BACKGROUND

ACE-I/ARBs are commonly prescribed medications for hypertension, congestive heart failure, diabetes, and renal disease, and providers across specialties often see patients taking an ACE-I/ARB. Lisinopril holds a place as the third most prescribed drug in the United States, with 87.4 million prescriptions written for it in 2010.1 TMP-SMX is a widely used antibiotic for both in- and outpatient settings, good for bacterial infections ranging from uncomplicated urinary tract infections to methicillin-resistant Staphylococcus aureus infections to respiratory tract infections. It is a staple medication on the WHO Model List of Essential Medicines.2 While both drugs are commonly prescribed, the safety of coadministration has not been fully evaluated. Both drugs are capable of increasing serum potassium and causing hyperkalemia, a metabolic abnormality that can cause weakness, cardiac arrhythmias, and death.

HYPERKALEMIA

Hyperkalemia can be a serious metabolic abnormality, manifesting with symptoms including weakness, paralysis, metabolic acidosis, arrhythmias, sudden cardiac arrest, and death.

Ovid-Medline, Web of Science, Google Scholar, and Ovid International Pharmaceutical Abstracts were searched using the terms TMP-SMX and ACE inhibitor and ARB was done. Eligibility criteria included studies in the English language, studies that included concurrent use of TMP-SMX and ACE inhibitors or ARBs, and studies focused on on-label uses of TMP-SMX. Three articles met inclusion criteria and were evaluated with GRADE criteria—one retrospective cohort study10 from Ehime, Japan examining hyperkalemia in patients on an ACE-I/ARB prescribed low-dose TMP-SMX and two population-based, nested case-control studies11,12 out of Ontario, Canada examining the risk of hyperkalemia-associated hospitalization or sudden death associated with concomitant TMP-SMX and ACE-I/ARB use.

All three studies,11,12 found an increased risk of ACE-I/ARB patients prescribed TMP-SMX having an adverse outcome. Higashioka et al found an increased risk for development of hyperkalemia in patients who already had renal insufficiency. Antoniou et al found an increased risk of hospitalization with a diagnosis of hyperkalemia in elderly patients. Fralick et al found an increased risk of sudden death in elderly patients. Both Higashioka et al10 and Antoniou et al12 showed a large magnitude of effect, suggesting results are worth considering in clinical practice even with study limitations. While Fralick et al11 may not have shown as large an effect, the seriousness of the outcome (sudden death) leads the prudent clinician to consider their results.

The GRADE quality of evidence for all three of these retrospective cohort studies is very low. Although they have large and robust sample sizes, Fralick et al11 and Antoniou et al12 draw from the same population database, leading to the possibility of some selection bias. While Higashioka et al10 draws from a different population, the population size is significantly smaller and comes from a single medical center in Japan. Higashioka et al10 was the only study to include patients younger than 66 years; despite this, this age range was still 66 years, leaving applicability to younger patients unknown.

Other limitations included lack of patient-centered outcomes, possible confounding due to antibiotic usage, lack of information on TMP-SMX and ACE-I/ARB dosing.

REFERENCES

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THE BOTTOM LINE

Providers should be aware that prescribing TMP-SMX to patients already taking an ACE-inhibitor or ARB, especially elderly patients and those with renal insufficiency, may lead to poor outcomes that include development of hyperkalemia, hospitalization, and sudden death. When treating these populations, clinicians should consider whether there is an alternative and equally efficacious antibiotic; if one is not available, consideration to renal function and potential metabolic monitoring should be given.

Future studies would benefit from continuing to utilize patient-centered outcomes, creating a head-to-head comparison of TMP-SMX risk with and without concomitant ACE-I/ARB use, eliminating possible confounding related to other antibiotic use, and including younger patients.

Case cohorts also had a higher likelihood of having a history of hyperkalemia or residing in a long-term care facility (Antoniou et al) or having renal disease, heart failure, or loop diuretic use (Fralick et al).7,8,10,11,12 Further research is needed to fully understand that potential risks of TMP-SMX use in patients already prescribed an ACE-I/ARB. A direct comparison of patients with/without ACE-I/ARB prescription who are taking TMP-SMX along with dose-dependent results for both ACE-I/ARB and TMP-SMX would provide valuable information. Additionally, reviewed studies are fairly limited to elderly patients, and the impact of concurrent medication use in younger patients with preserved kidney function would help clinicians identify population groups that may be able to tolerate this combination of medications. Future studies would also benefit from following the lead of Antoniou et al and Fralick et al in designing studies with patient-centered outcomes rather than laboratory measurements.