Evaluation of Hyperkalemia Associated with Trimethoprim-Sulfamethoxazole in the Intensive Care Unit

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ABSTRACT

Aim: The objective of this study was to determine the incidence and risk factors of hyperkalemia associated with trimethoprim-sulfamethoxazole (TMP-SMX) in the intensive care unit (ICU).

Study design: A single-center, retrospective observational study.

Materials and Methods: The study population consisted of patients who received TMP-SMX in the ICU. Patients were categorized into two groups based on the level of serum potassium: the group with hyperkalemia and the group without hyperkalemia.

Results: The incidence of hyperkalemia in the patients receiving TMP-SMX in ICU was 49% (25/51). Hyperkalemia occurred 6.2±3.8 days after the beginning of TMP-SMX treatment. Baseline serum potassium level determined as an independent risk factor for hyperkalemia (p<0.009). The optimal cut-off value of baseline serum potassium to predict hyperkalemia associated with TMP-SMX was 3.55 mEq/L.

Conclusion: Potassium levels should be closely monitored, especially in the first week of TMP treatment, in critically ill patients. Even if the baseline potassium level is within normal limits, care should be taken in terms of hyperkalemia. In addition, even if hyperkalemia is mild, potassium-lowering therapeutic approaches may be necessary.

Keywords: Hyperkalemia, Hyponatremia, *Pneumocystis Jirovecii*, Trimethoprim-Sulfamethoxazole, Intensive Care

Introduction

Trimethoprim-sulfamethoxazole (TMP-SMX) consists of two antimicrobial agents that act synergistically against the bacteria with a wide spectrum of antimicrobial activity (1,2). TMP-SMX is used to treat a variety of infections, especially *Pneumocystis Jirovecii* pneumonia (3). TMP-SMX has come into prominence as a popular choice due to its efficacy, ease usage of dosing, and relatively low cost (4). It is generally well tolerated at the standard doses and most medical practitioners have knowledge of its adverse reactions (4,5). Rash and gastrointestinal upset are the most commonly reported adverse drug events. More serious adverse drug events including hyperkalemia, serum creatinine elevation, bone marrow suppression, blood dyscrasias, hepatotoxicity, Stevens-Johnson syndrome, and toxic epidermal necrolysis are less common or rare (5). Hyperkalemia is associated with TMP. Trimethoprim has a similar structure to the potassium-sparing diuretic amiloride and reduces renal potassium excretion (1,3). The relationship between TMP and hyperkalemia has been shown in several studies (2,5-7). However, critically ill patients in the intensive care unit (ICU) have not been evaluated in previous studies.

The objective of this study was to determine the incidence and risk factors of hyperkalemia associated with TMP-SMX in the ICU.

Materials and Methods

This study was approved by the institutional research ethics board. The study population consisted of patients who received TMP-SMX in medical ICU between 01.01.2016-01.03.2018. All patients included in this study were evaluated with serum potassium levels during TMP-SMX treatment. Patients with acute or chronic renal failure/injury who received the dialysis were excluded from the study.

The records in the hospital automation system of patients were evaluated retrospectively. The age; sex; admission date to ICU; ICU admission diagnosis; presence of acute and chronic renal injury/failure; duration and dosage of TMP-SMX; serum potassium, serum creatinine, serum sodium, and estimated glomerular filtration rate (eGFR) at the time of TMP-SMX initiation; presence of hyperkalemia; TMP-SMX treatment day when hyperkalemia occured; concomitant the levels of serum creatinine, serum sodium, and eGFR with hyperkalemia; presence of hyponatremia; concomitant administration of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB), β-blockers, non-steroidal anti-inflammatory drugs, potassium-sparing diuretics, or corticosteroids with TMP-SMX; APACHE II score were retrospectively collected. Finally, ICU mortality and in-hospital mortality were determined. CKD-EPI formula was used for the eGFR. The formula:

$$GFR = 141 \times \min(\text{serum creatinine}/\kappa, 1)^{\alpha} \times \max(\text{serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{age} \times Sex \times Race\ (1.159\ \text{if African- American})$$

For females, the following values are used: Sex = 1.018; alpha (α) = -0.329; kappa (κ) = 0.7

For males, the following values are used: Sex = 1; alpha (α) = -0.411; kappa (κ) = 0.9

Patients were categorized into two groups based on the level of serum potassium: the group with hyperkalemia (group A) and the group without hyperkalemia (group B). Hyperkalemia was defined as a serum potassium level of ≥5 mEq/L. Hyponatremia was defined as a serum sodium level <136 mEq/L.

