Incidence of co-trimoxazole-induced hyperkalemia in a tertiary hospital in Qatar

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May 18, 2020

Abstract

Abstract Background: Co-trimoxazole is a broad-spectrum antibiotic associated with hyperkalemia, particularly in those with additional risk factors. Objectives: To determine the incidence of hyperkalemia and its risk factors in patients receiving co-trimoxazole. Methods: A retrospective observational study involving all patients who received co-trimoxazole between 1 January 2012 and 1 January 2013. Subjects were identified through a list generated from a computerized pharmacy system. The patients' demographic and clinical characteristics were retrieved from electronic medical records. Data were analyzed using univariate and multivariate logistic regression. Results: One hundred sixty-one patients fulfilled the eligibility criteria. Of these, 46 (28.6%) experienced hyperkalemia. Around 35 (76.1%) of the patients who experienced hyperkalemia received co-administered medications that might induce hyperkalemia. The co-administration of co-trimoxazole with other medications that may induce hyperkalemia was found to be associated with higher incidence of hyperkalemia when compared to co-trimoxazole administration alone [adjusted OR 3.2, 95% CI (1.4-7.3), p=0.005]. Additionally, age > 60 years was associated with an increased risk of hyperkalemia when compared to younger age group 18-39 years [adjusted OR 6.5, 95% CI (2.1-19.7); p=0.001]. Conclusion: Caution should be exercised in older patients and those receiving co-trimoxazole in combination with other medications, such as immunosuppressants and β-blockers that might contribute to hyperkalemia development. Keywords: Co-trimoxazole, co-administration, hyperkalemia, risk factors, adverse drug reaction

Introduction

Co-trimoxazole, a broad-spectrum antibiotic comprising trimethoprim and sulfamethoxazole, is widely used for the treatment and prophylaxis of Gram-positive, Gram-negative bacteria, and other parasitic infections[1]. Co-trimoxazole use has been associated with hyperkalemia, a severe and potentially fatal adverse drug reaction (ADR)[2,3]. Co-trimoxazole-induced hyperkalemia mechanism is mediated through the blockage of amiloride-sensitive sodium channels in the distal tubule, due the structural similarity of trimethoprim with potassium-sparing diuretics, leading to the impairment of renal potassium excretion [2]. Age and co-administered medications have been recognized as risk factors for co-trimoxazole-induced hyperkalemia [3]. Evidence suggests that concurrent administration of drugs such as angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin-II receptor blockers (ARBs), β-blockers, and spironolactone can increase serum potassium concentration, leading to increased incidence of severe hyperkalemia, hospitalization, and mortality [3]. ACE-Is, ARBs, and spironolactone have an additional mechanism of inducing hyperkalemia by decreasing the serum concentration of aldosterone, resulting in reabsorbing potassium at the distal renal tubule [4]. Several studies have also identified age as a factor potentially increasing the risk of hyperkalemia and mortality[3]. When potassium serum concentration reaches 6 mEq/L or more, treatment interruption and close monitoring are warranted to avoid cardiac toxicity [2]. Limiting potassium intake and avoiding other medications that might contribute to hyperkalemia are approaches to consider when the potassium level is

controlled below 6 mEq/L [2]. Despite the clinical significance of co-trimoxazole-induced hyperkalemia, this ADR has been neglected by many clinicians, and no clear guidelines are available to monitor patients.

Aim of the study

This study aimed to investigate serum potassium concentrations and the incidence of hyperkalemia in patients receiving co-trimoxazole in Qatar, and to identify potential risk factors.

Methods

Study design

This was a retrospective observational study of patients who received co-trimoxazole for therapeutic or prophylactic indications at Hamad General Hospital (HGH) in Qatar. Patients were identified through a computerized pharmacy system, via an automated report generated between 1 January 2012 and 1 January 2013. Baseline potassium serum level was considered as any level within one week prior to initiation of co-trimoxazole; all subsequent levels were follow-up. Hyperkalemia was defined as serum potassium level above 5.5 mEq/L [2]. Laboratory parameters (serum creatinine and serum potassium levels) were obtained from electronic medical records.

Ethics Approval

This study was reviewed and approved by the Institutional Review Board (IRB) of the Medical Research Center at Hamad Medical Corporation (HMC) in Qatar (approval number: #14425/14).

Eligibility criteria

Adult patients ([?]18 years) with normal renal function (GFR [?]60 mL/min/1.73 m^2) who received co-trimoxazole during the study period and had documented potassium serum levels during follow up, were included. Patients who received less than two doses of co-trimoxazole and/or had no potassium follow-up were excluded from the study.

Data collection

Electronic medical records were reviewed to obtain relevant data at baseline and follow-up: demographics (age and sex); dose, frequency, and duration of co-trimoxazole; concurrent medications potentially affecting potassium serum levels; and relevant laboratory data.

Data analysis

Data were analyzed using SPSS version 18 (IBM SPSS®Statistics for Windows; IBM Corp, Armonk, New York, USA). Both descriptive and inferential statistics were applied for the data analysis. The 95% confidence intervals (CIs) for each mean were also calculated. Chi-square was used to compare the incidence of hyperkalemia between different factors. Univariate and multivariate logistic regression analyses were conducted to determine the association between risk factors and development of co-trimoxazole-induced hyperkalemia and compute adjusted and unadjusted odd ratios (ORs). The factors included in the multivariate logistic regression analysis were: age, gender, total daily dose (the once and twice daily doses of the double strength (DS) tablet 800/160 mg) and the co-administered medications. The level of statistical significance was defined as p[?] 0.05.

