The Safety of TMP-SMX Use in Patients Taking an ACE-I or ARB

Aaron Inouye

Pacific University

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The Safety of TMP-SMX Use in Patients Taking an ACE-I or ARB

Abstract

Background: Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are commonly used medications for hypertension, heart failure, and diabetes. Trimethoprim-sulfamethoxazole (TMP-SMX) is a commonly used antibiotic for many bacterial infections. While hyperkalemia is a known risk of each drug, little has been studied about concomitant use of ACE-I/ARBs and TMP-SMX.

Methods: An exhaustive search of MEDLINE-Ovid, Web of Science, Google Scholar, and International Pharmaceutical Abstracts-Ovid using the search 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. Found studies were evaluated using GRADE criteria.

Results: Three studies met eligibility requirements. One retrospective cohort study showed that in patients with renal insufficiency receiving low dose of TMP-SMX, ACE-I/ARB use was a significant risk factor for developing hyperkalemia (adjusted OR 3.95, 95% CI 1.17-13.4). A large nested case-control study found patients taking an ACE-I/ARB prescribed TMP-SMX had an increased risk of hospitalization with diagnosis of hyperkalemia of when compared with those prescribed amoxicillin (adjusted OR 6.7, 95% CI 4.5-10.0). Another large nested case-control drawn from a similar population found patients taking an ACE-I/ARB had an increased risk of sudden death when prescribed TMP-SMX when compared with those prescribed amoxicillin (adjusted OR 1.54, 95% CI 1.29-1.84).

Conclusion: Studies suggest an increased risk with concurrent ACE-I/ARB and TMP-SMX use. As both are commonly prescribed medications, understanding these risks of concomitant use is important. Risks, including hospitalization and sudden death, are likely related to hyperkalemia and likely increase in patients with existing renal insufficiency. Before prescribing TMP-SMX in patients already taking an ACE-I/ARB, clinicians should consider alternatives. More research is needed to fully understand the risks associated with combining these medications.

Keywords: TMP-SMX, ACE inhibitor, Bactrim, trimethoprim-sulfamethoxazole, renin-angiotensin-aldosterone inhibitors, ARB

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The Safety of TMP-SMX
Use in Patients Taking an ACE-I or ARB

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A Clinical Graduate Project Submitted to the Faculty of the
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Abstract

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Conclusion: Studies suggest an increased risk with concurrent ACE-I/ARB and TMP-SMX use. As both are commonly prescribed medications, understanding these risks of concomitant use is important. Risks, including hospitalization and sudden death, are likely related to hyperkalemia and likely increase in patients with existing renal insufficiency. Before prescribing TMP-SMX in patients already taking an ACE-I/ARB, clinicians should consider alternatives. More research is needed to fully understand the risks associated with combining these medications.

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List of Abbreviations
ACE .......................................................... Angiotensin converting enzyme
ACE-I .......................................................... Angiotensin converting enzyme inhibitor
ARB .......................................................... Angiotensin receptor blocker
CI .......................................................... Confidence interval
HTN .......................................................... Hypertension
OR .......................................................... Odds ratio
TMP-SMX .................................................... Trimethoprim-sulfamethoxazole
The Safety of TMP-SMX Use in Patients Taking an ACE-I or ARB

BACKGROUND
Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are commonly used medications – lisinopril, a popular ACE-I, is the third most prescribed drug in the United States.\(^1\) Per multiple guidelines, use of an ACE-I/ARB is recommended as one of the primary options for initial treatment of uncomplicated hypertension, and is the recommended initial treatment for any hypertensive patient with diabetes or chronic kidney disease.\(^2\) In addition to their use for hypertension, ACE-I/ARBs are standard of care for patients who are post-myocardial infarction or have congestive heart failure, and also have a place in treatment for patients with renal disease and diabetes. Given that over a quarter, and potentially close to a third, of Americans suffer from hypertension, it is not unusual for providers to care for patients on an ACE-I/ARB.\(^2\)