Statistical analyses were performed using SPSS 24.0 statistics package software. The parametric variables were expressed as mean and standard deviation and were compared by Student's *t*-test between the groups. The categorical variables were presented as number and percentages (%) and were compared using chi-square test. Receiver operating characteristic (ROC) curves were plotted to determine the cut-off value of serum potassium to predict patients who will have hyperkalemia. P< 0.05 was accepted as statistically significant.

Results

In this study, 64 patients were prescribed TMP-SMX in ICU. Of those patients, 11 received the dialysis for acute renal injury and two received the dialysis for chronic renal failure. These 13 patients were excluded from the study. The study included 51 patients, 31 males and 20 females aged between 18 and 88 years.

ICU admission diagnosis were pulmonary diseases in 37 (72.5%), infection in five (9.8%), gastrointestinal disorders in three (5.9%), cardiovascular diseases in two (3.9%), trauma in two (3.9%), and neurological diseases in two (3.9%). Thirteen patients (25.5%) had acute renal injury and one patient (2%) had chronic renal failure. TMP-SMX was used for *Pneumocystis jirovecii* empirically in 37 patients (72.5%) and as an antimicrobial treatment for *Stenotrophomonas maltophilia* in 14 patients (27.5%). The duration of TMP-SMX treatment was 10.9±6.1 days. The dose of TMP was 11.2±4.7 mg/kg/day and total mean dosage of TMP was 844±333 mg/day.

Laboratory data at the time of TMP-SMX initiation were evaluated. Serum potassium was 3.7±0.6 mEq/L (range: 2.8-5.8 mEq/L). Serum sodium was 138±7 mEq/L (range: 123-152 mEq/L). Serum creatinine was 0.8±0.5 mg/dL (range: 0.1-2.7 mg / dL). Estimated glomerular filtration rate was 96.7±37.7 mL/min/1.73 m² (range: 16-177 mL/min/1.73 m²). Hyperkalemia was occurred 6.2±3.8 days after the beginning of TMP-SMX. The maximal level of serum potassium was 5.3±1.1 (range: 3.8-8.5) mEq/L. Twenty patients (39.2%) developed hyponatremia. Concomitant administration of ACEi/ARB, β-blockers, or potassium-sparing diuretics with TMP-SMX was 17.6% (9/51). Corticosteroids were received concomitantly with TMP-SMX in 21 patients (41.2%). The APACHE II score was 24.5±8.8 (range: 6-43). ICU mortality and in-hospital mortality were 58.8% (30/51) and 68.6% (35/51), respectively.

