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Drug interactions of non-dihydropyridine calcium channel blockers involving CYP3A enzymes and P-gp transporter protein

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ABSTRACT

Non-dihydropyridine CCBs such as verapamil and diltiazem are useful in the management of angina, certain arrhythmias and hypertension and they are known inhibitors of CYP3A enzymes and P-gp transporter. Hence, they can potentiate the adverse effects of substrates of CYP3A enzymes and P-gp transporter. This article focuses on the drug interactions of non-dihydropyridine CCBs involving CYP3A enzymes and P-gp transporter protein. To predict and prevent adverse outcomes, the prescribers and the pharmacists are required to be aware of the possible drug interactions of non-dihydropyridine CCBs.

Keywords: *Drug interactions; Pharmacokinetic interactions; Verapamil; Diltiazem; CYP3A enzymes; P-gp transporter.*

1. INTRODUCTION

Commonly used non-dihydropyridine (non-DHP) Calcium channel blockers (CCBs) include Verapamil and Diltiazem and they are useful in the management of angina, certain arrhythmias and hypertension [1]. They induce coronary vasodilation through the inhibition of influx of calcium during depolarization in select voltage areas of vascular smooth muscle and myocardium [2]. Non-DHP CCBs are more cardio selective than dihydropyridine CCBs. Verapamil produces more negative chronotropic effects and more negative inotropic effects than Diltiazem [3].

The modification of effects of a drug by other drug(s), vitamins, minerals, food, herbs, tobacco smoke, or alcohol coadministered, is termed Drug interaction [4, 5].

Cytochrome P450 (CYP) enzymes are hemeproteins by which most of the drugs are metabolized through oxidative reactions [6]. Many drug interactions can occur due to the inhibition or induction of CYP enzymes [7]. P- glycoprotein (P-gp) is an efflux transporter [8] that can decrease the absorption and oral bioavailability and increase the excretion of many drugs by promoting the efflux of drugs [9].

A drug that induces the drug interaction is known as a precipitant drug [10]. Verapamil and diltiazem act as precipitant drugs as verapamil induces weak inhibition of CYP3A4 and strong inhibition of P-gp transporter [11] while diltiazem is a moderate inhibitor of CYP3A4 and P-gp transporter [12].

A drug, which is affected by the drug interaction, is called object drug [10]. Cytochrome P450 (CYP) enzymes like CYP3A4, 3A5 and 2C8, predominantly metabolize verapamil [13]. Similarly, diltiazem is a substrate of CYP3A4 enzyme as well as P-gp transporter [14] and the drugs inhibiting or inducing these enzymes and P-gp transporter, may interact with verapamil and diltiazem.

Hence, verapamil and diltiazem can interact with many drugs and the prescribers and the pharmacists are required to be aware of the possible drug interactions of non-dihydropyridine CCBs to predict and prevent adverse outcomes.

2. MATERIALS AND METHODS

The databases such as Medline/PMC/PubMed, Google Scholar, Cochrane Library, Science Direct, Directory of open access journals (DOAJ) and reference lists were searched to identify related articles using the keywords Drug interactions, Pharmacokinetic interactions, Calcium channel blockers, Verapamil, Diltiazem, CYP3A enzymes and P-gp transporter.

3. RESULTS

3.1. Digoxin.

Digoxin is a cardiac glycoside obtained from digitalis plants and it helps to treat patients with conditions like congestive heart failure (CHF), atrial flutter, or atrial fibrillation [15, 16]. Patients with atrial fibrillation may use the combination of digoxin along with verapamil [17].

Serum concentrations of digoxin increased significantly in patients received the combination of digoxin and verapamil [18] as verapamil reduces the renal excretion of digoxin through the inhibition of P-gp mediated transport of digoxin resulting in digoxin toxicity [19]. Therefore, it is recommended to reduce the dose of digoxin, if the concomitant use of verapamil is necessary [18]. However, the concomitant use of diltiazem and digoxin in patients with cardiac disease resulted in increased steady-state plasma concentration of digoxin with no clinical signs of digitalis toxicity [20] and the patients on digoxin may prefer diltiazem over verapamil, as diltiazem in doses of 120 to 240 mg/day shows no effects on serum digoxin concentration or renal digoxin clearance [21].

