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Drug Interactions Associated With Therapies for Pulmonary Arterial Hypertension

Shraddha Narechania, MD[1] and Mark A. Malesker, PharmD, FCCP, FCCM, FASHP, BCPS[2]

Abstract

Objective: To evaluate the potential for drug interactions with therapies for pulmonary arterial hypertension (PAH). Treatments include calcium channel blockers, phosphodiesterase type 5 inhibitors, endothelin receptor antagonists, guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin receptor agonists. **Data Sources:** A systemic literature search (January 1980-December 2021) was performed using PubMed and EBSCO to locate relevant articles. The mesh terms used included each specific medication available as well as "drug interactions." DAILYMED was used for product-specific drug interactions. **Study Selection and Data Extraction:** The search was conducted to identify drug interactions with PAH treatments. The search was limited to those articles studying human applications with PAH treatments and publications using the English language. Case reports, clinical trials, review articles, treatment guidelines, and package labeling were selected for inclusion. **Data Synthesis:** Primary literature and package labeling indicate that PAH treatments are subject to pharmacokinetic and pharmacodynamic interactions. The management of PAH is rapidly evolving. As more and more evidence becomes available for the use of combination therapy in PAH, the increasing use of combination therapy increases the risk of drug-drug interactions. Pulmonary arterial hypertension is also associated with other comorbidities that require concomitant pharmacotherapy. **Conclusion:** The available literature indicates that PAH therapies are associated with clinically significant drug interactions and the potential for subsequent adverse reactions. Clinicians in all practice settings should be mindful that increased awareness of drug interactions with PAH therapy will ensure optimal management and patient safety.

Keywords

drug interactions, pulmonary hypertension, pulmonary vasodilators, clinical pharmacology, drug safety

Introduction

Pulmonary arterial hypertension (PAH) is a chronic progressive life-threatening disease associated with elevated pulmonary arterial pressures secondary to remodeling of the pulmonary arteries which eventually leads to right ventricular failure and death if left untreated.[1] It is defined by a mean pulmonary pressure of more than 20 mm Hg in conjunction with a pulmonary capillary wedge pressure of $<$15 mm Hg and a pulmonary vascular resistance of at least 3 Wood units.[2] Pulmonary arterial hypertension is included under group 1 pulmonary hypertension (PH). The prevalence of PAH has been estimated to be between 15 and 50 cases per million based on different registries.[3,4]

Treatment of PAH can be divided into general measures and PAH-specific therapies.[5] General measures include use of diuretics, anticoagulants, long-term oxygen, and digoxin. Calcium channel blockers (CCBs) are used in patients with PAH with positive acute vasodilator testing during right heart catheterization. Drugs used specifically for treatment of PAH act on 3 major pathways: the nitric oxide (NO) pathway, endothelin pathway, and prostacyclin pathway.[5] The past 2 decades have seen the development of multiple novel therapies for the treatment of PAH. The newest drugs that have been introduced to this field include riociguat, macitentan, selexipag, and orenitram. There have also been significant strides in the use of upfront dual as well as triple combination therapy for the management of PAH.[6-9]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, CHI Health Creighton University Medical Center, University Campus, Omaha, NE, USA
[2]Pharmacy Practice, Creighton University School of Pharmacy and Health Professions, Omaha, NE, USA

Corresponding Author:
Shraddha Narechania, Department of Pulmonary, Critical Care and Sleep Medicine, CHI Health Creighton University Medical Center, University Campus, 7500 Mercy Road, Ste 3000, Omaha, NE 68124, USA.
Email: drshraddhanarechania@gmail.com

Table 1. PAH-Specific Pharmacotherapy.[10-22].

