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See related article, "Epoetin Alfa and Outcomes in Dialysis amid Regulatory and Payment Reform," on pages 3129–3138.

Proton Pump Inhibitors and CKD

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Proton pump inhibitors (PPIs) are taken by millions of people around the world, often for many months or even years, and some take PPIs on a permanent basis. PPIs, which are available both by prescription and over the counter, generally have an excellent overall safety profile. However, over time, a number of concerns have been raised about adverse renal events, including hyponatremia, hypomagnesemia, calcineurin inhibitor–related drug interactions, and specifically, acute interstitial nephritis (AIN).[1,2] Although only a small proportion of patients develop AIN from PPIs, the widespread and prolonged use of these drugs has made them one of the most common causes of drug-induced AIN in the developed world.[3]

PPI-induced AIN is often subtle and without systemic allergic manifestations, making it challenging for clinicians to readily identify the problem. In fact, a recent study showed that only about one quarter of patients were suspected to have PPI-induced AIN before a kidney biopsy.[4] This relates to the somewhat atypical clinical presentation of PPI-induced AIN that fits neither the classic allergic manifestations noted with antibiotics nor the bland presentation observed with nonsteroidal anti–inflammatory drugs. For example, less than one half manifest fever, <10% develop rash, and about one third generate eosinophilia, whereas <5%–10% have the classic triad of hypersensitivity reactions.[5] PPI-induced AIN is often diagnosed late in the course of disease, generally weeks to months after drug initiation, likely leading to development of chronic interstitial fibrosis.[4,5] Taken together, it is clear that clinical features and available diagnostic tests are suboptimal for diagnosing PPI-induced AIN and that performance of kidney biopsy is required for definitive diagnosis.

PPIs were first recognized as a cause of AIN in 1992,[6] with numerous case reports and case series documenting the association.[7–9] Interestingly, an initial signal for CKD complicating PPI-induced AIN emerged when many of these patients did not return to their baseline kidney function after an AIN episode.[1,2,5–9] Subsequent studies examined the question of additional AIN risk with PPI exposure at a population level. A population–based nested case-cohort study in a cohort of patients from New Zealand receiving PPIs examined the risk of AIN resulting in hospitalization or death.[10] The cohort included 572,661 patients without a history of AIN or other kidney disease who were exposed to PPIs between 2005 and 2009. Current PPI users had fivefold higher odds of developing AIN. Importantly, the absolute risk in current users >60 years old was much higher than that for younger current users. Elderly PPI users had a greater risk of AIN (approximately 0.2/1000 person-years) compared with those ages 15–49 years old (0.02/1000 person-years). A second population–based study evaluated elderly Ontario residents who were hospitalized with AKI and AIN within 120 days of initiating PPI therapy.[11] Using a propensity score–matching algorithm, 290,592 patients exposed to PPIs were matched to an equal number of controls. Both AKI and AIN incidence and hazard ratio (HR) were higher among patients given PPIs than among controls (AKI: 13.49 versus 5.46/1000 person-years; HR, 2.52;

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95% CI, 2.27 to 2.79 AIN: 0.32 versus 0.11/1000 person-years; HR, 3.00; 95% CI, 1.47 to 6.14). These population-based studies suggest that AIN risk is increased in PPI users, particularly older individuals.

Although most clinicians accept that early AIN recognition with drug withdrawal and possibly, steroid therapy may lead to improved renal recovery, the potential burden of CKD is often forgotten. Long–standing unrecognized subclinical AIN may actually transition to chronic interstitial nephritis, leading to CKD and potentially, ESRD. This was suggested by a case series that showed development of CKD in patients after an episode of AIN.[3,5–9] Moreover, given the absence of a reliable non-invasive test, it is possible that a substantial proportion of PPI-induced AIN in the general population may be missed and may contribute to the burden of CKD. The existence of PPI-associated CKD has remained purely hypothetical, however, because CKD has not been definitely shown to be a complication of PPI therapy.