TMP-SMX is another commonly prescribed antibiotic, used to treat everything from urinary tract infections to methicillin-resistant Staphylococcus aureus infections to respiratory tract infections. Its wide bacterial coverage, relatively low cost, and tendency to be well-tolerated when taken either intravenous or orally have made it a mainstay of medicine and garnered it a place on the World Health Organization Model List of Essential Medicines.\(^3\)

While these drugs are commonly prescribed and usually well-tolerated, they have both been shown to increase serum potassium levels.\(^4,5,6\) ACE-I/ARBs have the potential to cause hyperkalemia due to blockade of the renin-angiotensin-aldosterone pathway. Aldosterone, the terminal product of this pathway, upregulates the Na+/K+ ATPase pumps found in the distal convoluted tubule of the kidney. This leads to an increase in serum sodium and a decrease in serum potassium. Free water follows the retained sodium, increasing intravascular volume and
blood pressure. ACE-I/ARBs decrease blood pressure by stopping the production of aldosterone, leading to increased urine output, decreased serum sodium, increased serum potassium, and decreased blood pressure.  

The trimethoprim component of TMP-SMX increases serum potassium due to its similarities to amiloride, a potassium-sparing diuretic. Instead of directly increasing potassium reabsorption like renin-angiotensin-aldosterone blockers, they indirectly increase serum potassium by decreasing sodium reabsorption in the distal convoluted tubule, leading to increased urine sodium, increased urine output, and a relative decrease in the amount of potassium excreted in urine. Trimethoprim may also have an effect on the Na+/K+ ATPase pumps in the distal tubule.  

Hyperkalemia can be a serious metabolic abnormality, manifesting with symptoms including weakness, paralysis, arrhythmias, metabolic acidosis, and sudden cardiac arrest. While the potential of both ACE-I/ARBs and TMP-SMX to increase serum potassium levels is well established, the effect of these drugs in combination has not been fully explored. As they are both widely prescribed and used medications within the general population, providers should be informed as to possible side effects and interactions before initiating treatment. 

METHODS  
An exhaustive search of Ovid-Medline, Web of Science, Google Scholar, and Ovid International Pharmaceutical Abstracts was conducted using the search terms “TMP-SMX” and “ACE inhibitor” and “ARB”. Web of Science was also used to search for articles citing found articles. Eligibility criteria included studies in the English language, studies that included concomitant use of TMP-SMX and ACE inhibitors or ARBs, and studies focused on on-label
uses of TMP-SMX. Results were then assessed for quality using the GRADE criteria.\textsuperscript{9} A summary of GRADE characteristics of studies can be found in Table 1.

RESULTS

Seventeen results were reviewed for relevancy and inclusion. Of these, three articles met inclusion criteria—one retrospective cohort study\textsuperscript{10} from Ehime, Japan examining hyperkalemia in patients on an ACE-I/ARB prescribed low-dose TMP-SMX and two population-based, nested case-control studies\textsuperscript{6,11} out of Ontario, Canada examining the risk of hyperkalemia-associated hospitalization or sudden death associated with concomitant TMP-SMX and ACE-I/ARB use. Two retrospective studies\textsuperscript{12,13} evaluating the incidence of hyperkalemia with high- and standard-dose TMP-SMX were found; although these studies did include some discussion of patients taking an ACE-I/ARB, they were excluded from this literature review as they were focused on off-label use of TMP-SMX that required a higher-than-normal dose. Results are summarized in Table 2.