Agent	Metabolism	Route	Usual adult dose
Phosphodiesterase-5 inhibitors			
Sildenafil (Revatio)	CYP3A (major) and CYP2C9 (minor)	Oral	20 mg TID
Tadalafil (Adcirca)	CYP3A4	Oral	40 mg once/day
Endothelin receptor antagonists			
Ambrisentan (Letairis)	CYPs 3A4, 2C19	Oral	5-10 mg once/day
Bosentan (Tracleer)	CYP3A4, 2C9, 2C19	Oral	62.5 mg BID × 4 weeks, then 125 mg BID
Macitentan (Opsumit)	Primarily CYP3A4, minor extent by CYP2C8, CYP2C9, CYP2C19	Oral	10 mg once/day
Soluble guanylate cyclase stimulator			
Riociguat (Adempas)	CYP1A1, 3A, 2C8, 2J2	Oral	1-2.5 mg TID
Prostacyclins			
Epoprostenol (Veletri)	Hydrolyzed in blood	IV	20-40 ng/kg/min continuous infusion
Epopostenol (Flolan)	Hydrolyzed in blood	IV	20-40 ng/kg/min continuous infusion
Trepostinil (Orenitram)	CYP2C8 (major) and CYP2C9 (minor)	Oral	0.25-21 mg BID
Trepostinil (Remodulin)	CYP2C8	SC or IV	40-160 ng/kg/min continuous infusion
Trepostinil (Tyvaso)	CYP2C8	Inhalation (nebulized)	9 (54 μg) breaths QID
		Inhalation (dry powder inhaler)	1 breath (48-64 μg) QID
Iloprost (Ventavis)	β-oxidation of the carboxyl side chain	Inhalation	2.5-5 μg/inhalation, 6-9 times/day
Prostacyclin receptor agonist			
Selexipag (Uptravi)	Hydrolysis to active metabolite, then CYP3A4 and 2C8 and glucuronidation by UGT1A3 and 2B7	Oral	400-1600 μg BID

Abbreviations: IV, intravenous; PAH, pulmonary arterial hypertension.

Combination therapy allows targeting of different pathways that are involved in the pathogenesis of PAH and improves treatment efficacy. Patients may require one or a combination of disease-specific therapies in addition to background general therapies for effective treatment of PAH. Furthermore, patients with PAH frequently have other comorbidities for which they require cotreatment with additional drugs. Concomitant administration of multiple drugs can predispose patients to adverse effects from drug-drug interactions and reduce treatment efficacy.

It is important for clinicians to identify and understand the clinical relevance of drug interactions with PAH therapies to better assist patients and improve clinical outcomes. This review was undertaken to provide health care providers with a clinically applicable review regarding the potential drug interactions attributable to PAH pharmacotherapy. The pharmacology of PAH-specific therapies is summarized in Table 1. Primary literature, case reports, and product-specific recommendations from the manufacturer are summarized by therapeutic class. Table 2 summarizes the drug interactions for CCBs and PAH-specific therapy.

Data Sources

A systemic literature search (1980-December 2021) was performed using PubMed and EBSCO to locate relevant articles. The mesh terms used included each specific medication available as well as "drug interactions." DailyMed was used for product-specific drug interactions. The search was limited to those articles studying human applications with PAH treatments and publications using the English language. Case reports, clinical trials, review articles, treatment guidelines, and package labeling were selected for inclusion.

Drug Interactions With CCBs

Calcium channel blockers are recommended only in patients with idiopathic, hereditary, and drug-induced PAH who have a positive response to acute vasodilator testing during right heart catheterization.[2] Commonly used agents include long-acting nifedipine, diltiazem, and amlodipine.[5] Verapamil use is not recommended in view of its pronounced negative inotropic effect which can depress right ventricular function. It is important to note that the dosage of CCBs used for PAH is much higher than conventional doses used for other indications.[5] β-blockers in combination with CCBs are generally well tolerated but caution should be exercised, and patients should be monitored for development of hypotension and bradycardia.[23-25] Calcium channel blockers are primarily metabolized by the CYP3A4 enzymes. Hence, inhibitors and inducers of CYP3A4 can

Table 2. Summary of Drug Interactions of Advanced Therapies for Pulmonary Arterial Hypertension.[10-24]