3.2. Cyclosporine.

Cyclosporine is a calcineurin inhibitor, it is used as an immunosuppressant medication in patients who receive solid organ transplants, and it has narrow therapeutic index [10]. Cyclosporine is predominantly metabolised by CYP3A4 enzyme and it is a substrate of P-gp transporter [22].

The plasma concentrations of cyclosporine was increased in renal transplant recipients taking cyclosporine and verapamil concurrently [23]. Similarly, the plasma concentrations of cyclosporine were increased by the coadministration of diltiazem [24] as diltiazem is a moderate inhibitor of CYP3A4 enzyme and P-gp transporter [25].

Administration of diltiazem in renal transplantation patients treated with cyclosporine led to decreased dosage requirement of cyclosporine resulting in reduced patients' economic burden, retained kidney function, promoted graft function recovery and decreased hepatic and renal toxicity [26].

3.3. Dofetilide.

Dofetilide is a class III antiarrhythmic agent, which may induce QT prolongation resulting in torsades de pointes as a consequence of therapy [27]. Verapamil increased the plasma concentrations of dofetilide by increasing its rate of absorption as verapamil may increase hepatic and portal blood flow [28]. Concurrent use of verapamil and dofetilide is not recommended as the risk of prolongation of QT interval and torsades de pointes is higher with this combination [29].

3.4. Lomitapide.

Lomitapide is an antihyperlipidemic drug decreasing plasma concentrations of Low-density lipoprotein (LDL) through the inhibition of Microsomal triglyceride transfer protein (MTP) [30]. Lomitapide is a substrate of CYP3A enzymes [31] and verapamil can increase the plasma concentrations of lomitapide resulting in enhanced risk of elevation of the liver aminotransferase levels, through moderate inhibition of CYP3A4-mediated metabolism of lomitapide. The patients on lomitapide should be advised to avoid verapamil administration [32].

3.5. Colchicine.

Colchicine is used to manage gout and Familial Mediterranean Fever (FMF) and it is also found to be useful in the management of conditions such as Behcet's disease (BD), pericarditis, coronary artery disease, and other inflammatory and fibrotic conditions [33]. Mainly P-gp transporter eliminates colchicine and a smaller portion of colchicine is metabolised by CYP3A4 enzyme [34]. The serum concentrations of colchicine have been increased by the verapamil administration as it inhibits both P-gp transporter and CYP3A4 enzyme [35].

Similarly, the plasma concentrations of colchicine were increased by the concomitant administration of verapamil or diltiazem and it was recommended to reduce the dosage of colchicine if concurrent therapy of verapamil or diltiazem is necessary [36]. It is recommended to avoid concomitant use of colchicine and verapamil or diltiazem in patients with renal or hepatic impairment [36].

3.6. Carbamazepine.

Carbamazepine is an antiepileptic drug and it is an inducer of various CYP enzymes including CYP3A4 [37]. The risk of elevation of plasma concentrations of carbamazepine and carbamazepine neurotoxicity potentiated by the concomitant administration of Verapamil [38, 39] or Diltiazem [40, 41]. To prevent the neurotoxicity associated with carbamazepine, it is recommended to monitor the blood levels of carbamazepine if verapamil or diltiazem used concurrently [42].

3.7. Cisapride.

Cisapride is a substrate of CYP3A4 enzyme and it is used mainly to treat adults and children with gastro-oesophageal reflux disease (GERD) [43]. QT-interval prolongation and near syncope occurred in a patient receiving cisapride and diltiazem concomitantly probably due to diltiazem-induced inhibition of cisapride metabolism resulting in increased levels of cisapride. Hence, caution is advised if both these drugs used concurrently [44].

3.8. Quinidine.

Quinidine is an antiarrhythmic agent and it is useful to manage almost all cardiac arrhythmias [45]. Quinidine is predominantly metabolized by CYP3A4 [46] and decreased oral clearance and increased half-life of quinidine noted with the pretreatment of verapamil [47] or diltiazem [48] probably due to the inhibition of CYP3A4-mediated metabolism of quinidine.

3.9. Benzodiazepines.

Benzodiazepines are a class of psychoactive drugs and they are used as sedatives, hypnotics, anxiolytics, anticonvulsants and muscle relaxants [49]. They include long-acting compounds such as diazepam, etc., intermediate-acting drugs such as lorazepam alprazolam, etc. and short-acting agents like midazolam Triazolam, etc. [50].

