Proton Pump Inhibitors and Kidney Disease—GI Upset for the Nephrologist?

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Widely regarded as safe and effective, PPIs are among the most commonly used medications in the world today. However, a spate of observational studies suggest an association between PPI use and adverse events, including infection, bone fracture, and dementia. This review details evidence linking the use of PPI therapy to the development of kidney disease, including early case reports of acute interstitial nephritis and subsequent large observational studies of AKI, CKD, and ESRD. The majority of studies showed higher risk of kidney outcomes among persons prescribed PPI medications, with effect sizes that were slightly higher for AKI ($\sim$2- to 3-fold) compared with CKD and ESRD (1.2- to 1.8-fold). Although observational pharmacoepidemiology studies are limited by the possibility of residual confounding and confounding by indication, many of the described studies conducted rigorous sensitivity analyses aimed at minimizing these biases, including new-user design, comparison to similar agents (e.g., histamine$_2$ receptor antagonists), and evaluation for a dose response, with robust results. Given the widespread use of PPIs, even a small effect on kidney outcomes could result in large public health burden. Timely cessation of PPI therapy when there is no clear indication for use might reduce the population burden of kidney disease.

As recently as the 1970s, surgery was a primary option for the management of peptic ulcer disease.[1] The advent of histamine$_2$ receptor antagonists and proton pump inhibitors (PPIs) in the 1970s and 1980s, respectively, largely supplanted surgery and revolutionized the treatment of peptic ulcer disease. Both medication classes reduce gastric acid suppression by the parietal cells; histamine$_2$ receptor antagonists block the histamine receptor, and PPIs bind irreversibly to the hydrogen–potassium adenosine triphosphatase enzyme of the proton pump.[2,3] Although both medication classes were thought to have a relatively mild side effect profile, PPI therapy quickly became the preferred treatment option over histamine$_2$ receptor antagonists because of reports of greater effectiveness and lower tachyphylaxis.[2] Today, PPIs are among the most frequently prescribed medications worldwide.[4,5]

Increasing data suggest that PPIs may not be as innocuous as initially thought. The use of PPIs has been associated with a higher risk of hypomagnesemia,[6] Clostridium difficile infection,[7] community-acquired pneumonia,[8] fractures of the hip and spine,[9] and the development of dementia.[10] The combination of PPI therapy with dual antiplatelet therapy has been linked to increased risk of cardiovascular events, although this association remains contested.[11] With respect to kidney disease, PPI use has been associated with acute kidney injury (AKI) as well as the development and progression of chronic kidney disease (CKD). However, the vast majority of evidence stems from observational data; thus, whether PPI use causes the adverse event is not yet clear.

Data Linking PPI Use and AKI

In 1992, a sentinel case report was published detailing a 74-year-old woman who developed acute interstitial nephritis (AIN) in the setting of PPI use. It was the first of many that raised the possibility of a causal association between PPI therapy and AKI. Following over a decade of isolated reports,[12–35] 2 case series were published in 2006 that systematically investigated the association between PPI therapy and AIN through retrospective review of biopsy reports (Table 1).[36,37] The first, a study from Australia, found 18 cases with biopsy-proven AIN in 2 hospitals over a 10-year period. In each case, PPI therapy was deemed the most likely precipitant of AIN based on the temporality of medication initiation (median duration of PPI

Table 1. Studies evaluating for an association between PPI exposure and kidney injury and corresponding findings

Author, year	Study design	Type of kidney injury evaluated	Reference group	Risk associations with PPI use
Geevasinga *et al.*, 2006[36]	Case series	AIN	NA	NA
Simpson *et al.*, 2006[37]	Case series	AIN	NA	NA
Leonard *et al.*, 2012[38]	Case-control	AIN	No PPI use	OR 3.20 (0.80–12.79)
Leonard *et al.*, 2012[38]	Case-control	AKI	No PPI use	OR 1.05 (0.97–1.14)
Klepser *et al.*, 2013[39]	Case-control	AKI	No PPI use	**OR 1.72 (1.27–232)**
Antoniou *et al.*, 2015[40]	Health system data	AKI	No PPI use	**HR 2.52 (2.27–2.79)**
Lazarus *et al.*, 2016[41]	Prospective cohort	AKI	No PPI use	**HR 1.64 (1.22–2.21)**
	Health system data		No PPI use	**HR 1.31 (1.22–1.42)**
	Prospective cohort	AKI	H_2RA use	**HR 1.58 (1.05–2.40)**
	Health system data		H_2RA use	**HR 1.31 (1.13–1.48)**
Lazarus *et al.*, 2016[41]	Prospective cohort	CKD	No PPI use	**HR 1.50 (1.14–1.96)**
	Health system data		No PPI use	**HR 1.17 (1.12–1.23)**
	Prospective cohort	CKD	H_2RA use	**HR 1.39 (1.01–1.91)**
	Health system data		H_2RA use	**HR 1.29 (1.19–1.40)**
Xie *et al.*, 2016[42]	Prospective cohort	CKD	H_2RA use	**HR 1.28 (1.23–1.34)**
Xie *et al.*, 2016[42]	Prospective cohort	ESRD	H_2RA use	**HR 1.96 (1.21–3.18)**
Peng *et al.*, 2016[43]	Case-control	ESRD	No PPI use	**OR 1.88 (1.71–2.06)**

