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Beta-Blockers, Trimethoprim-Sulfamethoxazole, and the Risk of Hyperkalemia Requiring Hospitalization in the Elderly: A Nested Case-Control Study

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Background and objectives: The simultaneous use of beta adrenergic receptor blockers (β-blockers) and trimethoprim-sulfamethoxazole (TMP-SMX) may confer a high risk of hyperkalemia.

Design, setting, participants, & measurements: Two nested case-control studies were conducted to examine the association between hospitalization for hyperkalemia and the use of TMP-SMX in older patients receiving β-blockers. Linked health administrative records from Ontario, Canada, were used to assemble a cohort of 299,749 β-blockers users, aged 66 years or older and capture data regarding medication use and hospital admissions for hyperkalemia.

Results: Over the study period from 1994 to 2008, 189 patients in this cohort were hospitalized for hyperkalemia within 14 days of receiving a study antibiotic. Compared with amoxicillin, the use of TMP-SMX was associated with a substantially greater risk of hyperkalemia requiring hospital admission (adjusted odds ratio, 5.1; 95% confidence interval [CI], 2.8 to 9.4). No such risk was identified with ciprofloxacin, norfloxacin, or nitrofurantoin. When dosing was considered, the association was greater at higher doses of TMP-SMX. When the primary analysis was repeated in a cohort of non-β-blocker users, the risk of hyperkalemia comparing TMP-SMX to amoxicillin was not significantly different from that found among β-blocker users.

Conclusions: Although TMP-SMX is associated with an increased risk of hyperkalemia in older adults, these findings show no added risk when used in combination with β-blockers.

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Adverse drug reactions among the elderly are common. It is estimated that 50 serious adverse drug reactions occur for every 1000 patient-years (1). Drug-induced hyperkalemia is of particular concern because of its association with commonly used medications and its significant potential for harm, including sudden death (2–5). Common cardiovascular agents such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics all impart a risk of hyperkalemia (2,6–10). Many studies have suggested an augmented risk of hyperkalemia associated with simultaneous use of two or more of these agents (11–15). However, there may also be significant risks associated with other combinations of common, hyperkalemia-inducing medications such as beta adrenergic receptor blockers (β-blockers) and trimethoprim-sulfamethoxazole antibiotics (TMP-SMX).

β-Blocker prescriptions have steadily increased over the last 10 years (16). Their role in hyperkalemia through inhibition of cellular adrenergic receptor-dependent potassium translocation has been extensively studied (17–19). TMP-SMX is also in common use, representing 30% of all antibiotics prescribed for urinary tract infections (20,21). Trimethoprim is structurally related to the potassium-sparing diuretic amiloride and has been shown to block sodium channels in the distal nephron thereby limiting the electrochemical gradient driving potassium elimination (22–27).

Given their popularity, β-blockers and TMP-SMX antibiotics are frequently co-administered. We conducted a nested case-control study using health administrative data to explore the risk of hyperkalemia conferred by this combination of drugs. We hypothesized that concurrent use of β-blockers and TMP-SMX would pose a substantially greater risk of hyperkalemia requiring hospital admission than would the use of TMP-SMX alone.

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Materials and Methods

Design

Using health administrative data from July 1, 1994 to March 31, 2008, we established two cohorts of outpatient residents of Ontario, age 66 years and older. One cohort included only those with evidence of continuous β-blocker use, and the other included only those without evidence of any β-blocker use. Within these cohorts, we conducted separate nested case-control studies comparing the risk of hyperkalemia posed by TMP-SMX to that of amoxicillin. To assess interaction between β-blockers and TMP-SMX, we compared the estimates of risk from the two cohorts. We acquired and analyzed exposure, outcome, and covariate data according to a predefined protocol. The study was approved by the institutional review board at Sunnybrook Health Sciences Center, Toronto, Canada. The reporting of this study follows the STROBE statement guidelines (28).

Setting

Ontario is the most populous Canadian province, with approximately 12 million residents in the year 2008, of whom 1.6 million were older than 65 years (29). All residents received universal access to hospital and physician services, and elderly residents received coverage for prescription medications. Coverage for medical services and medications from a single provincial payer provided a comprehensive set of health administrative data.

