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Polypharmacy in octogenarian: Proton pump inhibitor induced acute kidney injury

Madhavi Katikaneni

ABSTRACT

Introduction: Proton pump inhibitors are used very commonly for gastrointestinal prophylaxis in hospitalized patients. They become part of long list of medications used by older patients, who usually have multiple comorbidities and are on multiple medications. If they develop acute kidney injury, it is often difficult to identify the etiology. Case Report: An 80-year-old female on multiple medications presented with weakness, decrease in urine output, and rash. She was on pantoprazole for a long time due to many hospital admissions and continued taking it in between admissions. Previous admission kidney biopsy showed acute interstitial nephritis (AIN). Acute kidney injury (AKI) improved with steroid therapy. Antibiotics and furosemide were identified as likely cause of AKI, but pantoprazole was not suspected and was continued. Pantoprazole was held current admission, and was treated with steroids again with improvement in creatinine (Cr) to 2.2 mg/dL from 3.9 mg/dL in three weeks. Conclusion: Proton pump inhibitors (PPIs) are frequently used for prophylaxis in hospitalized patients and continued upon discharge. Proton pump inhibitors are an important cause of AIN and important cause of chronic kidney disease. During discharge of hospitalized patients and post-discharge visit, indication for use of PPIs should be looked at carefully. Histamine blockers may be used, if needed for gastrointestinal prophylaxis.

Keywords: Interstitial nephritis, Polypharmacy, Proton pump inhibitor

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INTRODUCTION

Proton pump inhibitors (PPIs) are used very commonly for gastrointestinal prophylaxis in hospitalized patients. They become part of long list of medications used by older patients, who usually have multiple comorbidities and are on multiple medications. If they develop acute kidney injury (AKI), it is often difficult to identify the etiology. Polypharmacy is an important cause of AKI, especially in elderly patients and it contributes increased morbidity and mortality. Proton pump inhibitors can cause AKI by causing acute interstitial nephritis (AIN), chronic kidney disease (CKD). Most cases of AIN do resolve, but some may be left with interstitial fibrosis and CKD. Elderly patients are more susceptible to both AKI and CKD. In addition, there are some reports of hyponatremia due to syndrome of inappropriate antidiuretic hormone associated with PPIs use [1, 2]. Proton pump inhibitors can also cause increase in clostridium difficile infection, community acquired pneumonia, hypocalcemia, hypomagnesemia, osteoporosis-related fractures, and calcineurin inhibitor-related drug interactions [3]. Medication review should be done frequently in elderly patients, and if PPIs need to be used for more than eight weeks, step down to Histamine-2 blockers should be considered.

CASE REPORT

An 80-year-old female with history of chronic obstructive pulmonary disease, chronic diastolic congestive heart failure, osteoporosis, gastroesophageal reflux presented with weakness, decrease in urine output, and generalized rash. Her home medications include ethacrynic acid 25 mg once a day, levetiracetam 250 mg twice a day, simvastatin 10 mg once a day, metoprolol XL 100 mg once a day, fluticasone/salmeterol inhaler 1 puff twice a day, and tiotropium inhaler 2 puffs once a day, and pantoprazole 40 mg once a day. She was on pantoprazole for a long time due to many hospital admissions and she continued taking it in between admissions. Three months back she was admitted with congestive heart failure and was treated with intravenous furosemide 40 mg once a day and discharged with oral furosemide 40 mg oral once a day. Creatinine (Cr) on admission was 3.27 mg/dL and discharge with Cr was 1.9 mg/dL. She was admitted one month later with AKI and rash on bilateral lower extremities. She was on amoxicillin and clavulanic acid 500 mg/125 mg twice a day for one week before this admission for cellulitis. Creatinine on admission was 3.5 mg/dL. Kidney biopsy showed acute interstitial nephritis and mild diabetic glomerulosclerosis, moderate arteriosclerosis. Prednisone 60 mg was given and tapered off in two months. Etiology was thought to be due to furosemide and or amoxicillin. Furosemide was changed to ethacrynic acid upon discharge. Creatinine improved to 2.2 mg/dL. Current admission laboratory values showed blood urea nitrogen 69 mg/dL, Cr 6.27 mg/dL, sodium 133 meq/L, potassium 4.4 mg/dL, bicarbonate 26 meq/L, chloride 94 meq/L, hemoglobin 10.8 g/dL, white blood cell (WBC) 9.4 per HPF with 16% eosinophils, normal complements, and urine analysis showed pyuria, urine culture negative. Ultrasound of kidneys was unremarkable except simple cyst in right kidney, chest radiograph showed small left-sided effusion, echocardiogram showed moderate pulmonary hypertension. She was treated with intravenous normal saline and prednisone 60 mg daily for two weeks later tapered off. Ethacrynic acid and pantoprazole were held. Creatinine improved to 2.6 mg/dL in three weeks. She had stable Cr for six months, but developed worsening kidney function due to diastolic congestive heart failure and is on hemodialysis currently.