However, this has now changed with recent studies examining the association of PPIs with CKD using the power of large databases. Lazarus *et al.*[12] performed an ancillary study from the Atherosclerosis Risk in Communities Study, a prospective epidemiologic study in United States communities that collects patient data at multiple phases of baseline examination visits and follow-up. Lazarus *et al.*[12] evaluated the association between self–reported PPI use at baseline and CKD at last follow-up in 10,482 patients without baseline CKD. The prevalence of PPI use increased from <5% at baseline visit in 1996–1999 to >25% at last follow-up at the end of 2011. PPI users had a higher rate of CKD (14.2/1000 person-years) compared with nonusers (10.7/1000 person-years) and a higher risk of being diagnosed with CKD on the basis of validated hospitalization diagnosis codes with an adjusted HR, 1.50 (95% CI, 1.14 to 1.96). The absolute risk increase for CKD in PPI users was 3.3% (number needed to harm =30). A finding that perhaps links CKD to AIN (AKI as the surrogate) was that PPI use was also associated with higher AKI risk with an adjusted HR, 1.64 (95% CI, 1.22 to 2.21). This association persisted on various sensitivity analyses, including using histamine 2 (H2) receptor antagonist users as controls and PPI ever use modeled as a time-varying variable [adjusted HR, 1.35 (95% CI, 1.17 to 1.55)]. To further support this association, Lazarus *et al.*[12] replicated their findings in a cohort of 248,751 patients without CKD from the Geisinger Health System. PPI use was associated with increased risk of CKD with an adjusted HR, 1.17 (95% CI, 1.12 to 1.23). Higher risk was observed with twice daily PPI dosing compared with once daily dosing. The 10-year absolute risk of CKD increase in PPI users was 1.7% (number needed to harm =59). H2 receptor antagonist use was not associated with higher CKD risk compared with nonuse in either cohort.

In this issue of the *Journal of the American Society of Nephrology*, Xie *et al.*[13] examined the association between PPI use and CKD over 5 years of follow-up in the Veterans Affairs National Database. The study included 173,321 PPI users and compared them with 20,270 H2 receptor antagonist users. The incidence of CKD was higher in PPI users compared with H2 receptor antagonist users [3.7 versus 2.6/1000 person-years; (95% CI, 1.23 to 1.34)]. Similarly, Xie *et al.*[13] also showed that, compared with H2 receptor antagonist users, PPI users had higher risks of eGFR<60 ml/min per 1.73 m^2 [HR, 1.22 (95% CI, 1.18 to 1.26)], doubling of serum creatinine [HR, 1.53 (95% CI, 1.42 to 1.65)], and ESRD HR, 1.96 (95% CI, 1.21 to 3.18). In addition, the risk for all renal outcomes increased significantly with longer duration of PPI use. Finally, consistent with the prior studies, AKI risk was increased in PPI users with an HR 2.15 (95% CI, 2.00 to 2.32), further lending support to the potential link between PPI-induced AIN and development and progression of CKD. Interestingly, the association of PPI use with CKD remained significant, despite adjustment for AKI, suggesting that the PPI-CKD connection may be mediated *via* unrecognized, subclinical AIN, which is consistent with the previously described clinical presentation of these drugs.

Taken together, these studies shed light on an important adverse event with long–term PPI use.[12,13] The results of these studies associating PPI use with CKD in the community lead one to conclude that, although observational studies cannot prove causation, there is an extremely strong association. These epidemiologic observational data provide preliminary support for an increased risk of CKD in patients using PPIs. This observation complements the past studies showing an increased risk of AIN and AKI in patients taking PPIs.[10,11] As clinicians digesting these data, we are compelled to speculate on the possible role of AIN as a mediator of the PPI-CKD connection. In our view, the increase in CKD is likely caused by undiagnosed and as a result, untreated PPI–induced AIN, which allows the inflammatory tubulointerstitial process to progress over time to chronic interstitial fibrosis. The currently described CKD findings may be only the tip of the CKD iceberg, because patients with CKD were excluded from both studies.[12,13] Accordingly, PPI use in patients with CKD, which is fairly widespread because of nonrenal clearance and ease of dosing in this population, may also be associated with a more rapid progression of underlying CKD. The mechanism would be similar—superimposed PPI–induced AIN on the underlying CKD lesion.

In the end, the message for physicians and patients is that PPI use should be discouraged when a clear cut indication does not exist, despite the apparent short–term safety. In those who require PPI therapy to treat acid–related gastrointestinal disease, some form of surveillance (serum creatinine and/or urinalysis testing) should probably be undertaken. Practitioners prescribing these drugs should be aware of both the short–term AIN and AKI risk as well as the long–term CKD risk. PPI-induced AIN should be considered in patients with unexplained serum creatinine rise or urinalysis abnormalities, prompting nephrology consultation and possibly, kidney

biopsy to verify (or rule out) AIN. It is more challenging for the medical community to monitor for the development of kidney disease in patients using over the counter PPIs. Although it is premature to consider eliminating PPIs from over the counter availability, clinicians should always query their patients about use of these nonprescribed drugs. Stopping the drug, switching to an H2 receptor antagonist for those with acid–related gastrointestinal disease (remembering that PPI-induced AIN maintains a class effect), and considering steroids are the standard clinical approaches to AIN. Ultimately, they may reduce the development of CKD.

DISCLOSURES

None.

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