Results

Of the 500 patients reviewed, 121 patients were excluded due to impaired renal function (GFR <60 mL/min/1.73 m^2), 168 did not have follow-up data, and 50 patients received less than two doses of co-trimoxazole. One hundred sixty-one patients who fulfilled the inclusion criteria were included. Of these, 57.1% (n=92) were male and 57.1% (n=92) were prescribed other medications known to contribute to hyperkalemia. Around 24% of the patients had hypertension, 56% had diabetes, and 46% were status-post

organ transplant. The patients were divided into two groups based on the co-trimoxazole (DS tablet 800/160 mg) dosing frequency; once daily vs. twice daily dosing regimen. The number of patients in each group was comparable (Table 1).

Hyperkalemia (potassium serum concentration >5.5 mEq/L) was observed in 46 (28.6%) patients, of whom, 25 (29 %) were in the twice-daily dosing group. Thirty-five (76.1%) of the patients who developed hyperkalemia were receiving concurrent medications known to increase potassium serum levels (Table 1). Receiving co-trimoxazole in combination with β-blockers, immunosuppressant agents alone or in combination with β-blockers was significantly associated with higher incidence of hyperkalemia when compared to receiving co-trimoxazole alone [OR 3.2, 95% CI (1.1-9.7), p=0.035, OR 3.2, 95% CI (1.2-8.3), p=0.019, OR 3.4, 95% CI (1.2-9.8), p=0.024] (Table 2). Moreover, patients with age >60 years were more prone to develop hyperkalemia when compared to younger age groups 18-39 years [OR 6.37, 95% CI (2.6-18.8), p=0.001]

[Please insert Table 1 here]

[Please insert Table 2 here]

After adjusting the confounders with the multivariate logistic regression analysis, only the following factors were found be significant. Patients with age >60 years were more prone to develop hyperkalemia when compared to the younger age groups 18-39 years [adjusted OR 6.5, 95% CI (2.1-19.7), p=0.001]. Moreover, the middle age group (40-60 years) was also found to have higher incidence of hyperkalemia than the younger age group 18-39 years [adjusted OR 3.5, 95% CI (1.2-10.5), p=0.023]. In addition, the co-administration of other medications that may induce hyperkalemia was found to be associated with higher incidence of hyperkalemia when compared to those receiving co-trimoxazole alone [adjusted OR 3.2, 95% CI (1.4-7.3), p=0.005].

Discussion

Almost one-third of patients developed hyperkalemia, with age >60 years was identified as high-risk. However, dosing frequency did not significantly influence hyperkalemia incidence. All patients with co-trimoxazole induced hyperkalemia were managed with the medical treatment including (stop the offending agents, shifting extracellular potassium into the cells and excreting the potassium out of the body) [2]. No cardiac arrests or hemodialysis was required secondary to the refractory hyperkalemia.

A previous study by Fralick et al. affirmed that co-trimoxazole use with an ACE-I or ARB was associated with increased risk of sudden death due to severe hyperkalemia [OR 1.38: 95%CI (1.09 to 1.76)] when compared with amoxicillin [3]. Noteworthy, the patient population of this study was older adults (>66 years); hence, the incidence of hyperkalemia was more pronounced. Additionally, a nested case-control study of a cohort of older patients (>66 years) concluded that the potential for hyperkalemia-associated hospitalization was increased seven-fold among older patients receiving ACE-Is or ARBs (adjusted OR, 6.7; 95% CI, 4.5-10.0) [5]. Furthermore, among the β-blocker users, Weir et al. found that the rate of hospitalization among co-trimoxazole users was considerably higher when compared to amoxicillin (OR 5.1; 95% CI 2.8 to 9.4) [6]. Studies have also demonstrated that older people receiving co-trimoxazole in combination with other medication known to contribute to hyperkalemia are at higher risk of hyperkalemia, [3,5] which is consistent with our findings.

The co-administration of immunosuppressants was significantly associated with increased incidence of hyperkalemia, either alone or in combination with β-blockers. Several studies and case reports found that tacrolimus and cyclosporine cause elevation in plasma potassium concentration, which can be further augmented by co-administration of ACE-I or ARBs[4,7].

A review by Perazella et al. reported that co-trimoxazole can cause hyperkalemia regardless of dose [2]. However, a retrospective study showed that hyperkalemia incidence was more frequent with the higher doses

of co-trimoxazole [8]. In this study, the results failed to confirm a correlation between hyperkalemia incidence and the total daily doses (once daily or twice daily of the DS 800/160 mg) of co-trimoxazole.

There is some evidence that pharmacists have a crucial role in monitoring drug therapy to detect and prevent ADRs [9]. Hence, pharmacists can contribute to active monitoring of potassium levels and additionally educating patients on the potential for interactions with other medication, conditions and food.

This study has the inherent limitations of a retrospective study design in that only the specific data collected and recorded during routine clinical practice could be captured. While we excluded those with renal impairment, hyperkalemia could be a result of other factors such as excess dietary potassium intake, electrolyte imbalance, and other factors. The limited sample size may have meant that the study was underpowered for the comparison made hence the results should be interpreted with caution. There may also be issues with generalizability to other populations and settings. Furthermore, the study was completed several years earlier, although clinical practice is relatively unchanged hence the data and findings remain valid. There is a need for prospective studies with more frequent monitoring of potassium and serum creatinine levels.

Conclusion

Co-trimoxazole administration was associated with an increased risk of hyperkalemia especially among older patients and those receiving other co-administered medications that may induce hyperkalemia. Caution should be exercised when co-trimoxazole is used in older people and patients receiving other medications affecting potassium levels such as immunosuppressants and the combination of an immunosuppressant and β-blocker.

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Acknowledgement

The authors would like to thank the Hamad Medical Corporation for proving the research funding. This work was supported by the Medical Research Center of Hamad Medical Corporation [grant number 14349/14].

Conflicts of Interest

The authors have no conflict of interest to declare

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