Hyperkalemia in Hospitalized Patients Treated with Trimethoprim–Sulfamethoxazole

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Objective: To determine the effect of standard-dose trimethoprim–sulfamethoxazole on serum potassium concentration in hospitalized patients.

Design: Prospective chart review.

Setting: Community-based teaching hospital.

Patients: 105 patients with various infections were hospitalized and treated. Eighty patients treated with standard-dose trimethoprim–sulfamethoxazole (trimethoprim, ≤320 mg/d; sulfamethoxazole, ≤1600 mg/d) composed the treatment group; 25 patients treated with other antibiotic agents served as the control group.

Measurements: Serum sodium, potassium, and chloride concentrations; serum carbon dioxide content; anion gap; blood urea nitrogen level; and serum creatinine level.

Results: The serum potassium concentration in the treatment group (mean ± SD) was 3.89 ± 0.46 mmol/L (95% CI, 3.79 to 3.99 mmol/L), and it increased by 1.21 mmol/L (CI, 1.09 to 1.32 mmol/L) 4.6 ± 2.2 days after trimethoprim–sulfamethoxazole therapy was initiated. Blood urea nitrogen levels increased from 7.92 ± 5.7 mmol/L (CI, 6.67 to 9.16 mmol/L) to 9.2 ± 5.8 mmol/L (CI, 7.9 to 10.5 mmol/L), and serum creatinine levels increased from 102.5 ± 49.5 μmol/L (CI, 91.4 to 113.6 μmol/L) to 126.1 ± 70.7 μmol/L (CI, 110.3 to 141.9 μmol/L). Patients with a serum creatinine level of 106 μmol/L (1.2 mg/dL) or more developed a higher peak potassium concentration (5.37 ± 0.59 mmol/L [CI, 5.15 to 5.59 mmol/L]) than patients with a serum creatinine level of less than 106 μmol/L (4.95 ± 0.48 mmol/L [CI, 4.80 to 5.08 mmol/L]). Patients with diabetes had a slightly higher peak potassium concentration (5.14 ± 0.45 mmol/L [CI, 4.93 to 5.35 mmol/L]) than did patients without diabetes (5.08 ± 0.59 mmol/L [CI, 4.93 to 5.23 mmol/L]), but the difference was not statistically significant. The serum potassium concentration in the control group was 4.33 ± 0.45 mmol/L (CI, 4.15 to 4.51 mmol/L), and it decreased nonsignificantly over 5 days of therapy.

Conclusions: Standard-dose trimethoprim–sulfamethoxazole therapy used to treat various infections leads to an increase in serum potassium concentration. A peak serum potassium concentration greater than 5.0 mmol/L developed in 62.5% of patients; severe hyperkalemia (peak serum potassium concentration ≥5.5 mmol/L) occurred in 21.2% of patients. Patients treated with standard-dose trimethoprim–sulfamethoxazole should be monitored closely for the development of hyperkalemia, especially if they have concurrent renal insufficiency (serum creatinine level ≥106 μmol/L).

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Hyperkalemia is a well-described complication of therapy with high-dose trimethoprim (20 mg/kg of body weight per day) in patients with the acquired immunodeficiency syndrome (AIDS) (1–3). In patients treated with trimethoprim, Velazquez and colleagues (1) noted an increase in serum potassium concentration of 0.6 mmol/L, and Greenberg and coworkers (2) showed an increase in serum potassium concentration of 1.1 mmol/L. Recently, three cases of hyperkalemia associated with standard-dose trimethoprim–sulfamethoxazole therapy were reported (4–6). We did a study to evaluate the effect of standard-dose trimethoprim–sulfamethoxazole on the development of hyperkalemia in hospitalized patients treated for various infectious processes.

Methods

All patients treated with trimethoprim–sulfamethoxazole from January 1994 to March 1995 at St. Mary's Hospital in Waterbury, Connecticut (Yale University Primary Care Residency Program) were identified through pharmacy records, and the charts of these patients were reviewed prospectively in the hospital. Patients treated with either oral or intravenous trimethoprim–sulfamethoxazole (trimethoprim, ≤320 mg/d; sulfamethoxazole, ≤1600 mg/d) for at least 5 days composed the treatment group. The control group consisted of patients identified by pharmacy records who were treated for an infectious process with an antibiotic agent other than trimethoprim–sulfamethoxazole for at least 5 days. The charts of these patients were also reviewed prospectively in the hospital.

