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Drug-drug interactions in pharmacotherapy of heart failure:Risk of electrolyte abnormalities

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ABSTRACT

Heart failure (HF) is associated with several systemic complications that require combination therapies. Considering the type and clinical manifestations of HF, several types of medications are used to overcome some harmful activated compensatory mechanisms. Angiotensin receptor–neprilysin inhibitors (ARNIs), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, mineralocorticoid receptor antagonists (MRAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors alongside with other classes like diuretics, vasodilators and/or positive inotropic agents constitute the medication basket for patients with heart failure. Polypharmacy with different classes of drugs increases the risk of drug-drug interactions during treatment. One of the main issues in these interactions is the risk of electrolyte abnormalities, especially regarding the potassium level, which would be so threatening. This mini review focused on specific aspects of drug-drug interactions that might occur during treatment and how they can be life-threatening.

Keywords:

Heart failure, ARNIs, SGLT2 inhibitors, ARBs, ACEIs, Drug-interaction, Electrolyte abnormalities.

Introduction

Chronic heart failure (CHF) is a progressive disease that affects the patient's quality of life over time. According to the 2024 update in heart failure, while decreasing the incidence of heart failure (3.20 cases per 1000 person/years), the prevalence of the disease is increasing because of the development of new therapies and having a higher life

expectancy (17.20 cases per 1000 persons) in uropean countries (1). Based on cardiac function, heart failure is classified into two types: diastolic and systolic heart failure. One of the main differences between the two types is the extent of changes in ejection fraction (EF). Diastolic heart failure is commonly caused by ventricular filling dysfuction; however, it is usually not associated with EF reduction, so cardiac output remains preserved (HFpEF) (2). In contrast, systolic dysfunction is usually associated with EF reduction caused by reduced cardiac muscle contraction tone which is abbreviated as HFrEF (2). Each form of HF is associated with a different degree of ventricular remodeling (3). Several physiological reflexes are activated in response to such pathological cardiac dysfunction. An increase in sympathetic tone and activation of the renin-angiotensin-aldosterone system (RAAS) occur to correct cardiac output and circulation state, which are beneficial just for a short time and could be harmful over time. Other beneficial compensatory mechanisms are also activatedover time. Significant rise in brain natriuretic peptide (BNP) secretion, as well as increase in production of kinins are examples of these beneficial compensatory mechanisms (4). Compensatory mechanisms, however, could be helpful for just a short period, and as cardiac dysfunction progresses, clinical demonstration worsens and requires the aid of pharmacological treatments. According to several types of disease manifestations, polytherapy is an obligation in these patients. Considering the type and clinical manifestations of HF, several types of medications are used to overcome these deleterious compensatory mechanisms. Pharmacotherapy in patients with HFrEF includes angiotensin receptor–neprilysin inhibitors (ARNIs) as first line selection, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), β-blockers, mineralocorticoid receptor antagonists (MRAs) and sodium–glucose cotransporter 2 (SGLT2) inhibitors (5). When it's necessary additional groups of medications such as vasodilators (hydralazine and nitrates) and/or positive inotropic agents could be added to other aforementioned treatments. In the cases of mild EF reduction or in HFpEF, SGLT2 inhibitors are recommended as the first-line treatment but other classes are also used including diuretics, RAAS and aldosterone receptor inhibitors (5). Therefore, owing to the obligatory combination of drugs, the occurrence of probable drug interactions must be seriously considered. One of the main considering issues of drug interactions is electrolyte abnormality. In this regard, abnormalities in serum potassium levels could be dangerous and require accurate medical consideration. Before stating some important drug interactions in pharmacotherapy for heart failure, we emphasized on drug interaction, as a separated concept.

