asthma and diabetes. None of the family line has sickle cell pathology.

Surgical History

Client has had myomectomy twice (11 and 6 years back)

Allergies

No known allergies involving medicine, food, or environment.

Client's Current Medications

Synthetics

Ibuprofen 400mg twice daily for 2 weeks
Cimetidine 400mg once daily for 2 weeks
Aluminum/Magnesium Hydroxide 20 ml as required

Natural products

An unregistered acclaimed potent antiulcer herbal remedy

Nutritional Intake:

Special intake

No special diet is adopted, only abstinence from selected spicy foods and carbonated drinks

Regular intake

Cereals such as rice, sorghum, maize with vegetables

Occasional intake

Pastries and ice-cream

Client's Lifestyle

Professional

The client is a self-supported student who also engages in trading and travels inter-state dealing on fabrics

Social

The client is an undergraduate student, a member of Rotary Club, and a Christian with no denominational preference.

Religious

The client admitted to a devoted Christian life after making a decision to this commitment

Social and Family History

The client quitted smoking six years ago, denies alcohol/illicit drug use, is in a monogamous relationship, employed in a bakery, and traveled to Mexico a year ago.

Physical Examination: (Performed by the Pharmacist and Pharmacist ordered laboratory-test)

Vital signs

Temperature 36.0°C (36.5-37.5); Heart rate 88 bpm (60-100); Respiratory rate 22 cc/min (**12-20**); BMI 28

(20-24.9)

General Examination

General appearance is unwell, anxious, with mild respiratory distress.

Skin and sclera appear pale.

Laboratory Investigations: (Pharmacist-ordered)

Imaging tests

Double contrast radiological imaging revealed benign ulcers located at the lesser curve measuring <2cm and of the posterior wall measuring >2cm of antrum (antral ulcers)

Biochemical tests

The following are outcomes of laboratory tests for the client: Malaria parasite test using microscopic protocols (+); Serology (HIV) Negative; Haemoglobin 8.9 g/dL (**12-16**); RBC 4.8 x 10^6 cells/mL (**3.8-5.2**); Mean Corpuscular Haemoglobin (MCV) 92 fL (**80 - 100**); Mean Corpuscular Haemoglobin Concentration (MCHC) 35g/dl (**32-36**); AST 30 IU/L (**8-33**); ALT 59 IU/L(**4-36**); AFP 15 ng/ml (**0-40**), GGT 22 IU/L (**5-40**); Total protein test 79 g/L (**60-83**); Faecal occult blood (FOB) test was positive.

Microbiological tests

No microbiological tests was ordered/performed

Pharmaceutical Audits

Drug-Disease Audits

The prescribed drugs are inadequate for the mitigation of the ailment. The prescribing of ibuprofen for pains in an ulcer condition will worsen the outcome therefore this should be removed.

Drug-Drug Audits

The currently filed drugs are compatible one with the other. There is need to space out the oral tablets from the Aluminium hydroxide may reduce the absorption of the co-administered medications.

Drug Laboratory Outcome Audits

Outcome of laboratory tests upon the use of the drugs indicated that there is need for build up of the body with haematinics and for the pathology to be arrested to avoid to prevent further loss of blood.

Decision to Dispense/Refill or otherwise of drugs a- Dispense/Refill- reasons b. Hold back- reasons if the pharmacists is not the original prescriber (23/100)

The drugs was dispensed with recourse to the prescriber on salient issues on drugs filed for re-consideration in addition to the recommended medications

Drug Therapy Problems Observed

Unnecessary Drug Use: NSAIDs in a client with a history of peptic ulcers.

Adverse Drug Reaction: Gastrointestinal bleeding due to NSAIDs.

Pharmaceutical Intervention (Reasons for the interventions /Suggestions for resolution

To resolve potential and actual drug therapy problem

Pharmaceutical Care Goals

Alleviate pain with safer analgesics. Prevent further gastrointestinal bleeding. To eradicate *H. pylori*.