Sources of Data

We identified prescription drug use using the Ontario Drug Benefits (ODB) database. The ODB program provides residents of Ontario 65 years of age or older with coverage for most prescription medications. We identified all hospitalizations attributed to hyperkalemia based on ninth and tenth editions of the *International Classification of Disease* (ICD-9 and ICD-10) codes recorded in the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD).We obtained covariate information from multiple databases including the ODB database, CIHI-DAD, and the Ontario Health Insurance Plan (OHIP) database. The OHIP database contains claims information on inpatient, outpatient, and laboratory services rendered to residents of Ontario. We obtained demographic data from the Registered Persons Database (RPD), which contains demographic information on all Ontarians ever issued a health card. Census data from Statistics Canada was linked to postal codes and used to determine neighborhood income quintile. These databases have been validated in previous epidemiologic studies (30–34). Data were complete except for 5% of income estimates that we imputed as the mean.

Participants

Cohorts. Drug coverage for each individual prescription in ODB is maximally 100 days duration; therefore, we established the cohort of continuous β-blocker users by including only those with repeated β-blocker prescriptions that were no more than 100 days apart. We established a cohort of nonusers by including only those without a β-blocker prescription in the ODB database.

Cases. Within the cohorts, we identified hospitalizations for hyperkalemia within 14 days after filling a prescription for one of the five study antibiotics: TMP-SMX, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin. These antibiotics are typically prescribed for urinary tract infections, which is one of the most common reasons for outpatient antibiotic therapy (35). We chose these antibiotics to help mitigate indication bias by restricting the range of possible infections underlying the prescriptions. We chose amoxicillin as the reference drug because it is one of the most commonly prescribed antibiotics and its use is not associated with hyperkalemia. We defined cases as hospitalizations attributed to hyperkalemia at the time of admission (ICD-9 or ICD-10 diagnosis codes 276.7 and E87.5, respectively). The date of hospital admission served the index date for all analyses. Among individuals with multiple episodes of hyperkalemia, we considered only the first hospitalization.

Controls. For each case, we randomly selected up to four patients who had filled a prescription for a study antibiotic but who had not been hospitalized for hyperkalemia. Potential controls had the same index date as their corresponding case patient and were included only if a study antibiotic prescription was detected in the preceding 14 days. Controls were also matched to cases on age at the index date (±1 year), sex, history of chronic kidney disease, and history of diabetes mellitus.

In both cases and controls, we excluded patients with prescriptions for multiple study antibiotics or a single nonstudy antibiotic within the 14 days before the index date. We also excluded those with evidence of end-stage renal disease or renal transplantation in the 3 years preceding the index date. All patients were at least 66 years of age at the time of analysis to ensure the availability of at least 1 year of drug use records preceding the index date.

Statistical Methods

We assessed differences between the baseline characteristics of case and control groups and those who received various types of antibiotics using standardized differences (36,37). We examined odds ratios (OR) for hyperkalemia comparing five groups of patients prescribed different study antibiotics. We used conditional logistic regression to estimate the OR and their 95% confidence intervals (CI). We adjusted for characteristics that may have predisposed to hyperkalemia in the multivariable model using all available data in the 3 years preceding the index date, including the Charlson comorbidity score (0, 1, ≥2) (38;39), the number of distinct prescriptions in the preceding year (≤5, 6 to 10, 11 to 15, 16 to 20, 21 to 25, ≥26) (40), socioeconomic status (quintiles 1 to 2, quintiles 3 to 5), congestive heart failure, coronary artery disease, and previous episodes of hyperkalemia. We adjusted for medications used within the 120-day interval before the index date that may have influenced serum potassium concentrations: Nonpotassium-sparing diuretics, potassium-sparing diuretics (7,8), potassium supplements, nonsteroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors (9), and angiotensin receptor blockers (6). We assessed for a statistical interaction by comparing the OR from the two cohorts using the technique of Altman and Bland, the OR from the first cohort reflected the risk of hyperkalemia among users of both β-blockers and TMP-SMX, and the OR from the second cohort reflected the same risk among users of TMP-SMX alone (41). Two-tailed P values of < 0.05 were interpreted as statistically significant. We conducted all analyses using SAS 9.1.3 software (SAS Institute, Carey, NC).

Additional Analyses

Severity of Hospital Admissions. For case patients, we determined the median duration of the hospital admission, whether there was an intensive care unit admission, and whether the patient died during the hospital admission.

Dose Response. To identify a dose-response relationship, we repeated the primary analysis with the TMP-SMX exposure stratified into single-strength (400 mg/80 mg) and double-strength (800 mg/160 mg) dose categories. We expected a higher risk of hyperkalemia with a larger dose of TMP-SMX.

