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Life-threatening Interaction Between Renin-angiotensin-aldosterone System Inhibitors and Trimethoprim-sulfamethoxazole in Older Adults

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ABSTRACT

Older adults comprise 13% of the population of the United States and often have multiple chronic diseases that lead to the consumption of numerous prescription medications. Among the diagnoses often affecting older adults are hypertension, diabetes, and chronic kidney disease. Because of these diagnoses and normal physiologic changes of aging, older adults often are prescribed an inhibitor of the renin-angiotensin-aldosterone system, which may increase their risk for hyperkalemia and life-threatening arrhythmias if they are prescribed trimethoprim-sulfamethoxazole for a urinary tract infection. Careful consideration of renal status and medication usage is important when considering antimicrobial treatment for urinary tract infections in older adults.

Keywords: adverse drug reaction, drug-drug reaction, hyperkalemia, older adult, renin-angiotensin-aldosterone-system, trimethoprim-sulfamethoxazole, urinary tract infection

There are more than 39 million adults who are at least 65 years old living in the United States, which comprises roughly 13% of the overall population.[1] Aging is associated with a greater risk for chronic medical conditions; 62% of adults over the age of 65 have at least 2 chronic medical conditions, and roughly 23% of this population has at least 5 chronic medical conditions.[2] For a variety of health and medical reasons, older adults consume 34% of all prescription medications and 50% of all over-the-counter medications, and nearly 30% of older adults take at least 5 prescription medications daily.[1,3] The use of multiple medications is 1 factor that puts older adults at risk for adverse drug reactions (ADRs) caused by drug-drug interactions (DDIs).

CHRONIC DISEASES IN OLDER ADULTS

According to Centers for Medicare & Medicaid Service 2010 data, more than 65% (21.4 million beneficiaries) of older adults had 2 or more chronic medical conditions. Sixty-one percent of Medicare beneficiaries aged 65 and older had high blood pressure (HTN), 28% had diabetes, and 15% had chronic kidney disease (CKD).[4] In a large study of community-dwelling older adults, cardiovascular disease was the most commonly reported chronic medical condition, and diabetes was the third most commonly reported chronic medical condition.[3] Medications that inhibit the renin-angiotensin-aldosterone system (RAAS) are part of evidence-based therapy for each of these conditions. Thus, older adults are more likely to be prescribed angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs). Angiotensin-converting enzymes and ARBs are repeatedly in the annual list of the top 10 most frequently prescribed medications.[5]

NORMAL PHYSIOLOGIC AND PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH AGING

In addition to polypharmacy and chronic medical conditions, older adults have a higher risk for ADRs because of normal physiologic changes that occur with aging that affect pharmacokinetics. Although

aging does have an effect on absorption, distribution, and metabolism, the clinical implications of normal physiologic changes for ADRs are minimal. However, nearly 40% of older adults have some amount of renal disease defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2.[6] Although this decrease has a more noticeable effect on renally excreted medications with narrow therapeutic windows, it may be 1 component in all DDIs in older adults.[7] Additionally, older adults with HTN and diabetes are at higher risk of alterations in excretion as well.

URINARY TRACT INFECTIONS PREVALENCE AND TREATMENT

Urinary tract infections (UTIs) are the second most common infections for which community-dwelling older adults seek medical attention.[8] In the US, there are more than 4 million clinic visits each year attributed to UTI.[7] Older adults are often more susceptible to UTIs because of normal physiologic changes of aging, mobility restraints, and pathophysiologic changes; UTIs account for 25% of diagnosed infections in this population.[9,10] Often, trimethoprim-sulfamethoxazole (TMP-SMX) is prescribed for UTIs in older adults because it is a first-line antimicrobial for use in acute, uncomplicated cystitis.[11]

POTENTIAL FOR ADVERSE DRUG INTERACTIONS BETWEEN RAAS INHIBITORS AND TMP-SMX IN OLDER ADULTS

The adverse drug interaction between RAAS inhibitors and TMP-SMX, which may lead to life-threatening hyperkalemia, is not a new phenomenon, and many of the studies that established this relationship were completed more than 15 years ago.[12-15] RAAS inhibitors, including ACE-Is and ARBs, ultimately inhibit the secretion of aldosterone, thereby decreasing sodium resorption and potassium excretion. The inhibition of sodium resorption reduces circulating blood volume and blood pressure. The inhibition of potassium excretion can lead to higher serum potassium levels. Trimethoprim also reduces sodium resorption and potassium excretion in the distal tubules.[16] In addition, many older adults have normal physiologic changes that affect pharmacokinetics by decreasing excretion. RAAS inhibitors are prescribed for HTN, diabetes, and CKD, and, therefore, many older adults taking these medications very likely have some pathological reduction in the glomerular filtration rate. The combined effects of normal physiologic changes, pathological changes of disease processes, and medications that decrease the excretion of potassium put many older adults at risk for potentially life-threatening hyperkalemia.

RAAS Inhibitors

It has become well-known that RAAS-inhibiting medications are associated with increased serum potassium. Sadjadi et al[17] performed a retrospective observational cohort study of more than 2,000 patients taking RAAS inhibitors and reported hyperkalemia (potassium $>$ 5 mEq/L) in 20.4% of patients taking ACE-Is and 31.0% of patients taking ARBs. Eschmann et al[18] studied DDIs in more than 76,000 hospitalized patients and reported the relative risk for patients taking more than 1 potassium-sparing drug of developing hyperkalemia was 3.3 ($P < .0001$) per additional potassium-sparing drug. Their group also reported that patients with diabetes and decreased renal function were at a higher risk of developing hyperkalemia.

Trimethoprim

In the historic 1975 clinical trial, Berglund et al[12] studied 21 participants and reported that trimethoprim increased serum creatinine concentration by 0.2 mg/dL. Witt et al[13] studied the effect of TMP-SMX or amoxicillin on the serum potassium concentration in 53 hospitalized men. The serum potassium in the men receiving TMP-SMX increased by 0.31 $\pm$ 0.38 mEq/L ($P < .001$) by the end of therapy, and the serum potassium of the amoxicillin group remained unchanged.[13] Alappan et al[14] studied 105 patients treated with TMP-SMX versus another antibiotic therapy and reported that 62.5% of patients receiving TMP-SMX had a serum potassium increase to $\geq$ 5.0 mEq/L and 21.2% of patients receiving TMP-SMX had a serum potassium increase to $\geq$ 5.5 mEq/L. In 1999, Alappan et al[15] conducted a prospective, randomized trial composed of 97 outpatient participants who were treated with TMP-SMX or another oral antibiotic. The serum