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Drug Interactions of Dihydropyridine Calcium Channel Blockers (CCBs) involving CYP3A4 Enzymes

Naina Mohamed Pakkir Maideen [a, *]

[a] Dubai Health Authority, Dubai, United Arab Emirates

Abstract

Dihydropyridine Calcium Channel Blockers (CCBs) are widely used as first-line agents to treat hypertension in black patients and in patients aged more than 55 years. They have been identified as the substrates of intestinal and hepatic CYP3A4 enzymes and this review focuses on possible drug-drug interactions of dihydropyridine CCBs involving CYP3A4 enzymes. As object drugs, the dihydropyridine CCBs involved in drug-drug interactions with drugs such as Macrolide antibiotics, Azole antifungals, Protease inhibitors and fruit juices like Grapefruit juice and Seville orange juice and increase the plasma concentrations of dihydropyridine CCBs resulting in enhanced adverse effects. In addition, the drugs like Rifampicin, Phenytoin, and other antiepileptics including Carbamazepine and Phenobarbital decrease the bioavailability of dihydropyridine CCBs. Moreover, as precipitant drugs dihydropyridine CCBs increase the plasma concentrations of Statins and Cyclosporine and decrease the therapeutic efficacy of Clopidogrel. The prescribers and pharmacists are required to be aware of the adverse drug interactions of dihydropyridine CCBs to prevent adverse outcomes.

Keywords: Drug interactions, Dihydropyridine Calcium Channel Blockers, CYP3A4 enzymes, Nifedipine, Amlodipine, Felodipine.

1. Introduction

Calcium channel blockers (CCBs) include Dihydropyridines (DHPs) such as Nifedipine, Amlodipine, Felodipine, Nicardipine, and others and non-dihydropyridines (non-DHPs) like Verapamil and Diltiazem (Whyte et al., 2016). The first-generation DHPs include Nifedipine and Nicardipine, the second-generation agents include Benidipine and Efonidipine, the third-generation DHPs include Amlodipine and Azelnidipine and fourth-generation drugs include Lercanidipine and Lacidipine (Chandra et al., 2013). The dihydropyridine CCBs are approved to manage the patients with hypertension and angina (Elliott et al., 2011).

The National Institute for Health and Care Excellence (NICE) guideline on the diagnosis and treatment of high blood pressure (hypertension) recommends CCBs as initial therapy to treat hypertension in black patients and in patients aged more than 55 years (Krause et al., 2011). Moreover, the guidelines from Eighth Joint National Committee (JNC 8) and American College of Cardiology/American Heart Association task force recommend CCBs as first-line antihypertensive agents along with Thiazide diuretics, Angiotensin converting enzyme inhibitors (ACEIs), Angiotensin receptor blockers (ARBs). Thiazide diuretics are preferred as initial drug to treat hypertension irrespective of age and race and CCBs are a good alternative choice for

* Corresponding author
E-mail addresses: nmmaideen@dha.gov.ae (N. Mohamed Pakkir Maideen)

initial therapy when thiazide diuretics are not tolerated. Similar to thiazide diuretics, CCBs have been identified to reduce all Cardio vascular disease (CVD) events except Heart failure (HF) (James et al., 2014; Whelton et al., 2018).

The dihydropyridine CCBs bind to L-type calcium channels and block the entry of calcium in vascular smooth muscle, which leads to vasodilatation and reduction of blood pressure (BP) (Meredith et al., 2004). The rate of premature death and disability is higher among patients with hypertension due to cardiovascular disease (CVD) including coronary artery disease (CAD), peripheral artery disease (PAD), congestive heart failure (CHF), and stroke and chronic kidney disease (CKD) induced by high blood pressure. It has been estimated that 7.6 million premature deaths were attributed to hypertension, in 2001 and hypertension also found to be associated with 54 % of stroke and 47 % of ischaemic heart disease (Lawes et al., 2001). In 2010, it has been estimated that 1.39 billion of people across the globe are affected by hypertension and the numbers are increasing daily (Bloch, 2016).

