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Mini Review

Pharmacologically Relevant Drug Interactions of Nitrovasodilators

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Abstract

Nitrovasodilators are used to treat many conditions including coronary artery disease, chronic congestive heart failure, and arterial hypertension. They induce smooth muscle relaxation by increasing intracellular cyclic Guanosine Monophosphate (cGMP) concentrations and activating K+ channels through the release of Nitric Oxide (NO). Thus, they could interact with the drugs preventing the breakdown or increasing the synthesis of cGMP and induce the accumulation of cGMP resulting in excessive vasodilation and severe hypotension. Pharmacologically relevant drug interactions of Nitrovasodilators are discussed in this review.

Coadministration of Nitrovasodilators and the drugs preventing the breakdown of cGMP like Phosphodiesterase 5 (PDE5) inhibitors or the drugs increasing the synthesis of cGMP like Riociguat could induce the accumulation of cGMP resulting in excessive vasodilation and severe hypotension. The prescribers and pharmacists are required to be aware of the drugs interacting with Nitrates to predict and prevent the adverse drug interactions.

Keywords: Drug Interactions, Nitrovasodilators, Nitrates, Nitroglycerin.

Introduction

Nitrovasodilators are the agents useful in the management of conditions like coronary artery disease, chronic congestive heart failure, and arterial hypertension and they include short-acting sublingual Glyceryl Trinitrate (GTN) and long-acting nitrates such as Isosorbide Mononitrate (ISMN) and Isosorbide Dinitrate (ISDN) and other drugs like Sodium Nitroprusside and Nicorandil.[1] They release NO which activates soluble Guanylyl Cyclase (GC) of smooth muscle to form cGMP. Smooth muscle relaxation is achieved through increased intracellular cGMP that inhibits calcium entry into the cell, thereby decreasing intracellular calcium concentrations. Smooth muscle relaxation is also induced by NO, which activates K^+ channels, leading to hyperpolarization and relaxation.[2]

Modification of the effects of one drug by concomitantly administered drugs, herbs or nutrients is termed “drug interaction” and the drug interaction resulting in increased adverse effects or decreased therapeutic efficacy is known as “adverse drug interaction”.[3,4] The pharmacokinetics or pharmacodynamics profile of the drugs are altered by the interacting drug.[5]

Results and Discussion

Nitrovasodilators increase the plasma concentrations of cGMP by stimulating soluble GC enzyme and the drugs preventing the breakdown or increasing the synthesis of cGMP can induce the accumulation of cGMP resulting in excessive vasodilation and severe hypotension. Hence, Nitrovasodilators could interact with PDE5 inhibitors and Riociguat.

Phosphodiesterase 5 (PDE5) Inhibitors

The Phosphodiesterase 5 (PDE5) inhibitors are recommended as first-line drugs to treat Erectile Dysfunction (ED) and they include Sildenafil, Tadalafil and Vardenafil.[6] The predominant phosphodiesterase in the corpus cavernosum is PDE5 and it’s inhibition by PDE5 inhibitors prevent the breakdown of cGMP leading to increased concentration of cGMP resulting in relaxation of arterial and trabecular smooth muscle, leading to arterial dilatation, venous constriction, and erection.[7]

Marked vasodilation and severe hypotension could occur in patients receiving Nitrates, PDE5 inhibitors concomitantly, due to excessive accumulation of cGMP as the Nitrates increase the production of cGMP, and the PDE5 inhibitors prevent the breakdown of cGMP.[8]

Nitrates are not recommended to be administered within 24 hours of use of Sildenafil or 48 hours of use of Tadalafil.[9] Hence, the patients can be administered with Nitrates after 24 hours of Sildenafil intake as it was suggested by the American College of Cardiology and American Heart Association.[10] The patients on Nitrates are recommended to withhold their Nitrates at least for 48 hours, after the intake of Tadalafil. Also, the restarting of Nitrates should be done with monitoring.[11]

Riociguat

Riociguat is a stimulator of the soluble Guanylate Cyclase (sGC) enzyme which is indicated in the treatment of pulmonary hypertension.[12] Riociguat increases the intracellular cGMP levels by stimulating sGC and sensitizing sGC to endogenous NO.[13] Additive hypotensive effect is expected in patients receiving Nitrates and Riociguat concurrently, due to excessive accumulation of cGMP [14].

Alteplase

Alteplase is a recombinant tissue Plasminogen Activator (rtPA) which is used as a thrombolytic drug to treat acute ischemic stroke, pulmonary embolism and acute myocardial infarction.[15] Concurrent use of Alteplase and Nitroglycerin (Glyceryl Trinitrate (GTN)) decreased the plasma concentration of Alteplase due to enhanced degradation of Alteplase in plasma while the thrombolytic activity of Alteplase has been decreased.[16,17]

Heparin

Heparin is an anticoagulant drug which is used to treat conditions like Acute Coronary Syndrome (ACS), Atrial Fibrillation (AF), Deep-Vein Thrombosis (DVT), Pulmonary Embolism (PE) etc.[18] Concomitant use of Nitroglycerin and Heparin resulted in an impaired anticoagulant activity of Heparin. Also, it is worth mentioning that the monitoring of the International Normalized Ratio (INR) is recommended when both drugs are used concurrently.[19]

Conclusion

The drugs preventing the breakdown or increasing the synthesis of cGMP could interact with Nitrovasodilators and induce the accumulation of cGMP resulting in excessive vasodilation and severe hypotension. The Phosphodiesterase 5 (PDE5) such as Sildenafil, Tadalafil and Vardenafil prevent the breakdown of cGMP while Riociguat increases the synthesis of cGMP. In addition, the thrombolytic activity of Alteplase and the anticoagulant activity of Heparin are affected by the coadministration of Nitroglycerin. The prescribers and pharmacists are required to be aware of the drugs interacting with Nitrates to predict and prevent the adverse drug interactions.

Conflicts of Interest

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