The incidence of hyperkalemia in patients receiving TMP-SMX in ICU was 49% (25/51). The characteristics of the groups with hyperkalemia and without hyperkalemia are summarized in Table 1. The only statistically significant difference between groups with hyperkalemia and without hyperkalemia was the serum potassium level at the beginning of TMP-SMX (3.98±0.63 vs. 3.52±0.48, p<0.005). In logistic regression analysis, serum potassium level at the beginning of TMP-SMX treatment was determined as an independent risk factor for hyperkalemia (p<0.009; OR: 6.07, CI: 1.57-23.4). The optimal cut-off value of baseline serum potassium to predict hyperkalemia associated with TMP-SMX was 3.55 mEq/L (sensitivity: 80%, specificity: 69%), (area under the curve: 0.742), (Figure 1).
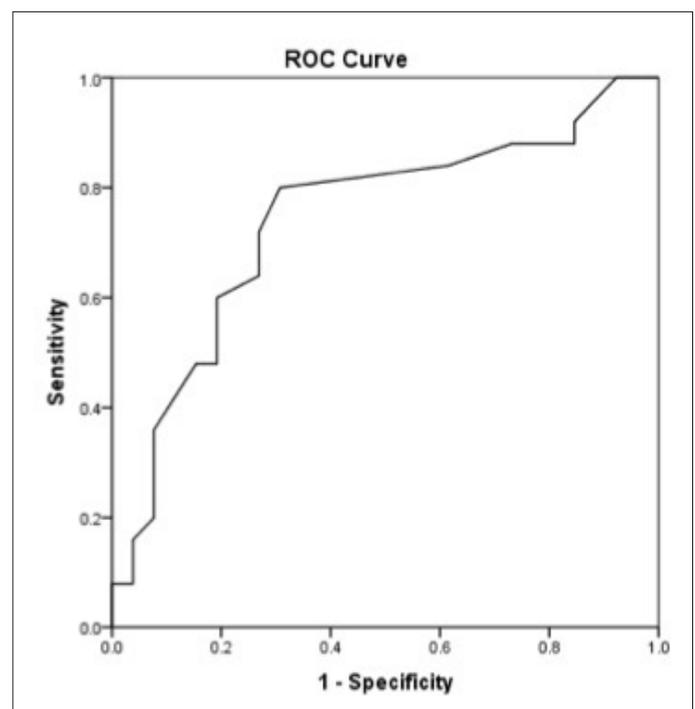
Figure 1. Receiver operating characteristic curves were plotted to determine the cut-off value of serum potassium to predict patients who will have hyperkalemia.

Table 1. The characteristics of the group with hyperkalemia (group A) and the group without hyperkalemia (group B).

	Group A n=25	Group B n=26	p
Demographics			
Age, mean±SD (range)	66.2±15.8 (18-83)	57.9±17.2 (19-88)	0.08
Sex, female/male	8/17	12/14	0.30
Admission diagnosis			
Pulmonary diseases, n (%)	19 (76%)	18 (69.2%)	0.59
Infection, n (%)	2 (8%)	3 (11.5%)	1.00
Gastrointestinal disorders, n (%)	2 (8%)	1 (3.8%)	0.61
Cardiovascular diseases, n (%)	0	2 (7.7%)	0.49
Trauma, n (%)	1 (4%)	1 (3.8%)	1.00
Neurological diseases, n (%)	1 (4%)	1 (3.8%)	1.00
Presence of acute and chronic renal injury/failure			
Acute renal injury, n (%)	8 (32%)	5 (19.2%)	0.30
Chronic renal failure, n (%)	1 (4%)	0	0.49
Indication of TMP-SMX			
Stenotrophomonas maltophilia, n (%)	7 (28%)	7 (26.9%)	0.93
Empiric antimicrobial therapy, n (%)	18 (72%)	19 (73.1%)	0.93
Duration and dosage of TMP-SMX			
Dose of TMP, mean±SD mg/kg/day (range)	12.1±4.6 (4.9-24)	11.9±7.5 (1.8-32)	0.91
Total dose of TMP, mean±SD mg/day (range)	870±274 (320-1280)	818±385 (160-1280)	0.58
Duration, mean ± SD day (range)	10.2±4.5 (2-18)	11.7±7.3 (1-25)	0.39
Laboratory data at the time of TMP-SMX initiation			
Serum potassium, mean±SD mEq/L (range)	3.98±0.63 (2.9-5.8)	3.52±0.48 (2.8-4.8)	<0.005
Serum sodium, mean±SD mEq/L (range)	138±6 (127-152)	137±8 (123-152)	0.58
Serum creatinine, mean±SD mg/dL (range)	0.95±0.63 (0.2-2.7)	0.68±0.37 (0.1-1.6)	0.06
Estimated glomerular filtration rate, mean±SD mL/min/1.73 m^2 (range)	87.6±36.4 (16-159)	105.5±37.4 (39-177)	0.09
Presence of hyponatremia, n (%)	12 (48%)	8 (27.6%)	0.21
Concomitant hyperkalemia-inducing medication			
ACEi/ARB/potassium-sparing diuretics/β-blockers, n (%)	4 (16%)	5 (19.2%)	0.76
Corticosteroids, n (%)	7 (28%)	14 (53.8%)	0.06
APACHE II, mean±SD (range)	25.1±9.1 (6-43)	23.9±8.6 (11-40)	0.63
Intensive care unit mortality, n (%)	17 (68%)	13 (50%)	0.19
In-hospital mortality, n (%)	18 (72%)	17 (65.4%)	0.61