Pharmaceutical Care Plans

To assess the therapeutic needs for the client. Develop client-specific management plans for the client. To direct client on the proper use of medications. To monitor outcomes of therapy on the client

Ensuing Drug Recommendation/ Prescription

Esomeprazole 20 mg tablet to be taken twice daily x 21 days

Celecoxib 200mg tablet to be taken 2 times daily x 21 days

Chymotrypsin tablets 2 tablets to be taken twice daily x 21 days

DISCUSSION

Drug Biopharmaceutics and Pharmacology

Esomeprazole

Proton-pump inhibitors (PPIs) represent a class of drugs most prominently known for their use in acid-related disorders. PPIs are derivatives of the heterocyclic organic molecule benzimidazole. They are often the first-line agents for the following diseases- eosophagitis, non-erosive reflux disease, peptic ulcer disease, prevention of non-steroidal anti-inflammatory drug-induced ulcers and Zollinger-Ellison Syndrome. PPIs may also be useful in conditions that may result in heavy NSAID use, such as acute coronary syndrome or chronic pain, as a preventative measure against NSAID-induced ulcers [10].

The parietal cells contain the H+/K+ ATPase enzyme, the proton pump that PPIs block. This enzyme serves as the final step of acid secretion into the stomach. Interestingly, PPIs are prodrugs activated only after undergoing an acid-catalyzed cleavage in the acidic secretory canaliculi of the parietal cells. Hepatic P450 enzymes degrade PPIs. While there are slight variations in the exact P450 enzymes that are dominant in the degradation of the variety of PPIs, most dominantly degrade by the action of CYP2C19 [11].

Understanding the metabolism of PPIs explains the reason some PPIs work better for some individuals than others. Furthermore, the bioavailability of PPIs increases with age, thus dosages in the elderly should also be closely monitored and adjusted accordingly. While other drugs can reduce acid secretion in the stomach, PPIs represent the most potent drugs [12].

The drug formulation of PPIs is often specifically designed to prevent premature activation by gastric acid. The delivery methods include: enteric-coated tablets, gelatin capsules, coated granules as a suspension and in combination with bicarbonate to

temporarily neutralize luminal gastric acid. For immediate acid suppression, there are intravenous formulations for lansoprazole, pantoprazole, and esomeprazole.

PPIs may lower magnesium to a level not easily replenished by supplementation and only corrected with removal of PPI. Hypomagnesemia is a serious complication that predisposes the client to tetany, seizure, muscle weakness, delirium, and cardiac arrhythmias [13]. It is not yet entirely clear what causes this adverse effect, but one hypothesis suggests that it may be due to decreased active intestinal absorption of magnesium by the transient receptor protein channels (TRPM 6/7) that are stimulated by extracellular protons [14].

The acidic environment of the stomach serves as an environment in which proteins become activated to perform certain functions as well as a chemical barrier against bacterial infection. PPIs have correlations with an increased amount of *Clostridium difficile* infections, other enteric foodborne infections and potentially increased risk of community-acquired pneumonia. An hypothesis proposed that the decreased acidic environment of the stomach leads to bacterial overgrowth and increased risk of bacterial aspiration [14]. PPIs increase the levels of gastrin, which in turn leads to increased proliferation of enterochromaffin-like (ECL) cells. ECL cells produce histamine, which under normal circumstances, stimulates parietal cells to activate their H+/K+ ATPase and produce acid into the stomach. Because PPIs act a step further than histamine, this side-effect does not negate the effect of PPIs. However, the problem lies in the discontinuation of PPIs after prolonged use, which has been shown in some cases to result in acid levels higher than before the initiation of PPIs. This effect has been referred to as rebound acid secretion [15].

Due to the frequency of PPI administration, numerous other potential associations have been reported and have received significant attention. Conflicting data have linked PPI use with osteoporosis and bone fracture; proposed mechanisms include calcium malabsorption, increased gastrin, decreased vitamin B12, and potential proton pumps in the bone. Likewise, isolated retrospective analyses have suggested a potential link between PPI use and dementia, kidney disease, and heart disease. Moreover, for dementia and heart disease, in particular, the findings, even in retrospective analyses, have been inconsistent. Following the initial development of PPIs, there was a concern for potential malignancy given prolonged gastrin elevation; however, while this was present in animal models, it has not been demonstrated in human clients [16].

PPI contraindications include clients with known hypersensitivity to that class of drugs, and their use requires caution in clients with severe hepatic disease. As mentioned above, PPIs undergo metabolism by the cytochrome P450 system of the liver, mostly by CYP2C19; hence, any severe dysfunction in this metabolization serves as a relative contraindication. That said, clinically, clinicians often use PPIs in clients with severe liver disease with increased monitoring. PPIs can also alter the activity of specific cytochrome enzymes and delay the clearance of certain drugs such as phenytoin, warfarin, and diazepam. As such, the use of these drugs requires caution in those undergoing PPI therapy. Furthermore, the stomach's acidic environment is necessary for the effective absorption of ketoconazole, and it is advisable to use other antifungals in the setting of long-term PPI use. Conversely, the same acidic environment potentiates the absorption of digoxin, and thus this drug's use merits extreme caution due to the severity of its side-effect profile [17].

