

Sulfamethoxazole-Trimethoprim and Hyperkalemia in an Infant

Samantha A. Hudzik^{a, b, c}, Hunter C. Johnson^c, Joseph D. Tobias^{a, b, c, d}

Abstract

Hyperkalemia is a potentially life-threatening electrolyte abnormality in both children and adults. In the setting of elevated serum potassium concentrations, cardiac conduction disturbances and cardiac arrest may occur. In the pediatric intensive care unit (PICU) setting, the differential diagnosis of hyperkalemia may be extensive including increased potassium intake or administration, increased endogenous production, decreased renal excretion, and intracellular to extracellular shifts related to changes in acid-base status. We present a 4-month-old infant who developed hyperkalemia during the recovery phase of her PICU course for respiratory failure. A thorough investigation demonstrated that the hyperkalemia was most likely the result of the commonly used antibiotic, trimethoprim-sulfamethoxazole (Bactrim[®]). Potential etiologies of hyperkalemia in the PICU patient are discussed and previous reports of hyperkalemia associated with trimethoprim-sulfamethoxazole presented.

Keywords: Trimethoprim-sulfamethoxazole; Hyperkalemia; Potassium

Introduction

Hyperkalemia is generally defined as a serum potassium level greater than 5.5 mEq/L in older children and adults. Neonates and infants have a slightly elevated upper limit of normal due to aldosterone insensitivity leading to reduced urinary ex-

cretion of potassium, as well as a lower baseline glomerular filtration rate. Although hyperkalemia may be asymptomatic when potassium values are in mild to moderate range (5.5 - 7.0 mEq/L), higher values may affect cardiac conduction leading to potentially life-threatening arrhythmias [1, 2]. In the pediatric intensive care unit (PICU) setting, hyperkalemia is a relatively common electrolyte abnormality [3]. Hyperkalemia may be the result of excessive potassium intake or administration, increased endogenous production (rhabdomyolysis), decreased renal excretion, or intracellular to extracellular shifts.

Through various mechanisms, medications may alter the renal handling of potassium resulting in hyperkalemia. We present a 4-month-old infant who developed hyperkalemia related to a commonly used antibiotic, trimethoprim-sulfamethoxazole (Bactrim[®]). Potential etiologies of hyperkalemia in the PICU patient are discussed, treatment options reviewed, and previous reports of hyperkalemia associated with trimethoprim-sulfamethoxazole presented.

Case Report

Presentation of this case report was in accordance with the guidelines of the Institutional Review Board (IRB) of Nationwide Children's Hospital. The patient was a 4-month-old female infant with a past medical history significant for prematurity (36 weeks' gestation), twin gestation, and Cesarean-birth who presented to the emergency department with a 1-day history of cough, congestion, fever to 40 °C, and increased work of breathing. She also had exhibited decreased oral intake and decreased urine output over the preceding 24 h. On arrival, the patient's oxygen saturation was 91% on room air, requiring the use of bilevel positive airway pressure (BiPAP) due to increased work of breathing and to maintain her oxygen saturation $\geq 92\%$. The rapid antigen respiratory viral panel was positive for respiratory syncytial virus (RSV). She was admitted to the PICU for respiratory failure secondary to RSV bronchiolitis with concerns for a superimposed bacterial infection, as the initial radiograph demonstrated bilateral opacities. The patient's trachea was intubated for progressive respiratory failure and she required a prolonged course of mechanical ventilation. Due to difficulty weaning from mechanical ventilation, diuresis was initiated to treat fluid overload and optimize her intravascular volume status. In addition to diuretic therapy, a second antibiotic course for pneumonia was completed while her trachea was intubated. She maintained normal renal func-

Manuscript submitted May 18, 2020, accepted June 9, 2020
Published online August 6, 2020

^aOhio University Heritage College of Osteopathic Medicine, Athens, OH, USA

^bDepartment of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, Columbus, OH, USA

^cDivision of Pediatric Critical Care Medicine, Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA

^dDepartment of Anesthesiology and Pain Medicine, The Ohio State University College of Medicine, Columbus, OH, USA