Time from Antibiotic Prescription. We altered the time from antibiotic prescription and index date first to 7 days and then 21 days rather than 14 days as used in the primary analysis.

β-1 Receptor Selectivity. We repeated the primary analysis and test for interaction differentiating between β-1-selective and nonselective β-blockers. Given the role of the β-2 adrenergic receptor in translocation of potassium, we expected to find a stronger relationship with hyperkalemia when TMP-SMX was used in the setting of nonselective β-blockers (17,42,43).

Serum Potassium Testing. For the purposes of billing, the performing of serum potassium tests but not the test results are recorded in Ontario administrative databases. We examined the number of outpatient serum potassium tests performed between the dates of antibiotic prescription and the index date.

Absolute Risk of Hyperkalemia. To obtain a crude estimate of the absolute risk of hospital admission for hyperkalemia, we ascertained the number of cohort patients who received at least one TMP-SMX prescription and the number of those who required admission for hyperkalemia within the following 21 days.

Absolute Risk of Death. To obtain a crude estimate of the absolute risk of death, we ascertained the number of cohort patients who received at least one TMP-SMX prescription and the number of those who died within the following 21 days.

Results

Primary Analysis

During the 14-year accrual period, we identified a cohort of 299,749 β-blocker users. Of these, 31,186 filled at least one prescription for TMP-SMX, and 195 were admitted to hospital for hyperkalemia. We excluded six cases that could not be matched to a control. The final sample comprised 189 cases of hyperkalemia and 641 controls.

Characteristics according to hyperkalemia and antibiotic use are shown in Table 1 and Table 2, respectively. Cases had slightly

Table 1. Characteristics of β-blocker users admitted to hospital with hyperkalemia and matched controls[a]

Demographic and medical characteristics	Cases (n = 189)	Controls (n = 641)
Age, years	80 (73 to 84)	80 (74 to 84)
Age groups		
65 to 74	56 (29.6)	189 (29.5)
75 to 84	88 (46.6)	305 (47.6)
≥85	45 (23.8)	147 (22.9)
Male sex	66 (34.9)	219 (34.2)
Income quintile		
1 to 2 (lower)	100 (52.9)	286 (44.6)[b]
3 to 5 (higher)	89 (47.1)	355 (55.4)[b]
Charlson Score		
0	30 (15.9)	224 (34.9)
1	26 (13.8)	115 (17.9)[b]
≥2	133 (70.4)	302 (47.1)[b]
No. of prescription drugs in previous year		
≤5	<6	17 (2.7)
6 to 10	13 (6.9)	156 (24.3)[b]
11 to 15	58 (30.7)	191 (29.8)
16 to 20	59 (31.2)	171 (26.7)[b]
21 to 25	31 (16.4)	59 (9.2)[b]
≥26	25 (13.2)	47 (7.3)[b]
Congestive heart failure	113 (59.8)	273 (42.6)[b]
Coronary artery disease	138 (73.0)	393 (61.3)[b]
Diabetes	81 (42.9)	245 (38.2)
Chronic kidney disease	99 (52.4)	316 (49.3)
Prior hospitalization for hyperkalemia	16 (8.5)	13 (2.0)[b]
Medication use in preceding 120 days		
Nonpotassium-sparing diuretics	124 (65.6)	319 (49.8)[b]
Potassium-sparing diuretics	52 (27.5)	72 (11.2)[b]
Potassium supplements	<6	8 (1.2)[b]
NSAIDs	69 (36.5)	231 (36.0)
ACE/ARB	133 (70.4)	343 (53.5)[b]

[a]Data presented as number (percent) with the exception of age, which is presented as median (interquartile range). In accordance with Ontario privacy law, patient values less than 6 are not reported. NSAID, nonsteroidal anti-inflammatory drug; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[b]Indicates a standardized difference between case patients and controls greater than 10%. Standardized differences are less sensitive to sample size than tradition hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation (36,37).