There is evidence supporting the monitoring of magnesium (especially in kidney transplant clients). Monitoring of vitamin B12 levels in clients on long-term PPIs is more controversial but reasonable to consider in select cases. Currently, there is limited evidence to support bone density scanning and/or calcium supplementation as an effective means of reducing osteoporosis.

Cimetidine

H2 receptor antagonists (H2RAs) are a class of gastric acid-suppressing agents frequently used in various gastric conditions. They are FDA-approved for short-term use in treating uncomplicated gastroesophageal reflux disease (GERD**),** gastric or duodenal ulcers, gastric hypersecretion, and mild to infrequent heartburn or indigestion. These drugs are also sometimes included in a multidrug regimen for *Helicobacter pylori* eradication [18]. H2RAs may also be used off-label for stress ulcer prophylaxis, esophagitis, gastritis, gastrointestinal hemorrhage, or urticaria. H2RAs are also sometimes included in a multidrug regimen for Helicobacter pylori. Although antacids are generally considered first-line agents for heartburn during pregnancy, H2RAs are pregnancy category B with no known teratogenic effects and may be used if needed. The overall therapeutic effectiveness of H2RAs greatly depends on the severity of gastric disease, dosage regimen, and duration of therapy. This activity describes the indications, contraindications, and use of H2 blockers and highlights the inter-professional team's role in promoting their safety.

Although antacids are generally considered first-line agents for heartburn during pregnancy, H2 receptor antagonists are pregnancy category B with no known teratogenic effects and may be used if needed. H2RAs have also been shown to be safe for use in children or

adolescents with mild or infrequent heartburn symptoms that do not respond to lifestyle changes. The overall therapeutic effectiveness of H2RAs greatly depends on the severity of the gastric disease, dosage regimen, and duration of therapy.

H2RAs decrease gastric acid secretion by reversibly binding to histamine H2 receptors located on gastric parietal cells, thereby inhibiting the binding and activity of the endogenous ligand histamine. H2 blockers thus function as competitive antagonists. Normally, after a meal, gastrin stimulates histamine release from enterochromaffin-like cells, which then binds to histamine H2 receptors on gastric parietal cells and leads to gastric acid release. This increase in gastric acid release occurs through the activation of adenylate cyclase, which raises intracellular cAMP levels. cAMP then activates protein kinase A (PKA), which, among other functions, phosphorylates proteins involved in the movement of H+/K+ ATPase transporters to the plasma membrane. The increase of H+/K+ ATPase transporters at the plasma membrane allows for the secretion of more acid from parietal cells [19].

By blocking the histamine receptor and thus histamine stimulation of parietal cell acid secretion, H2RAs suppress both stimulated and basal gastric acid secretion induced by histamine. The onset of gastric relief provided by H2RAs is approximately 60 minutes with a duration of action that ranges from 4 to 10 hours, making them useful for the on-demand treatment of occasional symptoms. All H2RAs have similar efficacy in decreasing gastric acid secretion [20].

H2 receptor antagonists are well-absorbed after oral administration, and are available as a tablet for oral use. Famotidine, one of the most commonly used agents, is available as a chewable tablet, oral powder for suspension, or in combination formulations containing calcium carbonate and magnesium hydroxide or ibuprofen. Of the H2RAs, famotidine is available as an intravenous solution for use in hospital settings [20].

H2 receptor antagonists may be used as needed for gastric symptom relief or prophylactically 30 to 60 minutes before known food or beverage triggers. H2RAs may also be taken concomitantly with antacids if both quick relief of symptoms and a longer duration of action are desired. For best results, clients should take once-daily doses of H2RAs at bedtime. The more common twice-daily doses can be taken once in the morning and once in the evening. Clients should not initially self-treat with H2RAs for longer than two weeks without consulting their primary care physician.

H2 receptor antagonists are generally well-tolerated. Mild side effects may include headache, drowsiness, fatigue, abdominal pain, constipation, or diarrhea. The use of H2RAs in clients with renal impairment, hepatic impairment, or who are over 50 years of age has correlated with central nervous system side effects such as delirium, confusion, hallucinations, or slurred speech. Cimetidine is generally considered the most frequent cause of these symptoms, although similar effects have also occurred with famotidine [21].