AIN, acute interstitial nephritis; AKI, acute kidney injury; H_2RA, histamine$_2$ receptor antagonists; HR, hazard ratio; NA, not applicable; OR, odds ratio; PPI, proton pump inhibitor.
Bold font indicates a positive and significant association. Odds and hazard ratios are followed by 95% confidence intervals.

therapy, 11 weeks), with no other medication change. Cases tended to be older individuals in their mid to late 70s, with presenting symptoms that were often insidious and nonspecific, such as fatigue and nausea. In the second case series, a study from New Zealand, all biopsies from 2002 to 2005 in the region of Auckland were reviewed. Of the 87 listing AIN as the primary diagnosis, 15 (17%) were deemed most likely due to PPI therapy. Six of the 15 patients were using no other medication than a PPI prior to the onset of AIN. Duration of PPI therapy ranged from 2 weeks to 18 months, with 2 patients experiencing AKI after an increase in PPI dose. In most cases, withdrawal of PPI therapy resulted in an improvement in renal function; the 1 patient who was inadvertently rechallenged with a PPI experienced AKI recurrence.

The publication of the 2 case series suggested a temporal relationship between PPI use and AKI. Additionally, they suggested a PPI class effect, rather than an adverse effect isolated to a single medication. Finally, they reported that, after an episode of suspected PPI-induced AIN, kidney function recovery was often only partial, even after withdrawal of the drug. This observation indicated that PPI-induced AIN might cause irreversible inflammation in the renal interstitium, sufficient to have negative long-standing effects on the kidney.

Not all studies have shown statistically significant associations between PPI use and AIN. A case-control study of the PPI-AIN association by Leonard *et al.*[38] evaluated both PPIs and traditional nonsteroidal anti-inflammatory drugs (NSAIDs). Cases were identified via the United Kingdom's General Practice Research Database, and each case was matched to up to 50 control subjects of the same age and sex. Medication exposure was classified as orally administered PPI, orally administered NSAID, a combination of both PPI and NSAID, or neither. In total, 68 cases of AIN were matched to 3347 control subjects. Cases differed from control subjects in that they had more comorbid diagnoses and were on more medications at baseline. Although the unadjusted odds ratio of AIN from PPI exposure was 6.15 (95% confidence interval [CI]: 2.29–16.53), this effect was attenuated and was no longer statistically significant after adjusting for confounders (odds ratio, 3.20; 95% CI: 0.80–12.79). No association was found between AIN and individuals coexposed to PPIs and NSAIDS, nor was there an association between PPI use and the more general outcome of AKI in a secondary analysis of 27,982 cases of AKI identified by diagnostic codes and 1,323,850 matched control subjects.

Several other studies have investigated the association between PPI use and the outcome of AKI identified using diagnostic codes. A case-control study of the association between PPI use and *International Classification of Diseases, 9th revision, Clinical Modification*–identified AKI in the United States showed a 2-fold increased risk of AKI associated with a PPI prescription in the previous 90 days.[39] In contrast, there was no observed association between H_2RA use and AKI, suggesting that the risk might be specific to PPIs rather than a function of the underlying peptic ulcer disease. A population-based prospective cohort study in Ontario, Canada, matched 290,592 people 66 years and older to an equal number of control subjects based on comorbid conditions, socioeconomic status, number of hospital admissions, long-term care

residence, concomitant medications, and number of medications prescribed.[40] Unlike in the United States, where PPIs can be obtained as over-the-counter medications, a prescription is required to obtain PPIs in Ontario, which significantly minimizes the possibility of misclassifying cases and control subjects. The incidence of AKI within 120 days of the index date (first PPI prescription, for the case group) was higher among PPI users, 13.49 versus 5.46 per 1000 person-years, with a corresponding hazard ratio (HR) of 2.52 (95% CI: 2.27–2.79). The increased risk of AKI was present irrespective of the presence or absence of CKD and similar across all 4 PPI medications evaluated. The incidence of AIN was also higher in the PPI group than in the control subjects, 0.32 versus 0.11 per 1000 person-years, with a corresponding HR of 3.00 (95% CI: 1.47–6.14). The increased risk of AKI and AIN among PPI-users remained even after controlling for situations in which a person had received another potential precipitant of AIN, such as an antibiotic, and excluding patients who had been recently hospitalized.