Table 2. Characteristics of β-blocker users by antibiotic use[a]

Demographics and medical characteristics	TMP-SMX (n = 223)	Ciprofloxacin (n = 210)	Norfloxacin (n = 109)	Nitrofurantoin (n = 108)	Amoxicillin (n = 180)
Age	80 (74 to 86)	80 (73 to 84)	81 (76 to 85)	81 (75 to 86)	78 (71 to 82)
Age group					
65 to 74	63 (28.3)	68 (32.4)	25 (22.9)	24 (22.2)	65 (36.1)
75 to 84	98 (43.9)	99 (47.1)	52 (47.7)	52 (48.1)	92 (51.1)
≥85	62 (27.8)	43 (20.5)	32 (29.4)	32 (29.6)	23 (12.8)
Male	77 (34.5)	83 (39.5)	35 (32.1)	20 (18.5)	70 (38.9)
Income quintile					
1 to 2	109 (48.9)	106 (50.5)	47 (43.1)	45 (41.7)	79 (43.9)
3 to 5	114 (51.1)	104 (49.5)	62 (56.9)	63 (58.3)	101 (56.1)
Charlson score					
0	59 (26.5)	52 (24.8)	41 (37.6)	35 (32.4)	67 (37.2)
1	40 (17.9)	35 (16.7)	19 (17.4)	13 (12.0)	34 (18.9)
≥2	124 (55.6)	123 (58.6)	49 (45.0)	60 (55.6)	79 (43.9)
Congestive heart failure	112 (50.2)	102 (48.6)	53 (48.6)	45 (41.7)	74 (41.1)
Coronary artery disease	146 (65.5)	145 (69.0)	67 (61.5)	61 (56.5)	112 (62.2)
Diabetes in past 3 years	93 (41.7)	78 (37.1)	41 (37.6)	43 (39.8)	71 (39.4)
Prior hospitalization for hyperkalemia	11 (4.9)	<6	<6	<6	<6
Chronic kidney disease	122 (54.7)	101 (48.1)	49 (45.0)	64 (59.3)	79 (43.9)
No. of prescription drugs in previous year					
≤5	<6	<6	7 (6.4)	<6	<6
6 to 10	32 (14.3)	36 (17.1)	26 (23.9)	17 (15.7)	58 (32.2)
11 to 15	80 (35.9)	61 (29.0)	33 (30.3)	29 (26.9)	46 (25.6)
16 to 20	65 (29.1)	65 (31.0)	24 (22.0)	32 (29.6)	44 (24.4)
21 to 25	24 (10.8)	25 (11.9)	11 (10.1)	13 (12.0)	17 (9.4)
≥26	20 (9.0)	18 (8.6)	8 (7.3)	14 (13.0)	12 (6.7)
Medication use in preceding 120 days					
Nonpotassium-sparing diuretics	127 (57.0)	122 (58.1)	51 (46.8)	58 (53.7)	85 (47.2)
Potassium-sparing diuretics	32 (14.3)	41 (19.5)	18 (16.5)	15 (13.9)	18 (10.0)
Potassium supplements	<6	<6	0	<6	<6
NSAIDs	83 (37.2)	83 (39.5)	38 (34.9)	21 (19.4)	75 (41.7)
ACE/ARB	146 (65.5)	128 (61.0)	46 (42.2)	58 (53.7)	98 (54.4)

[a]Data presented as number (percent) with the exception of age, which is presented as median (interquartile range). In accordance with Ontario privacy law, patient values less than 6 are not reported. TMP-SMX, trimethoprim-sulfamethoxazole.

lower incomes and greater comorbidity (Table 1). The distribution of baseline characteristics was relatively consistent across the five types of antibiotics (Table 2). As shown in Table 3, among patients receiving β-blockers, those receiving concomitant TMP-SMX were five times more likely to be hospitalized for hyperkalemia than patients using amoxicillin (adjusted OR, 5.1; 95% CI, 2.8 to 9.4). No significant associations were observed between the other study antibiotics and admissions for hyperkalemia.

Table 3. Association between hospitalization for hyperkalemia and antibiotic use among β-blocker users

Variable	Cases (n = 189)	Controls (n = 641)	Odds Ratio (95% CI)	
			Unadjusted	Adjusted
TMP-SMX	98 (51.9)	125 (19.5)	5.9 (3.4 to 10.2)	5.1 (2.8 to 9.4)
Ciprofloxacin	51 (27.0)	159 (24.8)	2.3 (1.3 to 4.1)	1.8 (0.9 to 3.3)
Norfloxacin	8 (4.2)	101 (15.8)	0.7 (0.3 to 1.5)	0.5 (0.1 to 1.2)
Nitrofurantoin	12 (6.3)	96 (15.0)	0.9 (0.4 to 2.0)	0.7 (0.3 to 1.7)
Amoxicillin[a]	20 (10.6)	160 (25.0)	1.0	1.0

[a]Amoxicillin users served as the reference group.