Diazepam is a substrate of CYP3A4 enzyme and its coadministration with diltiazem resulted in increased plasma concentrations and prolonged elimination half-life of diazepam in healthy volunteers [51].

The plasma concentrations of midazolam increased and its elimination half-life prolonged by the concurrent use of diltiazem or verapamil in healthy volunteers. Hence, it is recommended to reduce the dose of midazolam during concomitant treatment with diltiazem or verapamil to avoid profound and prolonged sedative effects [52]. Moreover, the plasma exposure of midazolam was increased by the addition of diltiazem [53]. It has been suggested that Timed-release formulation of diltiazem can prevent the drug-drug interaction between diltiazem and midazolam [54].

The addition of diltiazem in healthy volunteers taking Triazolam lead to increased plasma exposure and prolonged pharmacodynamic effects of triazolam probably due to the inhibition of CYP3A4 enzyme by diltiazem and the patients taking diltiazem are advised to avoid triazolam [55, 56].

3.10. Fentanyl.

Fentanyl is a synthetic opioid drug and it is metabolized predominantly by CYP3A4 enzyme [57]. Delirium has occurred in a patient taking fentanyl and diltiazem concomitantly. Potentiation of fentanyl toxicity might have occurred due to the possible inhibition of CYP3A4-mediated metabolism of fentanyl by diltiazem [58].

3.11. Dronedarone.

Dronedarone is an amiodarone analog and it is used as an antiarrhythmic agent to manage atrial fibrillation (AF) and atrial flutter (AFL) [59]. Dronedarone is metabolized predominantly by CYP3A4 and it is a substrate of P-gp transporter [60]. The plasma levels of dronedarone could be elevated by the concurrent use of

verapamil or diltiazem and it is recommended to use lower doses of verapamil or diltiazem with caution [61].

3.12. Flibanserin.

Flibanserin is a novel serotonergic agent and it is approved to treat female hypoactive sexual desire disorder (HSDD) [62]. Flibanserin is metabolized extensively by CYP3A4 enzyme [63] and its coadministration with verapamil or diltiazem may result in increased flibanserin exposure [64].

3.13. Beta-blockers.

Beta-blockers are competitive antagonists of beta-adrenergic receptors and are used mainly to manage various conditions including cardiac arrhythmias, hypertension, angina pectoris, etc. [65]. The plasma concentrations of propranolol and metoprolol were significantly increased in healthy volunteers receiving diltiazem concomitantly [66].

The risk of bradycardia and atrioventricular block is higher in patients receiving verapamil or diltiazem along with beta-blockers [67]. Hence, an adjustment of the dosage of beta-blocker may be required if combination therapy of diltiazem and propranolol or metoprolol is necessary [68].

3.14. Apixaban.

Apixaban is an anticoagulant drug, which is widely used to manage patients with atrial fibrillation, deep vein thrombosis (DVT) and pulmonary embolism (PE) [69]. Apixaban is a substrate of CYP3A4 enzyme and P-gp transporter [70] and its co-administration with diltiazem resulted in increased apixaban exposure probably due to the inhibition of CYP3A4-mediated metabolism of apixaban by diltiazem [71].

3.15. Statins.

Hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (Statins) are used as first-line drugs to lower plasma concentrations of total cholesterol, low-density lipoprotein (LDL), and triglycerides while elevating high-density lipoprotein (HDL) concentrations [72].

Statins like simvastatin and lovastatin are metabolised extensively by CYP3A4 enzyme [73] and are the substrates of P-gp transporter [74]. The area under the curve of simvastatin and lovastatin could be increased 3- to 8-folds and the risks of acute kidney injury, hyperkalemia, acute myocardial infarction, and acute ischemic stroke enhanced by the coadministration of Verapamil or Diltiazem [75].

Coadministration of atorvastatin with verapamil in healthy volunteers resulted in a significant increase in plasma concentrations and bioavailability of verapamil probably due to the inhibition of absorption of verapamil through the inhibition of P-gp and/or the metabolism of verapamil by CYP3A4 [76].