Modification of effects of one drug by the concomitant administration of other drug(s), supplements, food or alcohol is known as Drug interaction (Maideen, 2019). The drug which induces the drug-drug interaction is termed "precipitant drug" while the drug affected by the drug-drug interaction is called "object drug" (Pakkir Maideen, 2018). It has been estimated that the prevalence of Adverse drug reactions (ADR)-related hospital admissions was about 3.3 % and drug interactions were accounted for 49 % of those admissions (Pedrós et al., 2016). To prevent the adverse outcomes, the prescribers and the pharmacists are required to be aware of the possible drug interactions of dihydropyridine CCBs.

2. Discussion

Dihydropyridine CCBs as Object drugs

The dihydropyridine CCBs have been identified as the substrates of cytochrome P450 3A4 (CYP3A4) enzymes and they are metabolised in the gut wall and liver by them (Zhu et al., 2014). The drugs inhibiting or inducing CYP3A4 enzyme may increase the risk of adverse drug reactions of dihydropyridine CCBs including hypotension and shock.

Macrolide antibiotics

Macrolide antibiotics help to treat respiratory tract, skin, and soft tissue infections, mainly. The macrolide antibiotics such as Erythromycin and Clarithromycin have been identified as moderate to potent inhibitors of intestinal and hepatic CYP3A4 enzymes (Pakkir Maideen NM, 2018).

Administration of Erythromycin 250mg four times a day, in healthy men taking Felodipine 10mg resulted in elevated plasma concentrations of Felodipine due to the inhibition of CYP3A4-mediated metabolism of Felodipine by Erythromycin (Bailey et al., 1996). Similarly, concomitant use of Erythromycin in a 43-year-old patient taking Felodipine lead to increased symptoms of palpitations, flushing, and ankle edema, which might have occurred due to the inhibition of CYP3A4-mediated metabolism of Felodipine by Erythromycin (Liedholm et al., 1991).

Vasodilatory shock and heart block were occurred in a 77-year-old patient receiving Clarithromycin along with Nifedipine, possibly due to the inhibition of CYP3A4-mediated metabolism of Nifedipine by Clarithromycin resulting in elevated plasma concentrations and toxicity of Nifedipine (Gerónimo-Pardo et al., 2005). The risk of hospitalizations with acute kidney injury found higher in patients taking a Calcium channel blocker and Clarithromycin, concurrently (Gandhi et al., 2013).

Erythromycin and Clarithromycin were attributed to increased risk of hypotension-associated hospitalizations of patients taking calcium-channel blockers (Wright et al., 2011). Azithromycin is a weak inhibitor of CYP3A4 enzyme and it may be preferred when the use of macrolide antibiotic is necessary for a patient receiving calcium channel blockers (Henneman et al., 2012).

Azole antifungals

Azole antifungals such as Fluconazole, Itraconazole, Posaconazole and Voriconazole are frequently used to prevent or treat systemic fungal infections and they have been identified as the inhibitors of CYP3A4 enzyme. Itraconazole and Posaconazole are found to be potent CYP3A4 inhibitors more than Fluconazole and Voriconazole (Brüggemann et al., 2009). Hence, the azole antifungals may inhibit the CYP3A4-mediated metabolism of dihydropyridine CCBs. Concomitant

use of Itraconazole and Felodipine in nine healthy individuals resulted in elevated plasma concentrations of Felodipine leading to decreased blood pressure and increased heart rate (Jalava et al., 1997).

Administration of Itraconazole in a patient receiving Nifedipine resulted in increased the serum concentrations of Nifedipine and ankle edema (Tailor et al., 1996). It is recommended to avoid the combination of azole antifungals and dihydropyridine CCBs and dosage adjustments are required if their concomitant use is necessary (Jalava et al., 1997).