The cohort of non-β-blocker users had a distribution of baseline characteristics similar to that of the β-blocker cohort (tables available upon request). Among non-β-blocker users, we identified 1349 cases patients and 5378 controls (Table 4). The OR for hyperkalemia requiring hospital admission comparing TMP-SMX to amoxicillin was 5.8 (95% CI, 4.7 to 7.3). This was not significantly different from the risk associated with TMP-SMX use among β-blocker users (*P* value for interaction 0.65). This indicated the risk of hyperkalemia was attributable to TMP-SMX alone, rather than its combination with β-blockers.

Additional Analyses

Severity of Hospital Admissions. For the 189 hospitalizations for hyperkalemia within the β-blocker cohort, the median length of stay was 7 days (interquartile range 4 to 13 days); 17 patients (9%) were admitted to intensive care units, and 26 died during their hospital stay (14%).

Dose Response. There was graded association with hospital admissions for hyperkalemia when TMP-SMX use was stratified by dose. For single-strength tablets the adjusted OR was 3.4 (95% CI, 1.6 to 7.4) compared with 6.6 (95% CI, 3.5 to 12.6) for double-strength tablets.

Time from Antibiotic Prescription. When we altered the time from antibiotic prescription to index date, the risk of hospital admission for hyperkalemia with TMP-SMX compared with amoxicillin was unchanged (7 days: OR, 5.5; 95% CI, 2.3 to 13.0; 21 days: OR, 5.9; 95% CI, 3.3 to 10.4).

β-Blocker Selectivity. The prevalence of nonselective β-blocker usage (7.3%) was insufficient for meaningful analysis.

Serum Potassium Testing. Between the date of antibiotic prescription and index date, 26 (14%) of case patients and 33 (5%) of controls had an outpatient serum potassium measurement. There was no difference in the proportion of patients tested across the five types of antibiotic users (between 6% to 7% for all five types).

Absolute Risk of Hyperkalemia. Within the β-blocker cohort, for every 1000 TMP-SMX prescriptions, there were 6.9 (95% CI, 6.0 to 7.9) hospital admissions attributed to hyperkalemia within the subsequent 21 days. In comparison, there were 2.9 (95% CI, 2.4 to 3.4) admissions for every 1000 amoxicillin prescriptions.

Absolute Risk of Death. Within the β-blocker cohort, for every 1000 TMP-SMX prescriptions, there were 26.2 (95% CI, 24.5 to 28.0) deaths within the subsequent 21 days. In comparison, there were 15.7 (95% CI, 14.6 to 16.9) deaths for every 1000 amoxicillin prescriptions.

Discussion

Main Finding

Based on their pharmacodynamic interaction, we hypothesized that concomitant β-blocker and TMP-SMX use would be associated with an excess risk of hyperkalemia. While we did observe a significant risk of hyperkalemia among elderly users of TMP-SMX, concomitant β-blocker use did not augment this risk.

Interpretation

The role of β-blockers in hyperkalemia among elderly ambulatory patients may not be as great as originally anticipated. Historic evidence for this role comes largely from experimental studies, where β-blocker administration has been associated with transient rises in serum potassium concentrations in the local circulation of heavily exercising limbs, in anuric dialysis patients, or subsequent to potassium-chloride infusion (18,42-47). In some clinical studies of hyperkalemic events, the causal role of β-blockers has been assumed without the presence of a referent group (2,48), and in other studies their role has been examined only in high-risk patient populations (49–51). Conversely, in more rigorously conducted clinical studies, β-blockers were not associated with hyperkalemia (6,52,53). Our study does not refute the physiologic effects of β-blockers, but does suggest their contribution to hyperkalemia in ambulatory patients may be relatively minor. An important caveat is the high prevalence of β-1-selective agent use in our cohort. This distribution of β-blocker selectivity reflects the usage of these drugs in Ontario and does not threaten the external validity of our study; however, extension of our findings to a specific population of nonselective β-blocker users would not be appropriate. Furthermore, in detecting modest effects, tests of statistical interaction are of limited power, and failure to show significant effect measure modification does not rule out a biologic interaction.