^eCorresponding Author: Samantha Hudzik, Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA. Email: sh645916@ohio.edu

doi: <https://doi.org/10.14740/jmc3498>

tion throughout the course of mechanical ventilation. Immediately prior to tracheal extubation, blood and endotracheal tube (ETT) cultures were obtained due to intermittent fevers. The patient's trachea was extubated on day 23 in hospital and Unasyn[®] (ampicillin-sulbactam) was started on day 24 in hospital based on the results of the ETT culture. The following day, Unasyn[®] was discontinued and Bactrim[®] (trimethoprim-sulfamethoxazole) was started at 5 mg/kg every 12 h based on the results and sensitivities of the ETT culture. Prior to the first dose of Bactrim[®], the patient's serum potassium was stable at 4.2 - 4.5 mEq/L. Over the next 2 days, there was a slow increase in the serum potassium despite normal renal function and adequate urine output. After four doses of Bactrim[®], the potassium had increased to 6.3 mEq/L. Due to concern for hyperkalemia secondary to Bactrim[®], her antibiotic coverage was changed to Unasyn[®] and gentamicin. Furosemide (1 mg/kg intravenous (IV)) and Kayexalate[®] (sodium polystyrene sulfonate *per os* (PO)) were administered to assist with potassium removal. A repeat serum potassium that evening was 5.6 mEq/L and then 4.2 mEq/L the next day. The patient's serum potassium was maintained at normal levels and no additional therapy for hyperkalemia was required during the patient's hospitalization. The remainder of the hospital course included discharge from the PICU, unremarkable de-escalation of antibiotics, and further management of nasogastric feeding. The patient discharged home on day 44 in hospital.

Discussion

The etiology of hyperkalemia can generally be determined based on the patient's clinical history and a review of the hospital course, medications, and comorbid conditions. Spurious hyperkalemia or a false elevation of the serum potassium is commonly seen in the intensive care unit where labs are obtained frequently. The false elevation is often due to hemolysis during the process of obtaining the sample, placing the sample into the specimen tube, or its subsequent handling [4]. If such a scenario is suspected, it is common practice to repeat the laboratory value prior to initiating further investigation and treatment. However, delays in treatment of true hyperkalemia may occur while waiting for the repeat sample to be drawn and processed.

Iatrogenic causes for hyperkalemia must be identified quickly and corrected in the PICU where aggressive potassium replacement often occurs. Abnormalities in potassium elimination are frequently seen in the setting of acute or chronic renal disease, and potassium replacement may be inadvertently continued resulting in hyperkalemia. Intravenous fluids, parenteral nutrition, and blood products may also contribute to hyperkalemia in the intensive care setting. Furthermore, certain medications may decrease potassium excretion by inhibiting the renin-angiotensin-aldosterone system including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, or aldosterone antagonists (spironolactone). Other agents may directly impair potassium secretion at the level of the collecting duct (amiloride, triamterene). Nonsteroidal anti-inflammatory drugs, pentamidine, tacrolimus, cyclosporine, and amphotericin are among the multiple medications used in the

PICU that are also known to impair potassium removal. In addition, medications such as beta-adrenergic antagonists and digoxin impair the intracellular to extracellular exchange mechanism which can also result in hyperkalemia in certain settings [5].

When investigating the etiology of hyperkalemia in the PICU patient, the potential impact of all medications must be considered. As mentioned above, several pharmacologic agents may secondarily affect potassium excretion in addition to their primary therapeutic effect such as the antibiotic, trimethoprim-sulfamethoxazole (Bactrim[®]). The primary therapeutic effect of this agent is inhibition of folate synthesis, thereby inhibiting bacterial replication. Trimethoprim-sulfamethoxazole is active against a wide range of infections, including those caused by both gram-positive and gram-negative bacteria, such as *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella* species, and *Enterobacter* species. In pediatric patients, it is the most commonly used to treat urinary tract infections, bacterial gastroenteritis, otitis media, and as prophylaxis against and treatment of *Pneumocystis jirovecii* pneumonia. In general, trimethoprim-sulfamethoxazole is well-tolerated with a limited adverse effect profile, the most common being gastrointestinal irritation and skin rashes. More serious adverse effects include nephrotoxicity, hypoglycemia, hyponatremia, and Stevens-Johnson syndrome [6, 7].