Protease inhibitors

The protease inhibitors include Ritonavir, Saquinavir, Indinavir and others, which are used to treat the patients with human immunodeficiency virus (HIV). Ritonavir was found to be very potent CYP3A4 inhibitors while other protease inhibitors are also capable of inhibiting CYP3A4 enzyme (Eagling et al., 1997).

The plasma concentrations of Amlodipine was increased in healthy HIV- seronegative subjects when Indinavir-Ritonavir combination is administered to them (Glesby et al., 2005).

Administration of Nelfinavir in a 51- year-old man with HIV infection receiving extended-release Nifedipine developed symptomatic orthostasis and heart block. Recurrence of orthostatic symptoms noted, when he was switched to Ritonavir-Indinavir combination. The orthostatic symptoms have been managed by dosage reduction of Nifedipine (Rossi et al., 2002).

Concomitant use of Nifedipine and Lopinavir-Ritonavir in a 47-year-old man with HIV infection resulted in severe hypotension along with other symptoms such as malaise, oliguria, and progressive generalized edemas and the discontinuation of both the drugs brought the blood pressure back to normal (Baeza et al., 2007). The dihydropyridine CCBs should be initiated at low doses with careful monitoring, if the coadministration of CCBs and protease inhibitors is necessary (Glesby et al., 2005).

Grapefruit Juice

Furanocoumarins of grapefruit juice are potent inhibitors of CYP3A4 enzymes and it has been noted that CYP3A4-mediated metabolism of substrates could be inhibited by one whole grapefruit or 200 mL of grapefruit juice (Glesby et al., 2005).

The interaction between Felodipine and grapefruit juice was discovered accidentally, as the plasma concentrations of Felodipine was increased by the concomitant use of grapefruit juice in 10 healthy male subjects (Bailey et al., 2013). The plasma concentrations of Felodipine have been increased by the consumption of grapefruit juice (Bailey et al., 1989; Bailey et al., 1993) as well as unprocessed grapefruit (Dresser et al., 2000; Bailey et al., 2000).

Moreover, a single glass (250ml) of grapefruit juice was found sufficient to increase the plasma concentrations of Felodipine (Lundahl et al., 1998), Amlodipine (Josefsson et al., 1996) and Nimodipine (Fuhr et al., 1998). To prevent the adverse outcomes, the patients receiving dihydropyridine CCBs should be advised to avoid the consumption of grapefruit juice (Lim et al., 2003).

Seville orange juice

Seville orange inhibits intestinal CYP3A4 as it contains the furanocoumarins such as 6',7'-dihydroxybergamottin and bergamottin (Penzak et al., 2002). Administration of 10mg of Felodipine in healthy volunteers consuming 240 mL of Seville orange juice resulted in elevated plasma concentrations of Felodipine (Malhotra et al., 2001).

Rifampicin

Rifampicin is an antimycobacterial antibiotic extensively used to treat tuberculosis and leprosy and it has been identified as an inducer of CYP enzymes including CYP3A4 (Pakkir Maideen, 2018). The oral bioavailability of Nifedipine (Holtbecker et al., 1996) and Nilvadipine (Saima et al., 2002) were decreased in healthy volunteers taking Rifampicin due to the induction of intestinal CYP3A4-mediated metabolism of dihydropyridine CCBs. In addition, the blood pressure of the patients receiving Nisoldipine, Nifedipine, Barnidipine or Manidipine has been increased due to the initiation of Rifampicin in them the blood pressure fell once Rifampicin was withdrawn (Yoshimoto et al., 1996).

As the antihypertensive efficacy of dihydropyridine CCBs is expected to be diminished by Rifampicin, the blood pressure of the patients receiving this combination of drugs should be

monitored or other antihypertensive drugs which are not affected by Rifampicin should be employed in patients with hypertension as well as tuberculosis (Cordeanu et al., 2017).