Serum potassium, sodium, and chloride concentrations; serum carbon dioxide content; anion gap; blood urea nitrogen level; and serum creatinine level were measured and recorded daily before initiation of and during therapy with trimethoprim–sulfamethoxazole in both the treatment group and the control group. Age, sex, comorbid illnesses, and medications ingested both before and throughout hospitalization during the study period were recorded for each patient. Patients receiving medications that can alter potassium homeostasis or renal function were included in the study only if therapy with these medications had been initiated before hospitalization and if serum potassium concentration and renal function were stable before treatment with trimethoprim–sulfamethoxazole. Patients who did not meet these criteria were excluded from the study. All patients who did not have diabetes received a normal hospital diet (sodium, 4 g/d; potassium, 3 to 3.5 g/d); diabetic patients received an American Diabetic Association diet.

Table 1. Baseline Characteristics of the Treatment and Control Groups

Characteristic	Trimethoprim–Sulfamethoxazole Group	Control Group
Mean age ± SD, *y*	71.9 ± 16.0	75.9 ± 12.0
Age range, *y*	19–93	46–94
Men, *n(%)*	32 (40)	12 (48)
Diabetes, *n(%)*	19 (23.7)	5 (20)
Creatinine level ≥ 106 μmol/L, *n(%)*	28 (35)	12 (48)
Potassium-altering medications, *n(%)**	46 (62)	15 (60)
Mean potassium concentration, *mmol/L (95% CI)*	3.9 (3.8 to 4.0)	4.3 (4.15 to 4.5)
Mean blood urea nitrogen level, *mmol/L (95% CI)*	7.9 (6.65 to 9.2)	8.9 (8.0 to 10.2)
Mean serum creatinine level, *μmol/L (95% CI)*	102.5 (88.4 to 115.0)	117.6 (97.2 to 141.4)
Mean sodium concentration, *mmol/L (95% CI)*	138.0 (137.7 to 139.1)	138.0 (137.3 to 139.6)
Mean chloride concentration, *mmol/L (95% CI)*	101.7 (100.5 to 102.9)	102.0 (100.8 to 103.0)
Mean CO_2 level, *mmol/L (95% CI)*	25.0 (24.8 to 25.9)	25.0 (24.0 to 26.4)

* Angiotensin-converting enzyme inhibitor, potassium supplements, heparin, digoxin, nonsteroidal anti-inflammatory drugs.

Individual mean values and SDs for potassium concentration before treatment and at peak, as well as means and SEs, were determined. We also calculated 95% CIs for each mean. Both paired and independent two-tailed *t*-tests were used to compare the means. Significance was defined as $P < 0.05$. Results are expressed as mean ± SD unless otherwise noted.

Results

Eighty patients treated with standard-dose trimethoprim–sulfamethoxazole met the study criteria and composed the treatment group. The control group consisted of 25 patients treated with antibiotic agents (none of which are known to influence potassium homeostasis) other than trimethoprim–sulfamethoxazole who met the study criteria. Table 1 lists the baseline characteristics of the treatment and control groups. In the treatment group, 3 patients had AIDS, and 2 patients were positive for the human immunodeficiency virus. Although patients in the treatment group were treated for various infections, none was treated for *Pneumocystis carinii* pneumonia or received prophylaxis for *P. carinii* infection. Underlying illnesses that may have altered potassium homeostasis were urinary tract infection (6 patients), obstructive uropathy (2 patients), and pyelonephritis (1 patient). Importantly, the potassium values in these patients did not differ significantly from those in the rest of the patients in the treatment group. Also, the relative types of infection were similar in the two groups (3 controls had urinary tract infection, 1 had obstructive uropathy, and none had pyelonephritis). In addition, similar numbers of patients in the two groups received medications that may have altered potassium homeostasis, such as angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, heparin, potassium supplements, and digoxin (Table 1).