**Higashioka et al**

This retrospective cohort study\textsuperscript{10} examined adult patients who took prophylactic (subtherapeutic) doses of TMP-SMX for pneumocystis pneumonia at a hospital in Ehime, Japan. Of the 467 patients receiving TMP-SMX, those receiving a therapeutic dose of TMP-SMX (over 80/400mg/day), previously given TMP-SMX, without subsequent serum potassium levels within 30 days, with baseline hyperkalemia (greater than 5 mEq/L), and on dialysis were excluded leaving 186 patients in the cohort. Data collected included baseline serum potassium levels and serum potassium levels from day 5 to 30 after initiating TMP-SMX.\textsuperscript{10}

Within the cohort, 32 (17.2\%) developed hyperkalemia, defined as serum potassium greater than 5 mEq/L. Univariate analysis showed a statistically significant association between
ACE-I/ARB use and hyperkalemia in patients receiving low-dose TMP-SMX (odds ratio not provided). The multivariate analysis did not show a significant adjusted OR (1.97, 95% CI 0.82-4.71). However, within the subset of patients with renal failure ACE-I/ARB use was found to be a significant risk factor for development of hyperkalemia (adjusted OR 3.95, 95% CI 1.17-13.4).

Limitations include the retrospective nature of the study, using a lab value vs a true patient-centered outcome, the relatively small cohort from a single center, lack of information on ACE-I/ARB dosages, and exclusion of patients who already had an elevated serum potassium. Also, while these patients did include individuals as young as 20, the median age was 66 and approximately 60% were age 65 or over; because of this, results may not be as applicable to younger populations.

Antoniou et al
This retrospective, population-based, nested case-control study looked at patients aged 66 years and older living in Ontario, Canada who were receiving long-term ACE-I/ARB therapy for any reason. Information was taken from the Canadian Institute for Health Information Discharge Database and the Registered Persons Database. Data was collected for the interval between April 1, 1994 and March 21, 2008.

Hospitalizations with an associated admission diagnosis of hyperkalemia were identified for patients within the cohort who had received a prescription for TMP-SMX, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin within 14 days prior to hospitalization. Up to four controls who had not been hospitalized were selected from the same cohort for each incidence of hospitalization; these controls were also required to have received a prescription for one of the selected antibiotics. Cases and controls were matched for age, sex, renal disease, and diabetes.
There were 439,677 individuals in the cohort, 4148 with hospitalization with diagnosis of hyperkalemia, and 371 patients who were hospitalized within 14 days of being prescribed an antibiotic.\textsuperscript{6}

For the primary analysis, amoxicillin-receiving patients were used as a control group and compared to those receiving other antibiotics with a hyperkalemia-associated hospitalization. Secondary analyses were done using 7 and 21 day windows prior to hospitalization.\textsuperscript{6}

Authors found that patients prescribed TMP-SMX had an increased risk of hospitalization with diagnosis of hyperkalemia of when compared to patients prescribed amoxicillin (adjusted OR 6.7, 95\% CI 4.5-10.0). This increased risk was maintained through the secondary analyses at 7- and 21-day windows (OR of 6.8 and 6.5, respectively). There was no increased risk associated with any of the other antibiotics.\textsuperscript{6}

Limitations include the retrospective nature of the study, lack of baseline and post-prescription serum potassium measurements in all patients, lack of information on dose/duration of prescriptions for both ACE-I/ARB and antibiotics, lack of information on comorbidities aside from renal disease and diabetes, a primary outcome that may miss important patient outcomes (patients may expire before hospitalization), and possible confounding due to antibiotic usage (TMP-SMX may be prescribed for sicker patients than amoxicillin or other studied antibiotics). The case cohort also had a large percentage of patients with a history of hyperkalemia within the last three years and were more likely to reside in a long-term care facility. It is also unclear how these results would translate to younger patients.\textsuperscript{6,14,15,16}

\textbf{Fralick et al}

This retrospective, population-based, nested case-control study\textsuperscript{11} looked at patients aged 66 years and older living in Ontario, Canada who were receiving long-term ACE-I/ARB therapy
for any reason. Information was taken from the Canadian Institute for Health Information Discharge Database, the Registered Persons Database, and the Vital Statistics Database. Data was collected for the interval between April 1, 1994 and January 1, 2012.\textsuperscript{11}