Drug interaction is a broad-spectrum term, but almost always when using a "drug-interaction" term, one thinks about drug-drug interactions in which two or more medications negatively react with each other. Indeed, drug interactions have a wide domain, which can be explained by different types including drug-drug interactions, drug-food interactions, drug supplement interactions, drug-medicinal herbs/herbal medicine interactions, drug-laboratory test interactions and drug-disease state interactions.

Most of the time, the term of "drug interaction" has been used to convey a negative concept, but not all drug interactions are undesirable. There are several examples of pharmaceutical formulations purposely designed with one or more positive drug-drug interactions. The combination of triamterene and hydrochlorothiazide, known as Triamterene H, is one such example in which a thiazide diuretic, which leads to potassium loss, has been combined with a potassium-sparing diuretic that prevents such potassium loss, so such a purposed combination is associated with more potassium balance.

However, the undesirable "drug-drug interactions" require careful evaluation.

Abnormalities in serum potassium levels are one of the undesirable and sometimes harmful adverse effects. Based on the obligatory need for combination drug therapy in patients with heart failure, and considering the drug classes that they need, hypo-or hyperkalemia could occur. Although some drug interactions could be prevented by time management and interval correction, others could be dangerous and life-threatening and must be replaced with other classes.

Pharmacological management of heart failure

Although the pharmacotherapy of patients with heart failure is started based on combination therapy, the type and the chronology (acute or chronic) of HF as well as the patient's clinical symptoms are important to choose patient's medications (4). Dependent on the acute and chronic heart failure, several classes of medications are required to help patients with cardiac dysfunction overcome the sympathetic overactivation and to prevent RAAS stimulation. They also require diuretics to eliminate excessive volume overload, beta receptor blockers and/or vasodilators to reduce undesirable sympathetic tone. In cases of significant reduced cardiac EF, positive inotropic agents also should be added to other classes. Several published clinical trials have confirmed that the MRAs (6-8) and beta blockers may improve the patient survival (9, 10). When necessary, nonselective beta blockers as antiarrhythmic drugs could be replaced with the cardioselective one such as ivabradine, which has the minimal negative inotropic effect (11). Therefore, considering such obligatory drug combinations, harmful drug interactions can be expected.

Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) are two main classes that are widely used in patients with heart failure. According to preclinical and clinical evidence, blocking the over-activated-RAAS in this situation has several therapeutic benefits, such as prevention of cardiac hypertrophy and cardiovascular remodeling. These drug families can also positively affect patient survival (4).

Focusing on drug interactions, one of the main concerns of ACEIs and ARBs are the potential risk of hyperkalemia which could be ranged from mild to dangerous level (9). The risk is increased in patients with lower kidney function and/or simultaneous administration of other K+-sparing drugs. It needs attention that due to poor circulation and/or cardiac output, kidney disease might be more probable in patients with heart failure. Therefore, each class of medication associated with hyperkalemia risk should be carefully considered in such patients. Simultaneous administration of two RAAS-blocking agents, including ACEIs and ARBs, is a medical mistake with no rational reason and should be contraindicated. Drug- or renal-induced hyperkalemia can exacerbate cardiac abnormalities, even asystole, in patients with underlying heart problems.

The risk of hyperkalemia significantly increases when potassium-sparing diuretics and/or MRAs are added to ACEIs or ARBs. Spironolactone is an aldosterone receptor antagonist which also has therapeutic advantages in prevention of cardiovascular remodeling and improvement of patient's survival (12). The combination of these drug classes, which is clinically more probable or even common, is a critical drug-drug interaction issue that requires extraordinary attention and close monitoring.

Recently, the administration of a new drug combination with double-acting design, has created a new hope for the treatment of heart failure. Combination of angiotensin receptor/neprilysin inhibitor (ARNI), sacubitril/valsartan, simultaneously improves cardiac function and prevents deleterious complications of RAAS over-activation. It has been demonstrated that sacubitril/valsartan has several therapeutic benefits compared to each compound alone. Improvement in cardiac mitochondrial function and myocardial contractility, diminished

oxidative stress, inflammation, and antifibrotic effects, and prevention of cardiac remodeling are some of the therapeutic advantages of the combination (5, 13-15). Apart from its more efficient therapeutic abilities, the issue of hyperkalemia is still concerned. Although some reports have indicated a lower risk of hyperkalemia with sacubitril/valsartan (16, 17), theoretically, the incidence has not been removed.