Phenytoin

Phenytoin is an antiepileptic drug and it has been identified as a potent inducer of CYP enzymes including CYP3A4 (Hole et al., 2018). The plasma concentrations of Nisoldipine decreased in patients receiving Phenytoin concurrently, due to increased first-pass metabolism (Michelucci et al., 1996).

Other Antiepileptic Drugs

The antiepileptic drugs such as Carbamazepine and Phenobarbital have also been recognized as the inducers of CYP3A4 enzymes (Hole et al., 2018). Concomitant administration of Nimodipine in epileptic patients receiving antiepileptic drugs such as Carbamazepine and Phenobarbital resulted in decreased plasma concentrations of Nimodipine and the patients taking the combination of dihydropyridine CCBs and enzyme-inducing antiepileptic drugs may need to increase their doses of Nimodipine (Tartara et al., 1991).

Dihydropyridine CCBs as Precipitant drugs

The dihydropyridine CCBs are the possible inhibitors of CYP3A4 enzyme and Nicardipine found to be the strongest inhibitor of CYP3A4, followed by Lercanidipine, Cilnidipine, Nimodipine, and Amlodipine (Bernard et al., 2014). Coadministration of dihydropyridine CCBs and CYP3A4 substrates may increase the risk of toxicity of CYP3A4 substrates.

HMG-CoA reductase inhibitors (Statins)

Hydroxy methyl glutaryl-CoA (HMG-CoA) reductase inhibitors (Statins) are recommended primarily to treat atherosclerosis and to prevent myocardial infarction, and stroke (Davies et al., 2016). The risks of adverse effects such as acute kidney injury, hyperkalemia, acute myocardial infarction, and acute ischemic stroke increased due to combined therapy of CYP3A4-metabolized statins and CYP3A4-inhibiting CCBs (Wang et al., 2016).

The plasma concentrations of Simvastatin increased by the concomitant administration of Simvastatin and Amlodipine in patients with hypercholesterolemia and hypertension (Nishio et al., 2005). The probability of interaction between Simvastatin and Amlodipine may be decreased by non-concurrent dosing of them (Park et al., 2010).

Cyclosporine

Cyclosporine is an immunosuppressant drug and it is a substrate of CYP3A4 enzyme (Hu et al., 2007). The plasma concentrations of Cyclosporine increased in hypertensive renal transplant patients receiving Amlodipine (Pesavento et al., 1996; Cai et al., 2011) and Nicardipine (Guan et al., 1996).

Clopidogrel

Clopidogrel is an antiplatelet drug and it is useful to manage patients with acute coronary syndrome, ischemic stroke or peripheral vascular disease to prevent thrombotic events. It is a prodrug and it is metabolised to active form mainly by CYP2C19 and CYP3A4 enzymes (Tirkkonen et al., 2013). The antiplatelet efficacy of Clopidogrel found to be decreased in patients receiving dihydropyridine CCBs such as Amlodipine, Benidpine, Nifedipine and others (Seo et al., 2014; Gremmel et al., 2015).

3. Conclusion

Dihydropyridine Calcium Channel Blockers (CCBs) have been identified as the substrates of intestinal and hepatic CYP3A4 enzymes. The plasma concentrations of dihydropyridine CCBs could be increased by the concomitant administration of drugs such as Macrolide antibiotics, Azole antifungals, Protease inhibitors and juices like Grapefruit juice and Seville orange juice, which may result in enhanced adverse effects. In addition, the drugs like Rifampicin, Phenytoin, and other antiepileptics including Carbamazepine and Phenobarbital reported to reduce the bioavailability of dihydropyridine CCBs that could decrease the therapeutic efficacy.

Moreover, dihydropyridine CCBs increase the plasma concentrations of Statins and Cyclosporine and decrease the therapeutic efficacy of Clopidogrel. The prescribers and pharmacists are required to be aware of the adverse drug interactions of dihydropyridine CCBs to prevent adverse outcomes.

Conflicts of Interest
NIL

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