The trimethoprim component of the drug can also cause hyperkalemia, via a mechanism similar to the potassium-sparing diuretic, amiloride. Trimethoprim blocks the reuptake of sodium from the lumen of the tubule. Therefore, the sodium-potassium pump has no substrate to exchange for potassium, causing an increase of potassium in the interstitial fluid rather than elimination in the urine. Alappan et al reported that serum potassium levels increased by an average of 1.21 mEq/L within 2 - 6 days following the initiation of treatment with a standard dose [8]. Greenburg et al reported that 62.5% of patients had a peak serum potassium concentration of 5.0 - 5.5 mEq/L and 21.2% had a serum potassium concentration greater than 5.5 mEq/L compared to patients treated with other antibiotics who experienced no significant changes in serum potassium concentrations [9]. The incidence and severity of hyperkalemia may be greater when the dosing of the trimethoprim component exceeds 5 mg/kg/day [10, 11]. According to the package insert, current pediatric dosing recommendations for trimethoprim-sulfamethoxazole are 8 mg/kg/day (as measured by the trimethoprim component) for mild-moderate infections such as urinary tract infections and acute otitis media, and doses up to 15 - 20 mg/kg/day for serious infections such as *Pneumocystis jirovecii* pneumonia. Our patient received a dose of 5 mg/kg every 12 h for a total of 10 mg/kg/day.

Our patient experienced an increase in serum potassium coincident with the initiation of trimethoprim-sulfamethoxazole for treatment of bacterial tracheitis. During the days before the initiation of therapy, the patient's serum potassium was in the normal range, remaining below 4.5 mEq/L. After starting trimethoprim-sulfamethoxazole, a steady increase in potassium was observed, to a maximum value of 6.4 mEq/L. Other etiologies of hyperkalemia were excluded, therapy with trimethoprim-sulfamethoxazole was stopped, and following treatment with furosemide and Kayexalate[®], the serum potassium value returned to normal. No further hyperkalemia

was noted throughout the remainder of the patient's hospital course. Although previous reports have noted an association between therapy with trimethoprim-sulfamethoxazole and hyperkalemia in adults, we are not aware of previous reports in the pediatric population.

In summary, we present the development of hyperkalemia temporally related to the administration of antibiotic therapy with trimethoprim-sulfamethoxazole in a 4-month-old infant. Although we cannot definitely prove a causal relationship, other causes of hyperkalemia were ruled out, there was a temporal association of the increase in serum potassium with the administration of trimethoprim-sulfamethoxazole, and a resolution of the hyperkalemia when the antibiotic was discontinued. Monitoring of serum potassium may be indicated in patients treated with trimethoprim-sulfamethoxazole especially if there are other risk factors for the development of hyperkalemia.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

In accordance with the IRB guidelines of Nationwide Children's Hospital, IRB review and written informed consent are not required.

Author Contributions

Samantha Hudzik prepared the initial, subsequent, and final drafts; Hunter Johnson did the review of final draft, hospital care of patient; Joseph Tobias did the concept, review of all drafts, hospital care of the patient.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

References

1. Masilamani K, van der Voort J. The management of acute hyperkalaemia in neonates and children. *Arch Dis Child.* 2012;97(4):376-380.
2. Littmann L, Gibbs MA. Electrocardiographic manifestations of severe hyperkalemia. *J Electrocardiol.* 2018;51(5):814-817.
3. Cummings BM, Macklin EA, Yager PH, Sharma A, Noviski N. Potassium abnormalities in a pediatric intensive care unit: frequency and severity. *J Intensive Care Med.* 2014;29(5):269-274.
4. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. *N Am J Med Sci.* 2013;5(4):255-259.
5. Acker CG, Johnson JP, Palevsky PM, Greenberg A. Hyperkalemia in hospitalized patients: causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med.* 1998;158(8):917-924.
6. Smilack JD. Trimethoprim-sulfamethoxazole. *Mayo Clin Proc.* 1999;74(7):730-734.
7. Myers MW, Jick H. Hospitalization for serious blood and skin disorders following co-trimoxazole. *Br J Clin Pharmacol.* 1997;43(6):649-651.
8. Alappan R, Perazella MA, Buller GK. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. *Ann Intern Med.* 1996;124(3):316-320.
9. Greenberg S, Reiser IW, Chou SY, Porush JG. Trimethoprim-sulfamethoxazole induces reversible hyperkalemia. *Ann Intern Med.* 1993;119(4):291-295.
10. Perazella MA, Mahnensmith RL. Trimethoprim-sulfamethoxazole: hyperkalemia is an important complication regardless of dose. *Clin Nephrol.* 1996;46(3):187-192.
11. Gentry CA, Nguyen AT. An evaluation of hyperkalemia and serum creatinine elevation associated with different dosage levels of outpatient trimethoprim-sulfamethoxazole with and without concomitant medications. *Ann Pharmacother.* 2013;47(12):1618-1626.