Concurrent administration of drugs which may affect potassium level, either hypo- or hyperkalemia, with cardiac glycosides such as digoxin, is another important negative drug-drug interaction. Therapeutic efficacy and/or risk of toxicity of cardiac glycosides significantly depends on serum electrolyte levels such as calcium, potassium, and magnesium. According to digoxin mechanism of action, drug-induced hyperkalemia could negatively suppress the inotropic action of digoxin; therefore, it may worsen the cardiac dysfunction. Conversely, hypokalemia could increase the incidence of digoxin toxicity, which could be life-threatening (18).

One of the main causes of mortality in patients with HFrEF is life-threatening ventricular arrhythmias. The risk of ventricular arrhythmia could increase with several factors, including old age, ischemic conditions and/or myocardial infarction, and electrolyte abnormalities (16, 17). Therefore, antiarrhythmic drugs have beneficial effects and are commonly used to prevent cardiac dysrhythmia. Several reports have indicated the beneficial effects of beta-blockers, which are class II antiarrhythmic drugs, on the survival of patients with post-MI HF. However, hyperkalemia is one of the main concerns associated with these agents. Beta-blockers decrease cellular potassium uptake. They could also serve as inhibitors of renin release from juxtaglomerular cells (16, 17). Using these mechanisms, hyperkalemia may be possible with such agents. The existence of comorbidities, such as renal failure and/or insulin insufficiency, can exacerbate the risk of beta-blocker-induced hyperkalemia (18). Therefore, drug-drug interactions with other hyperkalemic agents should be considered.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are another multi-target drug formulation. They are preferred in patients with comorbidities such as diabetes and hypertension. The class of drug was added to HFrEF pharmacotherapy guidelines in 2022 and according to several clinical and experimental reports regardless to serum glucose level, they have significant cardiovascular benefits in patients with either HFrEF or HFpEF (18). Despite consistent benefits, they could be associated with electrolyte disturbances, including small increases in plasma potassium and magnesium concentrations (19). Although these minor electrolyte abnormalities are not important during monotherapy, concomitant polytherapy with other classes of drugs with similar electrolyte abnormalities may be problematic and should be carefully considered.

Hypokalemia is another electrolyte disturbance that may be caused by excessive fluid excretion due to the administration of loop diuretics such as furosemide. It should be noted that hypokalemia could facilitate the toxicity of cardiac glycosides. The simultaneous administration of loop diuretics with thiazide or thiazide-like diuretics could increase the risk of hypokalemia. However, with concurrent administration of at least one other pharmacological class, such as ARBs, ACEIs, ARNI, or MRAs, the risk of hypokalemia is low. Adjustment of potassium is a critical step in patients undergoing digitalization.

Conclusion

HF is associated with several systemic complications that require combination therapies. The use of combinations of drugs in patients with heart failure is an obligation, and such simultaneous administration is associated with some drug-drug interactions. Changes in serum electrolyte levels are among the most

important issues in this situation. Hyperkalemia and hypokalemia are of particular importance. ECG abnormalities and fatal cardiac arrhythmias occur when severe hyperkalemia is left untreated. Hypokalemia is also associated with cardiac abnormalities. Therefore, such poly-administration requires more attention to prevent harmful or even lethal drug-drug interactions. Dose-adjustment of drugs with such adverse effects, especially in patients with chronic kidney disease, as well as prevention of unnecessary drug combination, could be helpful in preventing or at least reducing the risk of electrolyte abnormalities.

Conflict of interest

The authors declare that here is no conflict of interest.

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