Case patients were identified as those who died suddenly (using to a previously validated approach and checked using Medicaid databases and death certificates) and had received a prescription for TMP-SMX, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin 7 or 14 days prior. Up to four controls who were alive at the index date were selected from the same cohort; controls were also required to have received a prescription for one of the selected antibiotics in the 7 or 14 days prior to the case’s date of death. Cases and controls were matched for age, sex, renal disease, diabetes, congestive heart failure, and recognized risk factors for hyperkalemia. There were 1,601,543 patients receiving ACE-I/ARB therapy. Of these, 39,879 died suddenly, 11,110 within 7 days of antibiotic prescription and 18,27 within 14 days.\textsuperscript{11}

Authors found that patients had an increased risk of sudden death within 7 and 14 days of being prescribed TMP-SMX when compared with those prescribed amoxicillin (adjusted OR 1.38 and 1.54, 95% CI 1.09-1.76 and 1.29-1.84 respectively). Ciprofloxacin was also associated with an increase in risk of sudden death at 7 days (adjusted OR 1.29, 95% CI 1.03-1.62); this increased risk was not present at 14 days (adjusted OR 1.18, 95% CI 1.00-1.39). There was no increased risk associated with the other antibiotics.\textsuperscript{11}

As pointed out in two reviews\textsuperscript{14,16} of this study, limitations include the retrospective nature of the study, limitations related to the definition of sudden death (while they used a validated approach, positive predictive value was 87%), possible misclassification of sudden death (either non-sudden classified as sudden or sudden classified as non-sudden), lack of information on medication dosages, and possible confounding due to antibiotic usage (TMP-
SMX or ciprofloxacin may be prescribed for sicker patients than amoxicillin or other studied antibiotics). There was also a statistically significant difference in the percentage of patients in case vs control groups that had renal disease, heart failure, or were taking a loop diuretic; these comorbidities may have had an effect on patient outcomes. It is also unclear how these results would translate to younger patients.  

**DISCUSSION**

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 in 2010. 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.

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. These three studies expand on existing knowledge by examining whether concomitant ACE-I/ARB use and TMP-SMX leads to an increase in hyperkalemia, hospitalizations due to hyperkalemia, and sudden death (authors of the final study posit that sudden death is related to hyperkalemia).

These studies attempt to answer the basic question of whether TMP-SMX is safe to use in patients already taking an ACE-I/ARB, although they approach the question in different manners. Higashioka et al attempted to answer whether prophylactic TMP-SMX dosing for
pneumocystis pneumonia would cause hyperkalemia and included a sub-population of patients taking an ACE-I/ARB as one of their subgroups. Antoniou et al\textsuperscript{6} attempted to answer whether TMP-SMX, when given to patients on an ACE-I/ARB, leads to an increase in hospitalizations due to hyperkalemia. Fralick et al\textsuperscript{11} attempted to answer whether TMP-SMX, when given to patients on an ACE-I/ARB, leads to an increase in sudden death.

All three of these studies found an increased risk of ACE-I/ARB patients prescribed TMP-SMX having an adverse outcome (Table 2). Higashioka et al\textsuperscript{10} found an increased risk for development of hyperkalemia in patients who already had renal insufficiency (eGFR <60 mL/min/1.73m\textsuperscript{2}). Antoniou et al\textsuperscript{6} found an increased risk of hospitalization with a diagnosis of hyperkalemia in elderly patients (>66 years). Fralick et al\textsuperscript{11} found an increased risk of sudden death in elderly patients (>66 years).

The GRADE quality of evidence for all three of these retrospective cohort studies\textsuperscript{6,10,11}, in and of itself a limitation to quality, is very low (Table 1). Although they have large and robust sample sizes, Fralick et al\textsuperscript{11} and Antoniou et al\textsuperscript{6} draw from the same population database of patients age 66+ from Ontario, Canada, leading to the possibility of some selection bias. While Higashioka et al\textsuperscript{10} draws from a different population, the population size is significantly smaller and comes from a single medical center in Japan. Higashioka et al\textsuperscript{10} was the only study to include younger patients; despite this, the average age of their cohort was still 66 years, leaving true applicability to younger patients unknown.