In the control group, no significant variations were noted in laboratory measurements when baseline values were compared with values during therapy. The mean serum potassium concentration was 4.33 ± 0.45 mmol/L (CI, 4.15 to 4.51 mmol/L) at baseline, and it decreased over the following 5 days of therapy (Figure 1). The mean serum creatinine level decreased nonsignificantly, from 117.6 ± 61 μmol/L (CI, 97.2 to 141.4 μmol/L) to 100.7 ± 54 μmol/L (CI, 79.1 to 122.3 μmol/L) at 5 days of therapy.

In the treatment group, the serum potassium concentration increased significantly ($P < 0.001$) from 3.89 ± 0.46 mmol/L (CI, 3.79 to 3.99 mmol/L) to a peak of 5.1 ± 0.56 mmol/L (CI, 4.98 to 5.22 mmol/L), a 1.21 mmol/L increase (CI, 1.09 to 1.32 mmol/L). The peak potassium concentration occurred at 4.6 ± 2.2 days of trimethoprim–sulfamethoxazole therapy. The mean potassium concentration in the

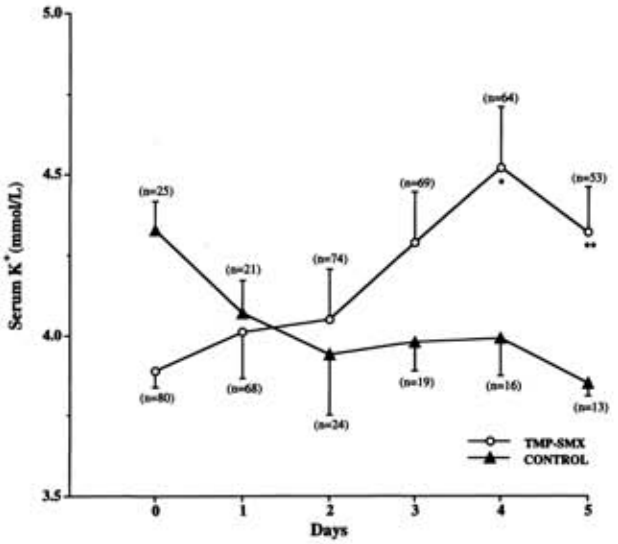

Figure 1. Baseline and peak daily serum potassium concentrations (mean ± SE) between the group treated with trimethoprim–sulfamethoxazole (*TMP-SMX*) and the control group. A statistically significant increase in potassium concentration occurred in the treatment group. K^+ = potassium; *n* = number of patients. *$P < 0.01$; **$P < 0.05$.