3.16. Palbociclib.

Palbociclib is an inhibitor of cyclin-dependent kinases (CDK) 4 and CDK6 and it is approved to treat advanced breast cancer as a first-line drug, in combination with Letrozole [77]. Palbociclib is predominantly metabolized by CYP3A4 enzyme and it is found to be a substrate of P-gp transporter [78]. Palbociclib toxicity occurred in a patient taking the combination of palbociclib and verapamil probably due to the inhibition of CYP3A4-mediated metabolism and P-gp-mediated efflux of palbociclib resulting in elevated plasma concentrations of palbociclib [79].

3.17. Buspirone.

Buspirone is an anxiolytic drug and it is found to be effective in patients with mixed anxiety/depression [80]. Buspirone is metabolized mainly by CYP3A4 enzyme [81] and the plasma concentrations of buspirone were increased by the coadministration of verapamil and diltiazem probably through the inhibition of CYP3A4-mediated first-pass metabolism of Buspirone [82].

3.18. Macrolide antibiotics.

Generally, the macrolide antibiotics are helpful to treat respiratory tract infections and commonly used macrolide antibiotics include erythromycin, clarithromycin and azithromycin [83]. Concomitant use of erythromycin and verapamil in a female patient resulted in the prolonged QT interval and a complete AV block, as both the drugs are inhibitors of CYP3A4 and of P-glycoprotein [84]. Hypotension and bradyarrythmia were reported in a patient taking verapamil and telithromycin concomitantly [85].

Hypotension has occurred in a 78 year-old patient receiving nifedipine, diltiazem and carvedilol when clarithromycin was prescribed, since clarithromycin increase the plasma concentrations of Calcium-channel blockers through the inhibition of CYP3A4-mediated metabolism of them [86].

The macrolide antibiotics like erythromycin and clarithromycin are known to prolong QT interval and the coadministration of either of them in patients receiving nondihydropyridines may increase the QT prolongation further through the CYP3A4-mediated metabolism of macrolides [87]. The patients on verapamil or diltiazem requiring macrolide antibiotic therapy should be monitored for adverse effects [88].

3.19. Amiodarone.

Amiodarone is primarily a class III antiarrhythmic drug and it is approved to treat life-threatening ventricular arrhythmias [89]. The plasma concentrations of diltiazem could be increased by the introduction of amiodarone therapy probably due to the inhibition of diltiazem metabolism by amiodarone. The patients requiring the concomitant use of diltiazem and amiodarone should be monitored closely to prevent the unintended effects of hypotension, atrioventricular block, and sinus node depression [90].

3.20. Rifampicin.

Rifampicin is an antimycobacterial agent that is used primarily in the treatment of tuberculosis and leprosy and it is a known inducer of CYP enzymes including CYP3A4 [91]. Concomitant use of rifampicin and verapamil resulted in decreased bioavailability and therapeutic efficacy of verapamil probably due to enhanced rifampicin-mediated metabolism of verapamil [92, 93].

4. CONCLUSIONS

Non-dihydropyridine CCBs such as verapamil and diltiazem are known inhibitors of CYP3A enzymes and P-gp transporter and hence they can potentiate the adverse effects of object drugs through the inhibition of their metabolism. As a precipitant drug verapamil increase the plasma concentrations of drugs such as digoxin, cyclosporine, dofetilide, lomitapide, colchicine, carbamazepine, quinidine, dronedarone, flibanserin, statins (simvastatin, lovastatin), palbociclib, buspirone, and

macrolide antibiotics (erythromycin, telithromycin) while diltiazem increasing the plasma concentrations of drugs such as cyclosporine, colchicine, carbamazepine, cisapride, quinidine, benzodiazepines (diazepam, midazolam, triazolam), fentanyl, dronedarone, flibanserin, beta-blockers (propranolol, metoprolol), apixaban, statins (simvastatin, lovastatin), and buspirone.

In addition, as an object drug verapamil interacts with rifampicin and bioavailability and therapeutic efficacy of verapamil decreased while the plasma concentrations of diltiazem increased by the drugs such as clarithromycin and amiodarone.

To predict and prevent the drug interactions of non-dihydropyridine CCBs, the prescribers and the pharmacists are required to be aware of the drugs being as substrates of CYP3A4 enzyme and P-gp transporter.

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