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RESEARCH ARTICLE

ANTIBIOTIC-INDUCED HYPERKALEMIA: ENEMY AT THE GATES?

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ABSTRACT

Antibiotics are commonly prescribed in the hospitals for different hospitalized patients. Although clinician might be familiar to the most common side effects of them, however, some issues about antibiotic therapy are might be neglected by most of the clinicians. Many antibiotics can cause electrolyte imbalance such as hyperkalemia. Hyperkalemia develops in wide range from Asymptomatic to life threatening presentations. Knowing about this threat is necessary for all clinician involved in the antibiotic prescription practice.

INTRODUCTION

Potassium (K+) is the most important intracellular cation and is crucial in many physiological functions.extracellular potassium concentration is balanced through renal and extrarenal mechanisms. Normal potassium levels are between 3.5 and 5.5 mmol/L.Hyperkalemia is categorized to mild (5.5–6.5 mmol/l), moderate (6.5–7.5 mmol/l) and severe (>7.5 mmol/l). (1)

Potassium filtered at the glomerulus is completely reabsorbed in the proximal tubule and ascending limb of loop of Henle and is then secreted into the distal convoluted tubule and collecting duct. The rate of potassium secretion is determined by a number of factors, including distal sodium delivery, aldosterone, and serum potassium.Mild hyperkalemia is usuallyasymptomatic however, severe hyperkalemia can cause cardiac arrhythmia, which could be fatal. (2,3) Obtaining electrocardiography (ECG) is necessary when serum potassium >6.5 mmol/l.

Antibiotic- induced hyperkalemia through various mechanisms is a neglected issue in routine clinical practice which can happen in both outpatient and inpatient settings. (table 1) (4-6) We divide antibiotics causing hyperkalemia to two different categories:

1. **Well known:** Trimethoprim-sulfamethoxazole (TMP-SMX), Penicillin G, Azoles, Amphotericin B and Pentamidine
2. **Rarely described:** Erythromycin, Daptomycin

Trimethoprim-sulfamethoxazole (TMP-SMX)

Trimethoprim-sulfamethoxazole is the most common mentioned antibiotic causing hyperkalemia in medical literature. Trimethoprim is structurally similar to amiloride, a potassium-sparing diuretic. It competitively inhibits the sodium channels of the epithelium in the distal nephron, thereby impairing renal potassium excretion by approximately 40%. (7,8) The incidence and severity of hyperkalemia may greater when the dosing of the trimethoprim component exceeds 5 mg/kg/day, (8,9) however, there are reports of occurring hyperkalemia with standard dose TMP-SMX (10,11), especially in elderly patients, even in the presence of a normal serum creatinine level. (12,13) The literature has long reported the occurrence of TMP-SMX-induced hyperkalemia in patients with acquired immunodeficiency syndrome (14,15) and patients with end stage renal disease (15).

Patients treated with standard-dose trimethoprim-sulfamethoxazole should be monitored closely for the development of hyperkalemia, especially if they have concurrent renal insufficiency. (15,16)Occasionally,

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hyperkalemia might be additive in conjunction to other drugs, especiallyangiotens in converting enzyme inhibitors (ACEIs) or angiotensin receptor blocker (ARBs) and potassium sparing diuretics (PSDs). (12,13,17-21, 31)

Penicillin G

Penicillin G is administered as the potassium or sodium salt. Penicillin G contains 0.33 mmol of sodium or 1.7 mmol of potassium per million units. There are case reports of cardiac arrest following penicillin-induced hyperkalemia (22-25)

Azoles

Azole antifungals may interfere with the biosynthesis of adrenal steroids and therefore can predispose patients to aldosterone deficiency. (26,27) They are not equivalent in potassium imbalance. Among azoles,voriconazole (28-30),fluconazole (31-34), ketoconazole (35,36)can cause hyperkalemia.Although it is unclear whether hyperkalemia can be induced by voriconazole alone (28), however, few cases of voriconazole-induced hyperkalemia have been reported, following high serum voriconazole level due by drug-drug interactions. (29,30)

Amphotericin B

Although hypokalemia is a commonly reported side effects of both conventional amphotericin B deoxycholate and its lipid formulations, however, hyperkalemia, which is sometimes could be fatal is also reported. (37,38)

Pentamidine

pentamidine is alternative antibiotic treatment of patients with acquired immunodefiency syndrome (AIDS) complicated with Pneumocystis carinii infection. Hyperkalemia is a well- known side effect of pentamidine and there several reports available. (39-43)

Erythromycin

Ericson *et al*. conducted a large retrospective cohort study on infants exposed to ≥1 dose of erythromycin and observed that the most common laboratory adverse event during exposure to erythromycin was hyperkalemia. (44)

Daptomycin

Daptomycin is mainly used for treatment of resistant gram-positive cocci, including staphylococcal and enterococcal infections. The mechanism of daptomycin- induce hyperkalemia is due to rhabdomyolysis, a known side effect of daptomycin. (45,46)

In conclusion, it is important to investigate the causes of hyperkalemia. Although antibiotics can be responsible, however, might be more than one cause are detectable at the same time. Patients under treatment with above antibiotics-mostly TMP/SMX- especially in conjunction with ACEIs, ABRs and PSDs should be monitored closely for serum potassium level.

Table1 Antibiotic- induced hyperkalemia

Main Mechanism	*Antibiotics*
Defective aldosterone signaling	Azoles
Defective distal electrogenic sodium reabsorption	Trimethoprim, Pentamidine
Cellular K+ translocation	Amphotericin B (conventional and lipid formulations)
Exogenous K+ load	Penicillin G (intravenous), Daptomycin

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