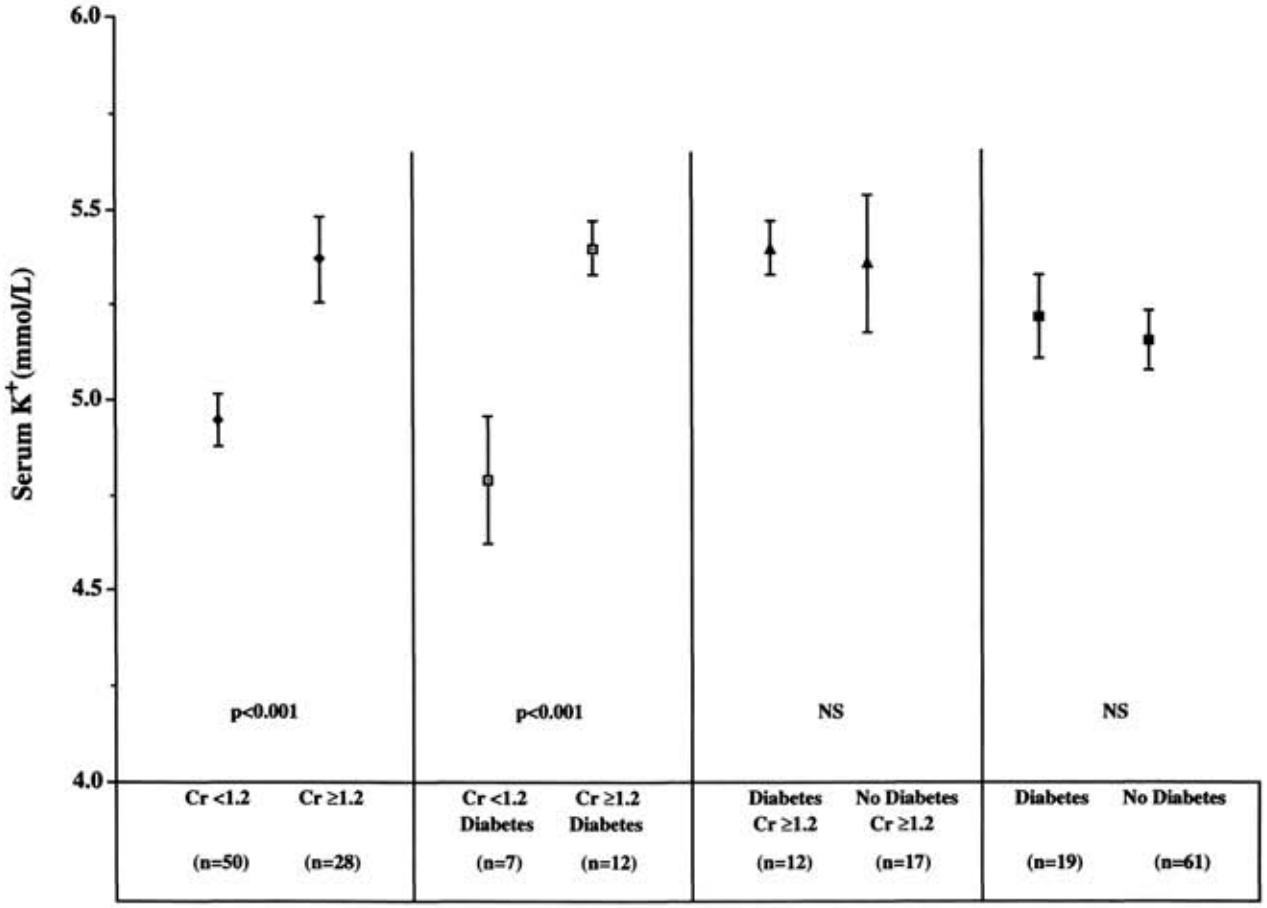

Figure 2. Peak serum potassium concentrations (mean ± SE) in the various subgroups of patients treated with trimethoprim–sulfamethoxazole. A statistically significant peak potassium concentration was seen only in patients with a baseline serum creatinine level of 106 μmol/L (1.2 mg/dL) or more, regardless of the presence or absence of diabetes mellitus. Cr = creatinine; K^+ = potassium; *n* = number of patients.

treatment group increased after trimethoprim–sulfamethoxazole therapy was initiated, and a statistically significant difference in the mean potassium concentrations in the treatment group and the control group was noted on days 4 and 5 of therapy (Figure 1). Potassium concentration subsequently decreased when therapy with the medication was discontinued or when patients received a potassium-lowering intervention, or both. However, the concentration remained elevated, albeit at levels slightly lower than peak, in patients who continued to receive trimethoprim–sulfamethoxazole. A peak potassium concentration greater than 5.0 mmol/L developed in 50 patients (62.5%), and a peak potassium concentration greater than 5.5 mmol/L was noted in 17 patients (21.2%).

Blood urea nitrogen levels increased nonsignificantly, from 7.92 ± 5.7 mmol/L (CI, 6.65 to 9.19 mmol/L) to 9.2 ± 5.8 mmol/L (CI, 7.9 to 10.5 mmol/L), and serum creatinine levels increased significantly ($P < 0.05$) from a baseline level of 102.5 ± 49.5 μmol/L (CI, 91.7 to 113.3 μmol/L) to 126.1 ± 70.7 μmol/L (CI, 110 to 141.6 μmol/L). No significant changes occurred in sodium or chloride concentrations, carbon dioxide content, or anion gap.

