Proton Pump Inhibitors and Acute Interstitial Nephritis

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See CME exam on page 525.

Background & Aims: **Proton pump inhibitors (PPIs) are a widely prescribed class of drugs, and their usage worldwide is increasing. Although well-tolerated, there have been case reports and a recent case series implicating these drugs in acute interstitial nephritis (AIN) and progression to acute renal failure (ARF). The aim of this study was to investigate how widespread this complication is in Australia, to identify which PPIs are implicated, and to establish whether PPI-induced AIN is a class effect.** ***Methods:*** **We undertook a retrospective case review of potential cases at 2 teaching hospitals and a review of registry data from the Therapeutic Goods Administration of Australia (TGA). Parameters sought included the drug implicated, concurrent medications, symptoms, signs, serum creatinine, and time of onset after prescription.** ***Results:*** **We identified 18 cases of biopsy-proven PPI-induced AIN causing ARF in the retrospective case review, which is the largest hospital-based case series to date. The TGA registry data identified an additional 31 cases of "biopsy proven interstitial nephritis." An additional 10 cases of "suspected interstitial nephritis," 20 cases of "unclassified acute renal failure," and 26 cases of "renal impairment" were also identified. All 5 commercially available PPIs were implicated in these cases.** ***Conclusions:*** **With the ever more widespread use of this class of medications, PPI-induced AIN is likely to become more frequent. There is now evidence to incriminate all the commercially available PPIs, suggesting there is a class effect. Failure to recognize this entity might have catastrophic long-term consequences including chronic kidney disease. Increased awareness might facilitate more rapid diagnosis and management of this potentially reversible condition.**

The proton pump inhibitor (PPI) class of drugs is extensively used in internal medicine and surgery and has been commercially available for approximately 20 years. These drugs are the third most frequently prescribed class of drugs in Australia (behind angiotensin-converting enzyme inhibitors and hydroxymethylglutaryl-CoA reductase inhibitors).[1] Their use has increased dramatically in recent years with the introduction of additional members into the class that are superceding H_2 receptor antagonists (H_2RAs). They have several therapeutic indications including treatment of duodenal and gastric ulceration, severe reflux esophagitis, scleroderma-induced esophagitis, Zollinger-Ellison syndrome, prevention of gastric ulcers induced by nonsteroidal anti-inflammatory drugs, and enhancing antibiotic therapy in the eradication of *Helicobacter pylori* infection.[2,3] The PPI class of drugs are well-tolerated, and reported side effects occur in less than 5% of patients, with headache, dizziness, and diarrhea the most commonly reported.[4–9] PPIs, together with H_2RAs, comprise a large proportion of national pharmaceutical expenses in most Western countries.[10]

Historically acute interstitial nephritis (AIN) was predominantly associated with infections, but with the widespread use of antibiotics this etiology is seen less commonly. Medications are now responsible for the majority of cases of AIN. Studies suggest that AIN is the cause of 6%–8% of episodes of acute renal failure (ARF).[11,12] The diagnosis of AIN seems to be most prevalent in renal biopsies in which there is unexplained renal impairment in the presence of an inactive urinary sediment, ie, lack of heavy proteinuria, significant hematuria, or presence of dysmorphic red blood cells. In this setting AIN has been reported to occur in as many as 25% of cases.[13]

Although as a class PPIs are well-tolerated, there have been case reports and a recent case series implicating these drugs in AIN progressing to ARF.[14–37] The first of these, in 1992, implicated omeprazole in the etiology of ARF caused by biopsy-proven AIN.[14] In 2004, lanso-

Abbreviations used in this paper: AIN, acute interstitial nephritis; ARF, acute renal failure; CKD, chronic kidney disease; GFR, glomerular filtration rate; H_2RA, H_2 receptor antagonist(s); PPI, proton pump inhibitor(s); TGA, Therapeutics Goods Administration.

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prazole and pantoprazole were also implicated in AIN.[11,36] PPIs featured as the most common cause of drug-induced AIN in the previous largest hospital series.[11]

The aim of this study was to investigate how common PPI-related AIN is in Australia, to identify which PPIs are implicated, and to establish whether enough evidence is available to support the hypothesis that PPI-induced AIN is a class effect.

Methods

We performed a retrospective case review of potential cases at 2 teaching hospitals and reviewed national registry data from the Therapeutic Goods Administration of Australia (TGA) to identify cases of PPI-related AIN.