TMP-SMX = Trimethoprim-sulfamethoxazole
ACEi = Angiotensin-converting enzyme inhibitors
ARB = Angiotensin receptor blockers

Discussion

In our study, the incidence of hyperkalemia associated with TMP-SMX in ICU was 49%. There are no reported data about the incidence of hyperkalemia in the patients receiving TMP-SMX in ICU to the best of our knowledge. In studies evaluating a more general population of patients receiving TMP, the incidence of hyperkalemia was determined in a wide range of 17-53% (2,3,6). We thought that this wide range was due to different patients' characteristics and treatment protocols.

First studies of hyperkalemia associated with TMP were reported in patients with human immunodeficiency viruses (HIV)/acquired immunodeficiency syndrome. The risk of hyperkalemia was determined to be increased in patients receiving high-doses of TMP (8-10). In the following period, non-HIV infected patients who received standard-dose TMP-SMX treatment developed hyperkalemia (11,12). A prospective study compared immunocompetent patients treated with standard-dose TMP-

SMX and similar controls treated with other antibiotics. The results confirmed the rise in serum potassium concentration associated with TMP-SMX treatment (7). More recent clinical studies have shown that hyperkalemia can be seen even with low-dose TMP treatment (2). In studies, a common definition for "standard-dose" TMP and "high-dose" TMP was not used. TMP dose ≤80 mg/day, which is the prophylaxis dose of *Pneumocystis* pneumonia, was used for "low-dose" definition (2,8,13). In our study, there were no patients receiving low-dose TMP (≤80 mg/day) treatment and the lowest dose of TMP was 160 mg/day.

In our study, the mean dose of TMP was 12±6.2 mg/kg/day and the total dose of TMP was 844±333 mg/day. TMP doses are quite different in the studies (3,5,13). In a study evaluating patients receiving high-dose TMP, the mean dose of TMP was 14.3±3.9 mg/kg/day (3). In another study evaluating low-dose, standard-dose, and high-dose of TMP, the dose of TMP is 145.7±24.9 mg/day (13). In that study evaluating low-dose, standard-dose, and

high-dose, the logistic regression analysis identified no association between hyperkalemia and TMP dose (13). Gentry et al. (5) retrospectively investigated patients receiving high-dose TMP-SMX (≥5 mg/kg/day) and standard-dose TMP-SMX (<5 mg/kg/day) and found that hyperkalemia developed more frequently in patients treated with the high-dose TMP-SMX. They categorized the patients into two groups as the group with hyperkalemia and the group without hyperkalemia and found that the dose of TMP-SMX was higher in the group with hyperkalemia (5). We found that the TMP dose was higher in the group with hyperkalemia but it was not statistically significant (p=0.91).

There are reports showing that advanced age increased the risk of hyperkalemia, as well as there are also studies showed that no relationship between TMP-SMX and advanced age (2,5,13). We found that the group with hyperkalemia was elder but it was not statistically significant (p=0.08).

In our study, no significant difference was found regarding eGFR and serum creatinine levels at the time of TMP-SMX initiation between the group with hyperkalemia and the group without hyperkalemia (p=0.09), (p=0.06). Additionally, there were no significant differences in chronic renal failure/injury between the groups (p=0.49). This is very interesting because many previous studies demonstrated that renal failure/injury was a risk factor for hyperkalemia (2,7,13). Also, serum creatinine elevation at the time of TMP-SMX initiation was showed to increase the risk of hyperkalemia (5).