Drug interactions with H2 receptor antagonists may occur as a result of the therapeutic increase in gastric pH because the absorption of drugs requiring an acidic environment for dissolution may become altered. Cimetidine is a potent cytochrome P450 (CYP450) enzyme inhibitor and should be avoided with other medications metabolized by CYP450 enzymes such as theophylline, selective serotonin reuptake inhibitors, or warfarin. Prolonged and high doses of cimetidine have also been linked to gynecomastia, reduced sperm count, and impotence in men and galactorrhea in women. This condition typically resolves with drug discontinuation. Many clinicians generally avoid cimetidine as a therapeutic recommendation for gastric symptoms.

Using H2 receptor antagonists on a scheduled basis may result in tachyphylaxis or tolerance, limiting their use as maintenance therapy for GERD symptoms. Tolerance to the effects of H2RAs can occur within 7 to 14 days of continued treatment. Intermittent, or as needed, H2RAs may help prevent the development of tachyphylaxis. Compared to proton pump inhibitors, H2RAs pose a minor risk for developing bacterial overgrowth and infections [23].

There are currently no absolute contraindications to H2RAs. Clients using H2RAs should be monitored for endoscopic improvement and decreased gastric symptoms to assess the clinical effectiveness and need for therapy adjustments. Clients should also be monitored for adverse effects and possible drug interactions, especially when taking cimetidine [23]

H2RAs are eliminated by a combination of hepatic and renal metabolism. Famotidine and nizatidine require dose adjustment for clients with a creatine clearance of less than 50 mL/min, while cimetidine doses should be reduced for clients with a creatine clearance of less than 30 mL/min. The half-life of cimetidine may become prolonged in clients with hepatic impairment, but for all H2RAs, no dose adjustments are required for hepatic impairment unless also accompanied by renal impairment.

Rarely, QT-prolongation or central nervous system effects have been observed in clients with impaired renal function whose dose was not properly adjusted. Famotidine use requires caution during renal impairment and in combination with other QT-prolonging medications or conditions. Elderly clients should also be monitored for central nervous system side effects such as dizziness or confusion that may

result from decreased drug clearance.

H2 receptor antagonists have a broad therapeutic index and, therefore, severe toxicity is rare. Toxicities of H2RAs may be associated with inhibition of H2 receptors in the myocardium and central nervous system. Central nervous system depression, hypotension, and bradycardia have rarely been reported and usually involve the rapid intravenous infusion of an H2RA. Treatment for toxicities related to H2RA use may include decontamination with gastric lavage or activated charcoal, discontinuation of the drug, and supportive care measures.

Many healthcare professionals prescribe H2 blockers, and there are also agents in the class available over the counter. While these drugs are relatively safe, they may produce severe adverse effects when combined with other CNS drugs. Client education by the pharmacist, nurse, and clinician, working as an interprofessional healthcare team, is key to preventing toxicity and driving improved client outcomes when using H2 receptor blocking therapy [24].

Pharmacist's Subsequent Assessment

He recommended medications has caused an improvement in the physical appearance of the client showed a better treatment outcome

Comments/Laboratory Outcome

After three days, JC showed improvement in symptoms, and haemoglobin levels stabilized. Adverse effects were monitored closely

Clients Self-Evaluation Report

Client reported a better perception of gastrointestinal wellness

Non-Pharmacological Advice:

Lifestyle counseling

JC was advised to avoid indiscriminate NSAIDs use, manage stress, and adhere to a gastro-friendly diet.

Monitoring Parameters for Progress

Periodic blood parameters indicating levels of blood such as Hb and PCV was advised.

Seeking medical Advice/Attention

The client had stabilized and may not require referral for higher care service

CONCLUSION:

This case highlights the importance of tailoring pharmaceutical care for NSAIDs-induced ulcer clients, focusing on pain management, ulcer healing, and prevention of complications.

ETHICAL CONSIDERATION

Data Availability

The data that supported the findings in this study are available on request from the corresponding author

Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest.

Compliance with Ethical Guidelines

Approval for this study and related cases was obtained from the University of Uyo Health Research Ethics Committee

Author's Contribution

The authors confirm contributions as follows: study conception and design by BUM; data collection by IAI and BUM; Analysis and interpretation of results by ASP; Draft manuscript preparation by ASO; all authors reviewed the result and approved the final version of the manuscript.

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