Proton Pump Inhibitors in Kidney Disease

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Proton pump inhibitors (PPIs) are one of the most frequently used classes of medications in the world, and they are particularly common among patients receiving hemodialysis. In 2015, nearly one half of all Medicare-enrolled patients on hemodialysis received a prescription for an acid suppressant (1). Unfortunately, patients receiving hemodialysis are underrepresented in most premarket drug safety studies and randomized, controlled trials, the optimal study design to evaluate benefits and risks of a medication in a particular group. Thus, observational data, such as those reported in the study by Vangala *et al.* (2) in this issue of the *Clinical Journal of the American Society of Nephrology* (CJASN), are required to inform clinical decisions regarding PPI use in patients receiving hemodialysis.

Only a few studies have evaluated the effectiveness of PPI therapy in patients receiving hemodialysis. In a prospective trial of 93 patients on maintenance hemodialysis in Taiwan, patients receiving omeprazole had a lower incidence of symptoms requiring upper endoscopy and lower cumulative incidence of peptic ulcer disease at 18 months compared with those who did not receive omeprazole, despite similar prevalence of *Helicobacter pylori* in both groups (3). In a single-center retrospective cohort study of 544 patients on hemodialysis in South Korea, PPI use was associated with a significantly reduced incidence of upper gastrointestinal bleeding (4). In a separate study of patients on hemodialysis with dyspepsia, quality of life scores were improved after a brief trial of PPI therapy (5). However, there was no control arm, and the duration of therapy was limited to 4 weeks.

Although generally viewed as low risk, PPIs have been associated with adverse effects in observational studies of the general population and small studies of patients receiving hemodialysis. In the general population, adverse outcomes associated with PPI use include kidney disease itself, hypomagnesemia, vitamin B12 deficiency, *Clostridium difficile* infection, pneumonia, and hip fractures (6). In the Nurse's Health Study, a prospective cohort of 79,899 postmenopausal women in the United States, regular PPI users had a 36% higher risk of hip fracture compared with nonusers, with higher risk associated with longer duration of use and resolution of risk 2 years after PPI cessation (7). Results were consistent when meta-analyzed with ten separate observational studies and in a patient-control study of patients with a kidney transplant (adjusted odds ratio, 1.39; 95% confidence interval, 1.04 to 1.84) (7,8). In patients receiving hemodialysis, studies have linked PPI use with alterations in electrolytes and mineral and bone disease parameters, including hypomagnesemia, hyperphosphatemia, arterial calcification, and reduced bone density (9–11). Thus, an increased risk of hip fracture associated with PPI use among patients receiving hemodialysis is biologically plausible.

In this issue of the CJASN, Vangala *et al.* (2) quantified the risk of hip fracture associated with PPI use in a retrospective patient-control study of patients receiving hemodialysis between 2006 and 2014. Patients were identified through the US Renal Data System registry, and inclusion criteria required that they receive prescription drug coverage *via* Medicare Part D and a low-income subsidy for at least 3 years. The 4551 patients were selected using diagnostic and procedural codes, and the 45,510 controls were randomly selected using incidence density sampling. Exposure to PPI and histamine-2 receptor antagonist medications were determined on the basis of Medicare Part D claims, a strength compared with an exposure solely on the basis of prescription. After adjustment for age, sex, race, body mass index, dialysis vintage, geographic region, comorbidities, and primary cause of ESKD, the adjusted odds ratio for hip fracture with any PPI use in the previous 3 years (compared with no PPI use) was 1.19 (95% confidence interval, 1.11 to 1.28). Prior histamine-2 receptor antagonist use was not higher in those with hip fracture (adjusted odds ratio, 1.02; 95% confidence interval, 0.95 to 1.10). Although it might be expected that the risks associated with PPI use *vis-à-vis* bone health would accumulate over time, there was no difference in risk of hip fracture with longer duration of PPI therapy.

As with all previous observational research focused on PPI use, aspects of the study by Vangala *et al.* (2) may impair our ability to infer a causal relationship. Patient-control studies allow assessment of the cumulative effects of a given medication, but this method does not eliminate confounding by indication, or the possibility that factors that prompt initiation of a specific medication also relate to the outcome. For example, PPI use may be more common among older adults and women, both strong risk factors for hip fracture. Although the authors adjusted for demographics and other clinical characteristics, many factors were not amenable to capture or perfect measurement. Medications that cause or treat mineral and bone disease in patients

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on hemodialysis may cause gastrointestinal discomfort, which may, in turn, lead to increased PPI use, confounding the association. In addition, PPIs may reduce the efficacy of some medications used to treat mineral and bone disease. In a crossover trial, pantoprazole use impaired phosphate binding by calcium carbonate, resulting in higher levels of phosphate and intact parathyroid hormone and lower levels of calcium compared with placebo (9).

The study results by Vangala *et al.* (2) do support current US Food and Drug Administration (FDA) labeling. Since 2010, the FDA has required that PPI manufacturers include the possibility of increased risk for bone fracture on the product label. Although the absolute risk of hip fractures associated with PPI use in the general population is likely to be small (in the Nurse's Health Study, the incidence of hip fracture was two events per 1000 patient-years for PPI users compared with 1.5 events per 1000 person-years for non-PPI users [7]), the absolute risks could be substantially higher in patients on hemodialysis. Patients on dialysis have a greater risk of hip fractures than the general population and a much higher rate of PPI use. Furthermore, Vangala *et al.* (2) report that long-term PPI use is common in the hemodialysis population, with nearly 15% of patients receiving PPIs for >2.4 of the previous 3 years.

In summary, this study suggests a modestly increased risk of hip fracture among patients receiving hemodialysis who use PPIs and provides valuable information on the prevalence and duration of PPI use in a hemodialysis population. The association between PPI use and hip fracture is biologically plausible, but—similar to the previous observational studies of PPI use and adverse events—the study cannot definitively assert that PPI use causes hip fracture. However, a randomized, controlled trial to address risks of PPI use in patients receiving hemodialysis is likely not practicable. On the basis of the available data, we suggest that PPI use in patients on hemodialysis be individualized, with discontinuation as soon as medically indicated, and that patients be counseled about possible adverse effects, including the possibility of heightened risk of hip fracture.

Disclosures

None.

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