Several studies showed contradictory results for hyperkalemia and concomitant administration of ACEi/ARB, β-blockers, or potassium-sparing diuretics with TMP-SMX (2,5,14). In the study of Higashioka et al. (2), ACEi or ARB increased the risk of hyperkalemia while there was no relationship between hyperkalemia and β-blockers or potassium-sparing diuretics. A large study evaluating 6162 patients with the use of TMP-SMX found that the risk of hyperkalemia increased when using ACEi or spironolactone (5). ACEi/ARB, β-blockers, or potassium-sparing diuretics was not a risk factor for hyperkalemia in our study. Corticosteroid is frequently used in patients with *pneumocystis* pneumonia (6). We found that corticosteroids did not increase the risk of hyperkalemia. This result contradicts previous studies (3,6). Glucocorticoid administration has been reported to cause an acute transient kaliuresis that is thought to be a direct result of an increased GFR and causing increased sodium delivery to the distal nephron (6). Glucocorticoid can also induce catabolic protein breakdown and triggers the release of potassium into the extracellular compartment (6). Due to the clear effect of these two opposite conditions, no association could be found between corticosteroid treatment and hyperkalemia in our study.

Previous reports showed that hyperkalemia developed 5-12 days after TMP-SMX initiation (5-7). In our study, this duration was 6.2±3.8 days and serum potassium level at the time of TMP-SMX initiation was an independent risk factor for hyperkalemia (p<0.009). The optimal cut-off value of baseline serum potassium to predict hyperkalemia was 3.55 mEq/L. This cut-off value is precious data. To the best of our knowledge, there is no reported data about baseline serum potassium level at the time of TMP-SMX initiation to determine the risk factor of hyperkalemia.

High-dose TMP-SMX is known to cause hyponatremia. In a retrospective study, hyponatremia was seen in a majority (72 %) of hospitalized patients treated with high dose TMP-SMX (3). We found that 20 patients (39 %) developed hyponatremia. We did not exclude the patients with comorbid conditions, complications, and medications that could cause hyponatremia, therefore the incidence of hyponatremia is likely even lower. Many critically ill patients could have severe complications such as renal failure and adrenal insufficiency which have profound effects on serum electrolytes. Therefore, it was difficult to interpret the action of TMP-SMX accurately.

In our study, ICU mortality was 59% in patients receiving TMP-SMX. The group with hyperkalemia had higher mortality but it was not statistically significant (p=0.19). In addition, the APACHE II score was higher in the group with hyperkalemia. ICU mortality rate was 68% in the group with hyperkalemia. However, we could not identify hyperkalemia-related mortality in the ICU. Therefore, this study underestimated the clinical consequences of this drug interaction.

Our study had a number of limitations, including its retrospective nature and small sample size. Another limitation is the lack of data about urinary findings, including direct measurement of potassium and urea nitrogen excretion rates. We evaluated a 2-year period data in ICU which reflects only a single-center experience. There is still a need for more homogenous, multicentered, and randomized studies including more patient data.

Conclusion

Critically ill patients in ICU have not been reported in previous studies evaluating the relationship between TMP and hyperkalemia. Therefore, the results of our study, which evaluated critically ill patients receiving TMP-SMX in ICU, are important. The incidence of hyperkalemia was 49%. This high rate showed that one of the two critically ill patients using TMP-SMX had hyperkalemia. We showed that baseline serum potassium level was an independent risk factor for hyperkalemia and the optimal cut-off value of baseline serum potassium to predict hyperkalemia associated with TMP-SMX was 3.55 mEq/L. Hyperkalemia occurred on average 6 days after the beginning of TMP-SMX. Therefore, we think that potassium should be closely monitored, especially in the first week of TMP treatment, in critically ill patients. Even if the baseline potassium level is within normal limits, care should be taken in terms of hyperkalemia. In addition, even if hyperkalemia is mild, potassium-lowering therapeutic approaches may be necessary.

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