Gosford Hospital is a 452-bed teaching hospital that serves an expanding population (250,000 people in 1993 and 310,000 in 2004). Because a single nephrologist performed the renal biopsies during 1993–2003, this time period was chosen. Westmead Hospital is a 975-bed tertiary referral center that serves a population of 1.5 million people. It is the largest teaching hospital in Australia and employs 7 renal physicians.

Once cases of biopsy-proven PPI-induced AIN were identified, demographics and clinical parameters were extracted and recorded including symptoms, signs, PPI implicated, concurrent medications, serum creatinine, and estimated time of onset after prescription (where available) by review of clinical files/case notes and computer records. Case notes were carefully reviewed to ensure that the only medication change recently made was the initiation of the PPI. The diagnosis of AIN was made by independent pathologists and was retrospectively sourced for the sake of this review.

Second, registry data from the TGA of Australia were reviewed from 1991–2004.[38] The TGA is a unit of the Australian Government Department of Health and Ageing. It carries out a range of assessment and monitoring activities to ensure therapeutic goods available in Australia are of an acceptable standard, with the aim of ensuring that the Australian community has access to therapeutic advances within a reasonable time. In Australia, there is a process of voluntary self-reporting of adverse drug reactions by medical practitioners to the Adverse Drug Reactions' Advisory Committee. The analysis undertaken comprised a data search through the TGA database of medical practitioner–reported cases of drug-induced AIN; these cases were then sorted for reported cases in which PPIs were implicated. The cases of PPI-induced renal disorders were classified as: "biopsy-proven interstitial nephritis," "suspected interstitial nephritis," "unexplained acute renal failure," and "renal impairment." Cases were excluded if there was concurrent multiorgan failure because renal biopsies were rarely performed in these circumstances. The TGA registry data were sorted to exclude any hospital-based cases.

These data were reviewed, and symptoms, signs, PPI implicated, concurrent medications, serum creatinine, and time of onset after prescription were extracted and recorded.

Summary results were expressed as mean with standard deviation unless otherwise indicated. Glomerular filtration rate (GFR) was calculated by using the Cockcroft-Gault equation for each patient at baseline, time of presentation to hospital, and 3 months and 6 months after initial presentation.[39] After testing that the assumption of normalcy held, paired t test was performed to examine change in GFR. Simple linear regression was performed to identify patient factors associated with poor recovery of renal function.

Results

Of a total of 28 cases of biopsy-proven AIN identified between the 2 hospitals, 18 (64%) cases were associated with PPI use (Table 1). There were 11 cases of omeprazole-associated, 3 cases of pantoprazole-associated, 3 cases of esomeprazole-associated, and 1 case of rabeprazole-associated AIN. The median age of the patients was 74 years (interquartile range, 65–79 years). The mean duration of PPI therapy before presentation was 11 weeks. The most common presenting symptoms were nonspecific; tiredness and nausea were present in 7 (39%) and weight loss in 4 (22%) of the cases (Table 2). The most common abnormalities detected on dipstick urinalysis were pyuria in 13 (72%), proteinuria in 12 (67%), and eosinophiluria in 11 (61%) cases. The most common laboratory abnormality was a normochromic normocytic anemia that was found in 16 (89%) of the cases and an increased C-reactive protein in 14 (78%) of the cases. On renal biopsy 15 of 18 (83%) patients had evidence of eosinophils in the interstitium, which is highly suggestive of AIN. To provide some idea of how prevalent PPI-induced AIN was at one of the teaching hospitals, we sought information on the number of biopsies performed for the last 10 years (1994–2004) and identified 15 of 673 (2.2 %) biopsies that were done for PPI-induced AIN.

The majority of patients exhibited some recovery of renal function by 3 months after diagnosis of AIN and withdrawal of the PPI. However, calculated GFR remained significantly reduced at both 3 months (mean reduction, 15.9 mL/min; 95% confidence interval, 7.9–23.9; $P < .001$) and 6 months (mean reduction, 11.5 mL/min; 95% confidence interval, 1.1–21.9; $P < .03$) after initial presentation when compared with baseline renal function (Figure 1).

Simple linear regression revealed no association between GFR 3 months after presentation and age ($P = .14$) or gender ($P = .99$), but it did show an association with level of hemoglobin at presentation. Those patients with a hemoglobin of <110 g/L at time of presentation with AIN had a 22 mL/min greater reduction in GFR at 3 months than those with hemoglobin >110 g/L ($P =$