Although the absolute rate of hospital admissions with a primary diagnosis of hyperkalemia was small, this finding must be interpreted judiciously. Our definition of hyperkalemia was very strict. We did not count events that did not prompt hospital admission, emergency room visits without hospital admission, hospital admissions attributed to another primary reason, or more severe events resulting in prehospital death. It is of concern that in absolute terms, the risk of death within 21 days of antibiotic use appeared higher in TMP-SMX users compared with those who took amoxicillin. Nonetheless, with all antibiotics there is a potential for adverse events that

Table 4. Association between hospitalization for hyperkalemia and antibiotic use among non-β-blocker users

Variable	Cases (n = 1349)	Controls (n = 5378)	Odds Ratio (95% CI)	
			Unadjusted	Adjusted
TMP-SMX	670 (49.7)	1064 (19.8)	6.3 (5.2 to 7.7)	5.8 (4.7 to 7.3)
Amoxicillin[a]	163 (12.1)	1603 (29.8)	1.0	1.0

[a]Amoxicillin users served as the reference group.

must be balanced against their benefits. We recognize the importance of TMP-SMX in the modern antibiotic armamentarium and do not suggest curtailing its use. Rather, it is likely that some cases of severe morbidity associated with TMP-SMX may be prevented through simple measures such as serum potassium testing. In this analysis, only a small proportion of patients had such testing in the days following TMP-SMX prescription.

Strengths and Limitations

Our study has a number of strengths. The interaction between β-blockers and TMP-SMX has not been previously examined in a population-based study. Although the results can be generalized only to the elderly, our study was free of the screening biases that arise in the setting of clinical trials and restrictive cohorts. Ontario's universal health care system allowed us to draw upon the records of approximately 1.4 million people over the age of 66 years. The large sample afforded a unique opportunity to examine a relatively rare yet serious adverse drug event. Furthermore, emigration out of the Ontario health insurance plan is less than 1% per year, making it a very stable data set (2001 Canadian Census).

The most important limitation of our study is the nonrandom allocation of the study antibiotics. Therefore, residual confounding is certainly a possibility in driving the findings. Information on risk factors such as dietary potassium intake, nonprescription medication use, and medication compliance is not recorded within the administrative databases. Confounding by indication could also have occurred because severe infections can predispose to hyperkalemia through sepsis and resultant kidney injury. TMP-SMX is active against common and virulent organisms such as *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus*, so it is possible that patients treated with TMP-SMX had particularly severe infections compared with patients using other types of antibiotics (54–56). We attempted to avoid this problem by restricting our case definition to patients admitted with a primary diagnosis of hyperkalemia, rather than hyperkalemia occurring secondary to sepsis or acute kidney injury. Furthermore, while we cannot know the impact of potential confounders, the magnitude of the risk estimate observed in the primary analysis provides reassurance of a true biologic effect. It is difficult to conceive of an unmeasured confounder that is predictive of hyperkalemia and differentially present among the various antibiotic types to the extent that it accounts for all of the excess risk we observed.

We relied upon administrative databases and diagnostic codes to define the study outcome. Although our definition of hyperkalemia has not been validated, we believe it to be reliable for two reasons. A similar definition of hyponatremia was shown to have a specificity greater than 99% (57). Also, electrolyte disturbances as a whole are accurately recorded in the CIHI-DAD with a sensitivity of 80% and a specificity greater than 95% (32). Misclassification of exposure and outcome variables can occur when using health administrative data. However, the occurrence of coding errors between cases, controls, and the β-blocker and non-β-blocker cohorts was unlikely to have occurred at differential rates.

Finally, knowledge of the hyperkalemic effects of β-blockers and TMP-SMX may have caused some physicians to more frequently measure serum potassium levels in patients who were using these drugs. However, there was no difference in rates of outpatient potassium measurement between antibiotic types. As well, serum electrolyte measurement is a routine component of emergency department assessment, making differential case ascertainment between exposure groups less likely.

Conclusions

Our study shows a significant, biologically plausible, dose-dependent risk of hyperkalemia among elderly users of TMP-SMX. Physicians should be cognizant of this risk and consider measurement of serum potassium in older patients treated with this antibiotic.

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Disclosures

All authors declare no competing financial interests. The Ontario Drug Policy Research Network had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Data sharing: A technical appendix and additional tables describing non-β-blocker cohort are available from the corresponding author at amit.garg@lhsc.on.ca.

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