PAH drug	Offending medication	Drug interaction result	Recommendation/management considerations
CCBs			
Diltiazem	Carbamazepine	Can increase risk of neurotoxicity	Monitor carbamazepine levels
	Cyclosporine	Can cause increase in cyclosporine levels	Monitor cyclosporine levels
	Methylprednisolone	Adrenocortical suppression due to increase in methylprednisolone levels	
	Rifampin	Can reduce exposure to CCB	Coadministration not recommended
	Statins: lovastatin, simvastatin	Can cause increased exposure to statin Can cause myopathy and rhabdomyolysis	Lower lovastatin/simvastatin dosing Monitor creatine kinase levels
	Tacrolimus	Can increase exposure to tacrolimus	Monitor tacrolimus levels
Nifedipine	Cimetidine (CYP3A4 inhibitor)	Can increase exposure to nifedipine	Cautiously titrate nifedipine
	Phenytoin (CYP3A4 inducer)	Can decrease exposure to nifedipine	Coadministration not recommended Consider alternate therapy
PDE-5 inhibitors			
Sildenafil (Revatio)	α-blockers, amlodipine	Can potentiate hypotension	Monitor blood pressure
	Potent CYP3A4 inhibitors (ritonavir, ketoconazole)	Can increase exposure to sildenafil	Coadministration not recommended
	Guanylate cyclase stimulator (riociguat)	Can potentiate hypotension	Coadministration contraindicated
	Nitrates	Can cause profound hypotension	Coadministration contraindicated
	Concurrent PDE-5 inhibitors	Can potentiate hypotension	Coadministration not recommended
Tadalafil (Adcirca)	α-blockers	Can potentiate hypotension	Monitor blood pressure
	Antihypertensives	Can potentiate hypotension	Monitor blood pressure
	CYP3A4 inhibitors (ketoconazole, itraconazole)	Can increase exposure to tadalafil	Coadministration not recommended
	CYP3A4 inducers (rifampin)	Can decrease exposure to tadalafil	Coadministration not recommended
	Guanylate cyclase stimulator (riociguat)	Can cause additive hypotension	Coadministration contraindicated
	Nitrates	Can cause additive hypotension	Coadministration contraindicated
	Ritonavir	Can initially inhibit and later induce CYP3A enzyme	Consider dose adjustment
Endothelin receptor antagonists			
Bosentan (Tracleer)	Cyclosporine	Can increase exposure to bosentan	Coadministration contraindicated
	CYP2C9 inhibitors (amiodarone, fluconazole)	Can increase exposure to bosentan	Coadministration not recommended
	CYP3A4 inhibitors (ketoconazole, itraconazole)	Can increase exposure to bosentan	Coadministration not recommended
	Ethinyl estradiol	Can reduce levels of ethinyl estradiol	Consider additional forms of contraception
	Glyburide	Can increase LFTs	Coadministration contraindicated
	Ritonavir (CYP3A4 inhibitor)	Can increase exposure to bosentan	Consider reducing bosentan dose
	Simvastatin	Can reduce simvastatin levels	Monitor cholesterol levels
	Warfarin	Can reduce warfarin levels	Monitor INR closely
Ambrisentan (Letaris)	Cyclosporine	Can increase exposure to ambrisentan	Limit ambrisentan dose to 5 mg once daily
Macitentan (Opsumit)	Potent CYP3A4 inhibitors (ketoconazole, ritonavir)	Can increase exposure to macitentan	Coadministration not recommended
	Potent CYP3A4 inducer (rifampicin)	Can reduce exposure to macitentan	Coadministration not recommended

(continued)

Table 2. (continued)

PAH drug	Offending medication	Drug interaction result	Recommendation/management considerations
Soluble guanylate cyclase stimulator			
Riociguat (Adempas)	Antacids (Al/MgOH)	Can reduce absorption of riociguat	Consider administering 1 hour apart
	Antihypertensives	Can potentiate hypotensive effects	Monitor blood pressure
	CYP and P-gp inhibitors (azoles, protease inhibitors)	Can increase exposure to riociguat	Consider starting at lower dose of 0.5 mg TID Monitor blood pressure
	Diuretics	Can potentiate hypotensive effects	Monitor blood pressure
	Nitrates	Can cause profound hypotension	Coadministration contraindicated
	PDE inhibitors	Can cause profound hypotension	Coadministration contraindicated
	Smoking	Can decrease serum levels of riociguat	Could consider titrating to doses higher than 2.5 mg TID Consider dose reduction when quitting smoking
Prostacyclins			
Epoprostenol (Flolan) (Veletri)	Anticoagulants	Can potentiate bleeding effects	Monitor for bleeding complications
	Antihypertensives	Can potentiate hypotensive effect	Monitor blood pressure
	Antiplatelet agents	Can potentiate bleeding effects	Monitor for bleeding complications
	Digoxin	Can cause digoxin toxicity	Use with caution or consider dose adjustment of digoxin
	Diuretics	Can potentiate hypotensive effect	Monitor blood pressure
	Vasodilators	Can potentiate hypotensive effect	Monitor blood pressure
Treprostinil inhalation solution (Tyvaso)	Anticoagulants	Can potentiate bleeding effects	Monitor for bleeding complications
	Antihypertensives	Can potentiate hypotensive effect	Monitor blood pressure
	Diuretics	Can potentiate hypotensive effect	Monitor blood pressure
	Gemfibrozil (CYP2C8 inhibitor)	Can cause increase in level and exposure to oral trepostinil	Reduce starting dose to 0.125 mg BID and titrate by 0.125 mg every 3-4 days
	Rifampin (CYP2C8 inducer)	Can decrease exposure to oral trepostinil	Monitor efficacy
	Vasodilators	Can potentiate hypotensive effect	Monitor blood pressure
Iloprost (Ventavis)	Anticoagulants	Can potentiate bleeding effects	Monitor for bleeding complications
	Antihypertensives	Can potentiate hypotensive effect	Monitor blood pressure
	Antiplatelet agents,	Can potentiate bleeding effects	Monitor for bleeding complications
	Diuretics	Can potentiate hypotensive effect	Monitor blood pressure
	Vasodilators	Can potentiate hypotensive effect	Monitor blood pressure
Prostacyclin receptor agonist			
Selexipag (Uptravi)	Clopidogrel (moderate CYP2C8 inhibitor)	Can cause increased exposure to active metabolite	Reduce frequency of selexipag to once daily
	Gemfibrozil (strong CYP2C8 inhibitor)	Can cause increased exposure to selexipag	Coadministration contraindicated
	Rifampin (CYP2C8 inducer)	Can cause reduced exposure to active metabolite	Consider doubling dose of selexipag

