CLINICAL VIGNETTE

Proton Pump Inhibitors: Complications of the Gut and Kidney

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Introduction

A 70-year-old Caucasian male presents to nephrology for evaluation of Acute Kidney Injury (AKI) with an increase in serum creatinine from 1.1 to 1.4 over 4 months. He was asymptomatic but recalled unrelenting acid reflux symptoms 4 months before and was started on empiric dexlansoprazole 30 mg twice daily, which immediately resolved his symptoms. However, a few weeks after starting the PPI, he developed diarrhea. The diarrhea was watery, without blood or mucous, and occurred up to 6 times daily. It was associated with abdominal cramps without notable weight loss. Stool studies for bacteria and parasites were negative, and he underwent colonoscopy after 6 weeks of symptoms. Biopsies revealed patchy mild intraepithelial lymphocytosis of the right and left large intestine, establishing a diagnosis of microcytic colitis.

Dexlansoprazole was suspected as the culprit of microcytic colitis and was discontinued. His diarrhea resolved after discontinuation of dexlansoprazole; however, his acid-reflux symptoms reappeared and was started on omeprazole.

The patient's past medical history was significant for depression, GERD, sleep apnea on CPAP, and hyperlipidemia. His medications included fenofibrate 145mg daily, niacin 25m daily, fluticasone nasal spray daily, citalopram 5mg daily, omeprazole 40mg daily, and atorvastatin 20mg nightly. He had no known allergies and denied over the counter medications including NSAIDS and herbal agents. Family history was non-contributory for renal failure. He is a retired lawyer and lives with wife and 2 sons; he denies tobacco and alcohol use.

Vitals included Temp 36.5°C, BP 137/82 mmHg, Pulse 66 SpO2, 98% BMI, and 33.76 kg/m2. Physical examination was notable for an overweight male in no clinical distress with normal cardiac and pulmonary exam There was no sign of volume depletion or volume overload. Basic labs included Hgb 14.4, Hct 43.2, Plt 231, and Wbc 5.10 with a normal differential. Electrolytes were notable for Na 141, K 4.2, CL 104, CO2 27, BUN 21, and Cr 1.4.

Additional studies included bland urinalysis, urine Na 128, urine Cr 114, undetectable urine microalbumin, and markedly positive urine eosinophils. Renal ultrasound noted moderate collecting system dilation of the left kidney with a normal left ureteral jet that ruled out a complete obstruction and minimal post-void residual. Nuclear medicine renal study showed borderline decrease in left renal perfusion with mild decreased left renal function compared to right and no obstruction.

The onset of AKI after starting proton pump inhibitor (PPI) was highly suggestive of PPI-induced Acute Interstitial Nephritis (AIN). The patient declined renal biopsy; however, he was agreeable to discontinue omperazole. In one month, his creatinine improved from 1.4 to 1.2. One year later, the creatinine is now 1.1. Although a gold standard renal biopsy was not obtained, it is presumed that the patient likely had PPI-induced AIN.

Discussion

Proton Pump Inhibitors - Renal Complications

PPIs are commonly prescribed and available as over-the-counter medications. They are taken by millions of people around the world, often for many months to years. While PPIs have an excellent overall safety profile, concerns have been raised about adverse renal events, specifically their association with acute interstitial nephritis (AIN).[1]

PPIs are a common cause of drug-induced acute interstitial nephritis.[2] The time interval from initiation of PPI therapy in the development of clinical AIN is quite variable, from one week to nine months.[1] Multiple studies have confirmed PPI-induced AIN; however, recently published data strongly support increased risk of developing Chronic Kidney Disease (CKD) and progression to End-Stage Renal Disease (ESRD).[2]

PPIs protect the gastric mucosa by decreasing acid secretion by binding to the H+/K+ ATPase at the secretary surface of gastric parietal epithelial cells. H+/K+ ATPase are present on the apical surface of renal tubular cells. However, omeprazole, when administered to healthy male subjects did not disrupt electrolyte balance or urinary pH. Thus, there is no in vivo effect on renal tubular handling.[1] However, evidence of kidney injury is noted on histological images.

In a case series of PPI-related AKI**,** kidney biopsies showed mixed inflammatory cells with interstitial infiltrate and tubulitis. Other series of PPI induced AIN have also described eosinophils within the tubular interstitium. In 88% of the cases, there is sparing of glomeruli and the vasculature.[3]

The treatment of PPI-induced AIN consists of immediate discontinuation of the offending agent. Delays in discontinuation of the culprit agent and initiating steroid treatment adversely affect recovery of kidney function. [3]

Proton Pump Inhibitors- Extra-Renal Complications

PPI have been recently associated with many extra-renal manifestations such as pneumonia, C. diff colitis, hypomagnesium, and abnormal bone density. Recently, several case reports and review articles have noted an association with PPIs and microscopic colitis (MC). Clinically, MC presents as chronic, watery diarrhea with diagnosis confirmed with histological biopsy during colonoscopy. There are two known subtypes of MC: lymphocytic and collagenous colitis. Grossly colonic mucosa appears normal; however, histological images confirm epitheal damage reflected by flattening, detachment, and inflammation within the lamina propria and mononuclear cells.[4] The subtypes differ by the amount of intraepitheal lymphocyte count and thickness of subepithealial collagen layer.[4]

Although the exact mechanism and pathogenesis is currently being evaluated, medications have been associated with the development of MC.[5] Drug-induced MC was suggested in the 1990s after histological changes were noted with both drug-exposure and drug-withdrawal.[4] A strong association between NSAIDS and collagenous colitis has been noted.

The incidence of MC has paralleled the increasing use of PPI. There have been several case reports suggesting a direct association. A retrospective study in 2012 noted a significantly elevated IEL infiltration and inflammation in the lamina propria in PPI treatment group, suggesting PPI may be associated with MC changes.[6] It is speculated that lansoprazole may cause MC by direct toxicity or an immune reaction. The treatment of drug-induced microcytic colitis is discontinuation of the drug.

Conclusion

This vignette describes a patient who developed both microcytic colitis and acute kidney injury. Both were presumably secondary to PPI exposure. Our patient was initially exposed to dexlansoprazole and later developed MC, which responded by discontinuation of dexlansoprazole. Dexlansoprazole ((R)- (+)-lansoprazole) has the same binding affinity to the proton pump as the (S)-enantiomer; however, it is associated with a higher area under the plasma drug concentration time curve. Our patient developed MC as a result of dexlansoprazole, its enantiomer, lansoprazole, has been associated with MC in several case reports.

Although a renal biopsy was not obtained, high clinical suspicion prompted us to discontinue omeprazole after he developed AKI. His creatinine did return to baseline after stopping the PPI. AIN is a well-established cause of PPIs; however, evidence now suggests that exposure can also lead to the development of CKD and ESRD.

In conclusion, several early and well-established studies suggest renal and extra-renal complications of proton pump inhibitors. These complications can be noted immediately or after months or years of PPI use. As PPI use increases with availability of OTC PPIs, physicians need to be aware of these potential side effects.

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