We also analyzed various subgroups. Figure 2 shows the peak potassium values in subgroups of patients receiving trimethoprim–sulfamethoxazole. Patients with a baseline serum creatinine level of 106 μmol/L (1.2 mg/dL) or more had a higher peak potassium concentration (5.37 ± 0.59 mmol/L [CI, 5.15 to 5.59 mmol/L]) than patients with a baseline serum creatinine level of less than 106 μmol/L (potassium concentration, 4.95 ± 0.48 mmol/L [CI, 4.80 to 5.08 mmol/L]), a statistically significant difference ($P < 0.001$). However, the mean increase from baseline to peak potassium concentration was not significantly different between the group whose creatinine level was 106 μmol/L (potassium concentration, 1.32 ± 0.55 mmol/L) or more and the group whose creatinine level was less than 106 μmol/L (potassium concentration, 1.136 ± 0.51 mmol/L). This was probably because the baseline potassium concentration was higher in the group whose creatinine level was 106 μmol/L or more (potassium concentration, 4.05 ± 0.51 mmol/L [CI, 3.86 to 4.24 mmol/L]) than

in the group whose creatinine level was less than 106 μmol/L (potassium concentration, 3.82 ± 0.41 mmol/L [CI, 3.7 to 3.93 mmol/L]). A greater percentage ($P < 0.001$) of patients with a baseline serum creatinine level of 106 μmol/L or more developed a peak potassium concentration of at least 5.5 mmol/L (10 of 28 patients; 35.7%) compared with patients who had a baseline serum creatinine level of less than 106 μmol/L (7 of 50 patients; 14.0%).

Diabetic patients had a slightly higher peak potassium concentration (5.14 ± 0.45 mmol/L [CI, 4.93 to 5.35 mmol/L]) than patients without diabetes (5.08 ± 0.59 mmol/L [CI, 4.93 to 5.23 mmol/L]), but the difference was not statistically significant. Diabetic patients with a baseline creatinine level of 106 μmol/L or more had a higher peak potassium concentration (5.4 ± 0.24 mmol/L [CI, 5.26 to 5.54 mmol/L]) than both diabetic patients (4.79 ± 0.44 mmol/L [CI, 4.46 to 5.11 mmol/L]) and nondiabetic patients (4.98 ± 0.48 mmol/L [CI, 4.83 to 5.12 mmol/L]) with a baseline creatinine level of less than 106 μmol/L. Both comparisons were statistically significant ($P < 0.001$ for both). However, in the group whose baseline serum creatinine level was 106 μmol or more, the difference in potassium concentration between diabetic patients (5.4 ± 0.24 mmol/L [CI, 5.26 to 5.54 mmol/L]) and nondiabetic patients (5.36 ± 0.74 mmol/L [CI, 5.0 to 5.4 mmol/L]) was not statistically significant.

Various age groups were evaluated for changes in potassium concentration during trimethoprim–sulfamethoxazole therapy. Comparison of the age group younger than 70 years of age with the group older than 70 years of age showed no significant difference in potassium concentrations, although peak potassium concentrations tended to be higher in the older patients. Specifically, the mean peak potassium concentration was 5.05 ± 0.46 mmol/L (CI, 4.86 to 5.22 mmol/L) in patients younger than 70 years of age ($n = 26$) and 5.13 ± 0.60 mmol/L (CI, 4.97 to 5.29 mmol/L) in patients older than 70 years of age ($n = 54$). No significant difference was noted in peak serum potassium concentrations between patients receiving medications capable of altering potassium homeostasis (5.06 ± 0.53 mmol/L [CI, 4.86 to 5.24 mmol/L]) and those not receiving these medications (5.13 ± 0.57 mmol/L [CI, 4.96 to 5.29 mmol/L]).

Discussion

Trimethoprim–sulfamethoxazole is a widely prescribed antibiotic. Its popularity stems from its wide spectrum of antimicrobial activity and its low cost. Adverse reactions have been documented with trimethoprim–sulfamethoxazole, but hyperkalemia is a little-known complication of standard-dose trimethoprim–sulfamethoxazole therapy (4–7). Our study, which compared patients receiving standard-dose trimethoprim–sulfamethoxazole with controls receiving other antibiotic agents, suggests that hyperkalemia develops in most patients receiving trimethoprim–sulfamethoxazole. All patients treated with trimethoprim–sulfamethoxazole had an increase in serum potassium concentration, and patients with concurrent renal insufficiency developed a higher peak potassium concentration. The peak potassium concentration occurred between 4 and 5 days of therapy. In contrast with controls, who had a modest decrease in potassium concentrations, 62.5% of treated patients developed a potassium concentration greater than 5.0 mmol/L, and 21.2% developed a potassium concentration greater than 5.5 mmol/L.