Abbreviations: CCB, calcium channel blockers; INR, international normalized ratio; LFT, liver function test; PAH, pulmonary arterial hypertension; PDE, phosphodiesterase.

affect the metabolism of CCBs and potentially cause drug interactions. Macrolides like erythromycin and clarithromycin can increase CCB levels via inhibition of CYP3A4 causing clinical adverse effects of hypotension and bradycardia necessitating dose reduction or discontinuation of CCB. Conversely, antiepileptic medications like phenytoin, phenobarbital, and carbamazepine can reduce CCB levels via CYP3A4 induction and alternative agents may need to be considered.[23] Out of the 3 commonly used CCBs used for PAH, diltiazem is known to have the most drug interactions. Diltiazem is not only a substrate of CYP3A4, but it also causes inhibition of CYP3A4 and decreases the metabolism of drugs that are primarily cleared by CYP3A4 pathways. Diltiazem can increase the neurotoxicity of carbamazepine when coadministered by increasing carbamazepine serum levels.[26] Diltiazem is also known to increase area under the curve (AUC) of several statins like lovastatin and simvastatin due to CYP3A4 inhibition.[23,27,28] This can lead to increased risk of rhabdomyolysis and myopathy and patients should be monitored for the development of these adverse effects.[23,29] Statins like pravastatin that are not mediated by CYP3A4 should be considered in these situations.[27] Nifedipine and amlodipine have fewer drug interactions compared with diltiazem. Coadministration of nifedipine and cimetidine has been shown to increase peak plasma concentrations of nifedipine due to inhibition of CYP3A4 by cimetidine.[30] Amlodipine is relatively well tolerated among the CCBs and has not been shown to have any clinically significant interactions.[25]

Drug Interactions With Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors act on the NO pathway to cause pulmonary vasodilation which is mediated via activation of soluble guanylate cyclase and production of the messenger cyclic guanosine monophosphate (cGMP). Increased expression of PDE-5 in the lungs causes increased cGMP degradation which is blocked by the PDE-5 inhibitors leading to pulmonary vasodilation.[31] Phosphodiesterase-5 inhibitors also have antithrombotic and antiproliferative effects via their action on platelet aggregation and vascular smooth muscle proliferation.[31] Available PDE-5 treatments include sildenafil (Revatio) and tadalafil (Adcirca). Sildenafil has been shown to improve exercise capacity, hemodynamics, and functional class in patients with PAH.[31,32] Tadalafil has been shown to improve exercise capacity, time to clinical worsening, as well as quality-of-life measures in patients with PAH.[33] Phosphodiesterase-5 inhibitors are principally metabolized by the CYP3A4 and CYP2C9 isoenzymes of CYP450. Inhibitors of CYP3A4 therefore can reduce clearance of sildenafil as well as tadalafil and potentiate its effect.[34] Phosphodiesterase-5 inhibitors when used in conjunction with nitrates can cause profound hypotension and hence this combination is contraindicated. Coadministration of PDE-5 inhibitors with α-blockers or other antihypertensive drugs like amlodipine can also have an additive effect on reducing blood pressure and should be used with caution.[10,11]

