Problematic Medications

Q At a lecture I recently attended, the speaker said sulfamethoxazole/trimethoprim is a potentially dangerous medication. I use it all the time. Is there any data to support her comments? Where did she get her information?

Sulfamethoxazole/trimethoprim (SMX/TMP) is a combination of two antibiotics, each of which has the potential to interact with other substances.

It is well documented that sulfamethoxazole can inhibit the metabolism of cytochrome P450 2C9 substrates. Frequently prescribed medications that also use the cytochrome substrate include warfarin and oral antihypoglycemic agents.

Trimethoprim's distinct properties also lead to drug interactions. Trimethoprim inhibits sodium uptake by the appropriate channels in the distal tubule of the kidney, preventing reabsorption and altering the electrical balance of the tubular cells. As a result, the amount of potassium excreted into the urine is reduced, yielding an accumulation of serum potassium.[1]

High serum potassium retention can manifest as hyperkalemia in patients with chronic kidney disease (CKD). Use of potassium-sparing drugs by patients with comorbidities, including CKD, can increase risk for hyperkalemia; concurrent use of these drugs with ACE inhibitors or angiotensin II receptor blockers (ARBs) compounds the risk.[2] The first reports of hyperkalemia with trimethoprim use occurred in HIV patients treated with large doses for *Pneumocystis carinii* infection.[3]

In a population-based case-control study, the results of which were published in the *British Medical Journal*, Fralick and colleagues analyzed data on older patients (age 66 or older) who were taking either ACE inhibitors or ARBs in combination with an antibiotic.[4] They found a significantly increased risk for sudden death within seven days of prescription of SMX/TMP, compared to amoxicillin; a secondary analysis also revealed an increased risk for sudden death within 14 days with SMX/TMP. The researchers speculated that this excess risk, which translated to 3 sudden deaths in 1,000 patients taking SMX/TMP versus 1 sudden death in 1,000 patients taking amoxicillin, "reflects unrecognized arrhythmic death due to hyperkalemia."

Since more than 250 million prescriptions for ACE inhibitors/ARBs and 20 million prescriptions for SMX/TMP are written each year, there will be instances of overlap. The prudent clinician would prescribe a different antibiotic or, if avoidance is not possible, use the lowest effective dose and duration of SMX/TMP. Close monitoring of serum potassium levels is warranted in patients with comorbidities, especially CKD, who are taking ACE inhibitors or ARBs—and of course, in our geriatric population. **—DLC**

Q I am getting calls from patients saying they heard a "stomach medicine" would hurt their kidneys. What is the basis, and how should I respond?

Emerging evidence is suggestive of a causal association between proton pump inhibitor (PPI) use and acute kidney injury/interstitial nephritis. Acute kidney injury is defined as either a decrease in urine output to less than 0.5 mL/kg/h for six hours, a rise in serum creatinine of 0.3 mg/dL or more within 48 hours, or an increase in creatinine of 50% or more above baseline within a week. Acute interstitial nephritis is often definitively diagnosed by renal biopsy, with findings of acute inflammatory cells, interstitial edema, and infiltration. Medications are the most common etiology for acute interstitial nephritis and account for more than 75% of cases.[5]

According to results published in the *American Journal of Kidney Diseases*, a retrospective study of 133 biopsy-proven cases of acute interstitial nephritis found 70% were associated with medication use. Of these, 14% were linked to use of a PPI (other drug culprits included antibiotics and

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NSAIDs, responsible for 49% and 11% of cases, respectively). Overall, omeprazole was the top drug cause, at 12%.[6]

In a nested case-control study of 572,661 subjects (mean age, 65.4) taking either lansoprazole, omeprazole, or pantoprazole, 46 definite cases and 26 probable cases of first-time acute interstitial nephritis were identified. Omeprazole was the most commonly dispensed PPI in this study. The crude incidence rate per 100,000 person-years for current use of a PPI was 11.98 and for past use, 1.68.[7]

Another nested case-control study of 184,480 subjects (ages 18 and older) reported 854 cases of acute kidney injury, with a positive association between use of a PPI and development of renal disease, even after controlling for confounding factors ($P < .0001$). Of note, no significant relationship was found between acute renal injury and use of H_2 blocker therapy.[8] **—CAS** **CR**

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