Data Linking PPI Use and CKD

Recent studies have extended the line of investigation between PPI use and kidney outcomes to evaluate long-term outcomes after PPI exposure, including the development of CKD and end-stage renal disease (ESRD). The development of incident CKD was evaluated by Lazarus et al.[41] in a large, prospective cohort, the Atherosclerosis Risk in Communities (ARIC) study, with replication in a cohort selected from an electronic medical record. Among 10,482 participants in the ARIC cohort, cases of incident CKD were identified by diagnostic codes or inclusion as an incident ESRD case in the US Renal Data System registry, and medication exposure was measured by direct visual inspection of pill bottles at baseline and thereafter by an annual telephone check-up in which patients read the names of all medications. The risk of developing CKD was approximately 1.5-fold higher among PPI users than among nonusers in both unadjusted and adjusted analyses, and the association persisted when PPI users were compared with H_2RA users (i.e., an active comparator analysis). Similar, if somewhat weaker, results were demonstrated in the replication cohort, which included 248,751 individuals from Geisinger, a health system representing a rural community in Pennsylvania. Cases of incident CKD were defined as a repeated outpatient estimated glomerular filtration rate <60 ml/min per 1.73 m^2 or a diagnosis of incident ESRD, and medication use was defined by clinician prescription. As before, PPI use was associated with an increased risk of incident CKD in both unadjusted and adjusted analyses, HR 1.20 (95% CI: 1.15–1.26) and HR

1.17 (95% CI: 1.12–1.23), respectively. There was suggestion of a dose-response relationship, with higher risk with twice-daily dosing of PPI medications (HR: 1.46; 95% CI: 1.28–1.67). Of note, the use of histamine$_2$ receptor antagonists was not associated with incident CKD in either the ARIC or the replication cohort.

Similar findings linking PPI use and the development of CKD were reported by Xie et al.[42] Using a new-user analysis to compare the risk of incident CKD between initiators of PPI and H_2RA therapy in the Department of Veterans Affairs national database, the risk of developing CKD was 1.2- to 1.3-fold higher among PPI users, similar to the magnitude of association observed in the Geisinger cohort. In addition, the association was consistent across other long-term kidney outcomes, including doubling of serum creatinine, estimated glomerular filtration rate decline >30%, and ESRD. There was also a greater association with higher cumulative exposure, whereby risk was higher with longer duration of PPI use.

A Taiwanese case-control study of patients with extant kidney disease also reported that the risk of CKD progression was higher among PPI users compared with those who did not use PPI therapy.[43] Peng et al.[43] identified patients with CKD in the Taiwan National Health Insurance Research Database and matched the 3808 who developed ESRD from 2006 to 2011 to 3808 control subjects with baseline CKD who did not develop ESRD. Cases and control subjects were evaluated for exposure to 1 of 5 commercially available PPIs in Taiwan. Cases were 1.88-times (95% CI 1.71–2.06) more likely to have taken PPIs when compared with control subjects, with effect sizes that were slightly larger among pantoprazole and esomeprazole compared with omeprazole, lansoprazole, and rabeprazole. However, there was no adjustment for level of kidney function, difficulty identifying adequate control subjects, and no consistent dose response across medications, limiting inference from these associations.

Future Research Directions

Taken together, there is strong observational evidence of an association between PPI use and acute and chronic kidney disease. As with all observational studies, there is the possibility of residual confounding, and one cannot definitively conclude that the use of PPI therapy causes reversible or irreversible kidney damage. However, associations between PPI use and kidney disease have persisted in many analyses designed to account for confounding by indication, or the possibility that PPI users might simply be sicker than the comparison group and thus more likely to experience adverse outcomes. Additionally, there are various biologically plausible mechanisms for how

PPI exposure might lead to chronic renal damage, such as recurrent (or undetected) episodes of AIN and AKI,[44,45] chronic hypomagnesemia,[6,46,47] and interference with the potentially renoprotective alkaline tide phenomenon.[48]

One could argue that only a randomized controlled trial would definitively prove a causal association between PPI exposure and renal injury; however, the required number of subjects and duration of follow-up as well as the already demonstrated benefit of PPI therapy for peptic ulcer disease render such a study unlikely to take place. Perhaps the most important public health message derived from studies linking PPI use and kidney disease is the need for heightened awareness. PPIs remain among the most frequently prescribed medications worldwide. They are often used without an indication[49] and continued beyond the recommended length of time.[3,50,51] In a setting where CKD prevalence and its associated morbidity remains high,[52–54] careful monitoring of kidney function while on PPI therapy and cessation of PPIs when there is no clear indication for use might reduce the population burden of CKD.

DISCLOSURE

ACKNOWLEDGMENTS

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