Primary outcomes varied between these papers, as well. One limitation of Higashioka et al\textsuperscript{10} is that they did not use a patient-centered outcome, instead looking at laboratory measurements of serum potassium. This does have the advantage of showing typical serum potassium changes from baseline, as well as maximal change, but does not take into account any
patient outcomes such as increased morbidity/mortality. Antoniou et al. used hospitalization with a diagnosis of hyperkalemia as their outcome. While this is a patient-centered outcome, it may be subject to some bias as patients prescribed TMP-SMX may be sicker or more likely to require hospitalization than patients receiving amoxicillin, ciprofloxacin, or other antibiotics. This same concern is brought up regarding Fralick et al—namely that the increase in sudden death in patients taking TMP-SMX and ciprofloxacin may be indicative of the use of these drugs in seriously ill patients vs drugs such as nitrofurantoin or amoxicillin.11,14,15,16

Both Higashioka et al10 and Antoniou et al6 showed a large magnitude of effect (adjusted OR of 3.96 and 6.97, respectively), suggesting that results are worth considering in clinical practice even with study limitations. While Fralick et al11 may not have shown as large an effect (adjusted OR of 1.54), the seriousness of the outcome (sudden death) leads the prudent clinician to consider their results when prescribing.

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 given 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 concomitant 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.
CONCLUSION

Due to the frequent use of both ACE-I/ARB and TMP-SMX medications for common ailments, understanding the potential risks of concomitant use is important for medical providers across many specialties. Risks, including hospitalization and sudden death, are likely related to hyperkalemia secondary to ACE-I/ARB and the trimethoprim component of TMP-SMX, and are likely increased in patients who already suffer from renal insufficiency. When prescribing TMP-SMX in patients already taking an ACE-I/ARB, 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.
References


### Table 1 – GRADE characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higashioka et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Unlikely</td>
<td>Very Low</td>
</tr>
<tr>
<td>Antoniou et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Population based nested case-control study</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Unlikely</td>
<td>Very Low</td>
</tr>
<tr>
<td>Fralick et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Population based nested case-control study</td>
<td>Serious&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Unlikely</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

<sup>a</sup>Very wide CI, low precision of results

<sup>b</sup>Confounding variables present and case vs control groups not clearly equal
### Table 2 – Summary of findings

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adjusted OR of developing hyperkalemia (95% CI)(^{10})</th>
<th>Adjusted OR of hospitalization with diagnosis of hyperkalemia at 14 days post-antibiotic prescription (95% CI)(^{b})</th>
<th>Adjusted OR of sudden death at 14 days post-antibiotic prescription (95% CI)(^{11})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose TMP-SMX</td>
<td>1.97 (.82-4.71)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Low-dose TMP-SMX with renal insufficiency (eGFR &lt; 60mL/min/1.73m(^2))</td>
<td>3.96 (1.17-13.4)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Amoxicillin (reference)</td>
<td>---</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>TMP-SMX, dose unknown</td>
<td>---</td>
<td>6.7 (4.5-10.0)</td>
<td>1.54 (1.29-1.84)</td>
</tr>
<tr>
<td><em>Ciprofloxacin</em></td>
<td>---</td>
<td>1.4 (0.9-2.2)</td>
<td>1.18 (1.00-1.39)</td>
</tr>
<tr>
<td><em>Norfloxacin</em></td>
<td>---</td>
<td>0.8 (0.4-1.5)</td>
<td>0.83 (0.65-1.05)</td>
</tr>
<tr>
<td><em>Nitrofurantoin</em></td>
<td>---</td>
<td>1.1 (0.6-2.0)</td>
<td>1.03 (0.81-1.30)</td>
</tr>
</tbody>
</table>