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Pharmacologically Relevant Drug Interactions of Potassium-Sparing Diuretics

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ABSTRACT

Potassium-sparing diuretics are useful in the treatment of resistant hypertension and salt sensitive forms of hypertension common in black, obese, diabetic and elderly patients and they include Spironolactone, Eplerenone, Amiloride and Triamterene. Potassium-sparing diuretics interact pharmacodynamically with the drugs such as ACE inhibitors, angiotensin receptor blockers, direct renin inhibitor, potassium supplements, trimethoprim and cyclosporine and elevate the risk of hyperkalemia. To predict and prevent the adverse drug interactions, the prescribers and the pharmacists are needed to be aware of the possible drug interactions of Potassium-sparing diuretics.

Keywords: Drug interactions, Potassium-sparing diuretics, Spiranolactone, Eplerenone, Amiloride, Triamterene

INTRODUCTION

Potassium-sparing diuretics are useful in the treatment of resistant hypertension and salt sensitive forms of hypertension common in black, obese, diabetic and elderly patients [1]. They include Mineralocorticoid Receptor (MR) antagonists (aldosterone antagonists) such as Spironolactone and Eplerenone and Epithelial sodium transport channel blockers like Amiloride and Triamterene [2].

The interference of effects of a drug by the drugs, herbs, supplements or food administered concomitantly, is termed "Drug interactions" [3,4]. Potassium-sparing diuretics have the potential of causing hyperkalemia as the Aldosterone antagonists decrease secretion of potassium by inhibiting the binding of aldosterone to its cytoplasmic receptors while Epithelial sodium transport channel blockers reducing the secretion of potassium by decreasing sodium reabsorption [5]. Hyperkalemia is an electrolyte abnormality and it is associated with cardiac arrhythmias such as ventricular fibrillation and asystole, muscle weakness, paralysis and sudden cardiac death [6].

METHODS

The literature was searched in databases such as Medline/PMC/PubMed, Google Scholar, Science Direct, Cochrane Library, Directory of open access journals (DOAJ) and reference lists to identify related articles using the keywords drug interactions, potassium-sparing diuretics, mineralocorticoid receptor antagonists, aldosterone antagonists, spironolactone, eplerenone, epithelial sodium transport channel blockers, amiloride, triamterene. Hyperkalemia inducing drugs and pharmacodynamics interactions.

RESULTS AND DISCUSSION

The use of potassium-sparing diuretics is associated with the risk of hyperkalemia and hence the drugs inducing hyperkalemia could interact pharmacodynamically with Potassium-sparing diuretics. To predict and prevent the adverse drug interactions, the prescribers and the pharmacists are needed to be aware of the possible drug interactions of Potassium-sparing diuretics.

ACE inhibitors (ACEIs)

Angiotensin Converting Enzyme (ACE) inhibitors are recommended as first-line drugs to treat hypertensive patients particularly those having comorbidities such as diabetes, heart failure, ischemic heart disease and chronic kidney disease [7] and they include Captopril, Lisinopril, Perindopril, Enalapril, Ramipril, Trandolapril, Cilazapril and Fosinopril [8].

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ACE inhibitors induce hyperkalemia by affecting the secretion of potassium through the inhibition of stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland [9]. Concomitant use of Potassium-sparing diuretics and ACE inhibitors may lead to severe hyperkalemia particularly in patients with advanced age, type 2 diabetes and reduced renal function [10] and it is recommended to monitor the blood potassium levels when the concomitant use is necessary in the treatment of congestive heart failure [11].

Angiotensin receptor blockers (ARBs)

Angiotensin Receptor Blockers (ARBs) are used as first-line drugs to treat hypertensive patients particularly those having comorbidities such as diabetes, heart failure, ischemic heart disease and chronic kidney disease [7]. The patients who cannot tolerate ACE inhibitors due to persistent dry cough, angioedema and other adverse effects can take ARBs [12] and they include Losartan, Valsartan, Candesartan, Olmesartan, Irbesartan and Telmisartan [13].

ARBs can also induce hyperkalemia by affecting the secretion of potassium through the inhibition of stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland [14]. Co-administration of potassium-sparing diuretics and ARBs may also lead to severe hyperkalemia particularly in patients with advanced age, type 2 diabetes and reduced renal function [10] and it is recommended to monitor the blood potassium levels if they are used concomitantly to treat congestive heart failure [11].

Direct renin inhibitor (DRI)

Aliskiren is a Direct Renin Inhibitor (DRI) and it helps to manage hypertension in diabetic patients, as an add-on therapy [15]. Serum potassium levels may increase when potassium-sparing diuretics and DRI are used concurrently and it is advised to monitor the blood potassium if their concomitant use is necessary [16].

Potassium supplements

The risk of development of hyperkalemia is higher among the patients using potassium supplements and the co-administration of potassium-sparing diuretics further increase the risk of hyperkalemia. If concomitant use of these drugs is necessary, close monitoring of serum potassium concentrations [17].

Trimethoprim

Trimethoprim is a synthetic antibacterial drug and it is approved to treat uncomplicated urinary tract infection, respiratory tract infection and other infections [18]. The serum potassium levels could be elevated by the administration of Trimethoprim, which inhibits potassium excretion through the blockade of epithelial sodium channels in the distal nephron [19]. Higher risk of hyperkalemia was demonstrated in elderly patients receiving a potassium-sparing diuretic and trimethoprim concomitantly and it is recommended to monitor blood potassium levels if both these drugs are used together [20].

Cyclosporine

Cyclosporine is a calcineurin inhibitor and it is used as an immunosuppressant agent blocking calcineurin's phosphatase activity and decreases the production of inflammatory cytokines by T-lymphocytes [21]. Cyclosporine decreases the excretion of potassium and increase the risk of hyperkalemia through decreased activity of the renin-angiotensin-aldosterone system, impaired tubular responsiveness to aldosterone and altered function of several transporters [22]. The concomitant use of a Potassium-sparing diuretic and Cyclosporine may induce additive hyperkalemia which warrants close monitoring of blood potassium levels [23].

Digoxin

Digoxin is a cardiotonic drug, which is obtained from digitalis, and it helps to manage cardiac conditions such as congestive heart failure (CHF), atrial flutter or atrial fibrillation [24,25]. The renal tubular secretion of Digoxin could be reduced by the administration of Potassium-sparing diuretics, which may result in increased Digoxin concentrations [26].

Eplerenone and CYP3A4 inhibitors

Eplerenone is an aldosterone antagonist and it has been identified as a substrate for Cytochrome P450 3A4 (CYP3A4) enzyme [27]. Hence, the concomitant use of potent CYP3A4 inhibitor such as Ketoconazole in patients receiving Eplerenone caused a fivefold increase in exposure of Eplerenone and while less potent CYP3A4 inhibitors like erythromycin, saquinavir, verapamil and fluconazole increasing twofold exposure of Eplerenone, which may result in eplerenone-induced hyperkalemia or hypotension [28].

CONCLUSION

The drugs having the potential of inducing hyperkalemia such as ACE inhibitors, Angiotensin Receptor Blockers, Direct Renin Inhibitor, Potassium supplements, Trimethoprim and Cyclosporine could interact pharmacodynamically with Potassium-sparing diuretics and further elevate the risk of hyperkalemia. To predict and prevent the adverse drug interactions, the prescribers and the pharmacists are needed to be aware of the possible drug interactions of potassium-sparing diuretics.

CONFLICTS OF INTEREST

Nil

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