Renal insufficiency was the only factor associated with a statistically significant increase in serum potassium concentration. Surprisingly, diabetes mellitus alone was not a significant risk factor for the development of hyperkalemia. Old age was not associated with statistically significant hyperkalemia, although a slightly higher peak potassium concentration occurred in older patients. Potassium-altering medications had no significant effect on the development of hyperkalemia in the treatment or control groups. The increase in potassium concentration in the treatment group cannot be explained by the presence of potassium-altering medications, because similar numbers of persons in the treatment and control groups received these medications.

A statistically significant increase in serum creatinine level occurred in the treatment group compared with the control group. The ability of trimethoprim to inhibit the proximal tubular secretion of creatinine, in the absence of a reduction in glomerular filtration rate, probably explains the elevated serum creatinine level seen in the patients treated with trimethoprim–sulfamethoxazole (8). Although trimethoprim–sulfamethoxazole therapy has been associated with renal failure, on the basis of either allergic interstitial nephritis or sulfonamide crystal-associated tubular injury (9, 10), no clinical or laboratory evidence supported this association in our patients. Furthermore, the nonsignificant increase in blood urea nitrogen levels tends to support inhibition of tubular creatinine excretion as the explanation for the elevated serum creatinine levels.

The association of high-dose trimethoprim–sulfamethoxazole with hyperkalemia was first noted in a group of patients with AIDS who were treated for *P. carinii* pneumonia (1, 2). Subsequently, Velazquez and colleagues (1) examined the effects of perfusing trimethoprim, 1 mmol/L, into the lumen of distal tubules in rats. Using micropuncture techniques,

they found a 59% reduction in potassium secretion and a 66% decrease in transepithelial voltage (1). Trimethoprim has also been shown to reversibly inhibit amiloride-sensitive short-circuit current in cultured distal tubule cells (3). Thus, trimethoprim, which is structurally similar to the potassium-sparing diuretic amiloride, was thought to act like amiloride to inhibit distal tubule sodium reabsorption and potassium secretion. This is the presumed mechanism for the development of hyperkalemia in our patients. Importantly, the urinary concentration of trimethoprim may reach 1.1 mmol/L after a single oral dose of 200 mg (11); this suggests that the dose of trimethoprim given to our patients (320 mg/d) was more than adequate to block distal tubule potassium secretion. The hyperkalemia reported in three elderly patients treated with standard-dose trimethoprim–sulfamethoxazole, in the absence of an apparent defect in potassium homeostasis, was almost certainly the result of the potassium-sparing effect of trimethoprim in these patients. An associated age-related decline in glomerular filtration rate may also have contributed (4–6). Finally, sulfamethoxazole has no effect on sodium channel reabsorptive activity in cultured A6 cells (distal tubule principal cells) and probably does not play a role in the development of hyperkalemia (12).

Our data have a few limitations that need to be considered. Our control group was relatively small, but it was large enough to allow us to effectively show that, during hospitalization, patients treated with antibiotics other than trimethoprim–sulfamethoxazole for various infections did not develop hyperkalemia. This suggests that trimethoprim–sulfamethoxazole was integral to the development of hyperkalemia in the treatment group. Additionally, the presence of certain types of comorbid illness that necessitate antibiotic therapy, such as pyelonephritis, may predispose some patients to hyperkalemia in the absence of trimethoprim–sulfamethoxazole therapy.

In conclusion, standard-dose trimethoprim–sulfamethoxazole causes hyperkalemia in a significant percentage of hospitalized patients, particularly 4 to 5 days after the initiation of therapy. Concurrent renal insufficiency is a risk factor for the development of more severe hyperkalemia in patients treated with trimethoprim–sulfamethoxazole, and these patients should be monitored closely.

Appendix

The conversion of traditional units of serum creatinine (normal range, 0.6 to 1.2 mg/dL) to SI units (normal range, 50 to 110 μmol/L) requires multiplication of mg/dL by 88.4 to obtain μmol/L. The conversion of traditional units of blood urea nitrogen level (normal range, 8 to 18 mg/dL) to SI units (normal range, 3.0 to 6.5 mmol/L) requires multiplication of mg/dL by 0.357 to obtain mmol/L.

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