DISCUSSION

Acute kidney injury due to AIN occurs in 0.5–2.6% of kidney biopsies, of which two-thirds are drug induced. Proton pump inhibitors, antibiotics, and non-steroid anti-inflammatory agents are common etiologies. Most common etiology is PPIs due to increase in prescription and over the counter availability [4]. Use of proton pump inhibitor is associated with 20–50% higher risk of CKD [5]. Most cases of AIN are due to omeprazole, as it is longest available agent since its introduction in 1989. Proton pump inhibitors work by binding to gastric hydrogen potassium ATPase and reduce acid production. They are metabolized by cytochrome P450 system, and inactive metabolites are excreted in urine. Less than 1% of active drug is excreted in urine so it does not have significant dose-related renal effects [6].

Pyuria, hematuria, and non-nephrotic range proteinuria are common rather than classic triad of fever, rash, and eosinophilia. Average duration between drug introduction and onset of AKI is one week to nine months, but 10–11 weeks are commonest. If patients are rechallenged AKI can develop early. Mechanism of nephritis is type B idiosyncratic non-immunoglobulin-E-mediated immune reaction with cell-mediated immune reaction. Renal interstitium and tubules are mainly involved. Hallmark features are interstitial edema, interstitial inflammation and tubulitis with predominance of CD4 T lymphocytes and mononuclear cells with variable number of eosinophils [7]. Acute inflammation may progress to chronic form with interstitial fibrosis and tubular atrophy. Retrospective review of all cases of biopsy proven AIN in two Australian teaching hospitals for a period of 10 years showed 28 cases of AIN of which 18 were due to PPIs [8].

Withdrawal of offending drug helps to recover renal function and early use of corticosteroid can hasten renal recovery as per observational studies and case reports. A multicenter retrospective study to determine the influence of steroids in drug-induced AIN showed steroids should be started early with two weeks preferably to avoid chronic kidney damage [9]. Renal biopsy is useful to confirm the diagnosis and identify patients with chronic interstitial fibrosis and glomerulosclerosis who may not benefit from steroids [10]. Recovery may be incomplete if initiation of steroids is delayed. Prognosis is good if recognized early and drug is withdrawn.

Recognizing PPIs as a cause of AKI especially when they are on multiple medications is important, and when there is suspicion of AIN, PPIs should be promptly withdrawn. Since the risk of AIN is specific to PPIs, alternatives such as h2 blockers could be used whenever possible, limit the duration of use as much as possible, if PPIs need to be used. Chronic kidney disease may develop without prior AKI episode [11]. Unrecognized subclinical AIN may lead to CKD and possible end stage kidney disease [12]. Prescribers need to monitor patients frequently keeping in mind short-term AKI risk and long-term KD risk associated with PPIs use. Medication review should be frequently done in elderly patients and unnecessary medications should promptly be discontinued. Our patient had multiple hospital admissions (3) within short period of time. First one was for congestive heart failure, but other two were for acute on CKD. She had renal biopsy in her 2nd admission which showed acute interstitial nephritis. She was on three medications which can be possible causes (amoxicillin, pantoprazole, and furosemide). Autoimmune condition was not considered

as she does not have prior history. Amoxicillin and furosemide were discontinued but she had recurrence of AKI while she was on pantoprazole. Acute kidney injury improved after discontinuing pantoprazole and with steroid therapy.

CONCLUSION

Acute kidney injury and CKD are important complications of PPIs. Acute kidney injury may not always precede CKD, and patients can have progressive CKD and end-stage renal disease. Use of PPIs should be discouraged without clear indication. If prolonged use is needed there should be monitoring with urine analysis, serum creatinine measurement. Use of over the counter medications including PPIs should be probed during physician visits. Discontinuation of drug and early steroid therapy may help in recovery of AKI.

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Author Contributions
Madhavi Katikaneni – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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All relevant data are within the paper and its Supporting Information files.

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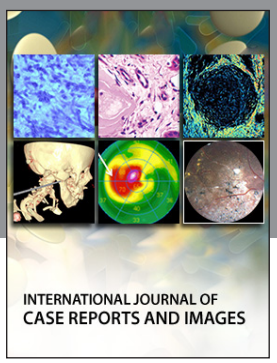

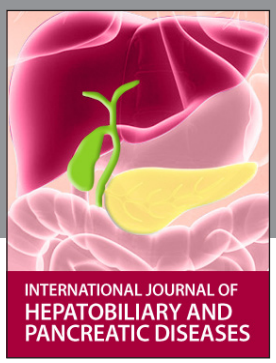

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