Sildenafil

A pharmacokinetic study evaluating the drug interaction between protease inhibitors and sildenafil showed that ritonavir increased the AUC_t and peak concentration (C_{max}) of sildenafil by 11-fold and 3.9-fold, respectively.[35] The AUC_t and C_{max} for saquinavir were increased to a lesser extent compared with ritonavir at 3.1-fold and 2.4-fold, respectively.[36] Clinically, this increase in exposure to sildenafil was not associated with increase in systemic adverse effects.[37] The manufacturer's label, however, does not recommend administration of sildenafil along with potent CYP3A4 inhibitors (ritonavir, saquinavir, erythromycin, ketoconazole).[10] Coadministration of sildenafil and bosentan leads to significantly decreased sildenafil plasma concentrations and increased bosentan concentration. In a study of 10 patients with PAH, administration of a single dose of sildenafil of 100 mg along with bosentan 62.5 mg twice daily was associated with a 50% decreased exposure to sildenafil with a 2-fold increase in sildenafil clearance.[36] Use of 125 mg twice daily of bosentan increased clearance and decreased plasma concentration of sildenafil even further.[36] In a randomized, placebo-controlled trial of concomitant use of sildenafil (20 mg three times a day titrated up to 80 mg three times a day) and bosentan (125 mg twice daily) in healthy volunteers, the AUC_t of sildenafil was decreased by 62.6% and that of bosentan was increased by 49.8%.[38] Caution is advised when using the combination, but no dosage adjustment is recommended.[10]

Tadalafil

Tadalafil may require dosage adjustment when used with CYP3A4 inhibitors. CYP3A4 inducers like rifampin increase clearance and reduce the effects of tadalafil although no dosage adjustment is recommended in the package label.[11] Tadalafil can also potentiate the hypotensive effect of alcohol.[11] When tadalafil 40 mg daily and bosentan 125 mg twice daily were coadministered for 10 days in healthy volunteers, the exposure to tadalafil was reduced by 41.5% whereas the effect on bosentan was clinically insignificant.[39] No dosage adjustments are recommended when this combination is used as larger studies are needed to study their interactions and the clinical relevance of it.[39]

Drug Interactions With ERAs

Endothelin-1 is a potent endogenous pulmonary vasoconstrictor which also causes vascular smooth muscle cell proliferation through its effect on the endothelin A (ET_A) and endothelin B (ET_B) receptors located on the smooth muscle cells of the pulmonary vasculature.[5] Bosentan and macitentan are nonselective endothelin receptor antagonists (ERAs), whereas ambrisentan is a selective ERA of the ET_A receptor. Bosentan and ambrisentan have been shown to improve exercise capacity, functional class, as well as time to clinical worsening in PAH.[40,41] Macitentan has been shown to decrease the rate of clinical worsening as well as reduce hospitalizations in PAH.[7] Given the teratogenic potential of ERAs, all female patients need to be enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program to have access to either of the drugs in this category.[42] It is also recommended that all patients on ERAs use contraception.

Ambrisentan

Ambrisentan is a selective antagonist of the ET_A receptor.[5] Ambrisentan is principally metabolized through hepatic glucuronidation with only about 20% of the drug being metabolized by the CYP3A4 and CYP2C19 isoenzymes of the CYP450 system.[12] Therefore, ambrisentan has a low potential for drug-drug interactions. Dosage adjustments may be needed in case of concomitant administration with strong inhibitors or inducers of CYP3A4 and CYP2C19.[36] Coadministration of ambrisentan with cyclosporine has been shown to increase the C_{max} and AUC_t of ambrisentan by 1.5-fold and 2-fold, respectively.[12] Conversely, ambrisentan did not have any significant effect on the pharmacokinetics of cyclosporine. A maximum dose of 5 mg of ambrisentan is recommended when coadministered with cyclosporine.[12,43] A crossover study in 22 healthy subjects evaluated the interaction between ambrisentan and warfarin and found that when a 25 mg dose of warfarin was given to patients after 8 days of ambrisentan 10 mg daily, ambrisentan did not affect the C_{max} or AUC_t of warfarin or affect the prothrombin time.[38] Hence, no dosage adjustment is required when using warfarin and ambrisentan together.[38] A randomized controlled trial studying the interaction between sildenafil and ambrisentan in 19 healthy volunteers showed no significant change in the C_{max} or AUC_t of sildenafil or ambrisentan. No dosage adjustments are recommended with this combination.[44]

Bosentan

Bosentan is a nonselective ET_A and ET_B receptor antagonist.[5] Bosentan is shown to have more interactions than ambrisentan. P-glycoprotein (P-gp) is required for the absorption of bosentan. Hence, drugs like cyclosporine that interact with P-gp can cause interactions with bosentan.[45] Coadministration of bosentan with cyclosporine is contraindicated due to marked increase in bosentan levels in the plasma. A crossover study studying the pharmacokinetic interactions between bosentan and cyclosporine showed that bosentan when given at a dose of 500 mg twice daily along with cyclosporine (dosage adjusted based on target trough level of 200-250 g/L) significantly increased the C_{max} as well as AUC_t of bosentan. Conversely, it also reduced exposure to cyclosporine and the dose of cyclosporine had to be increased by 35% to achieve the same target trough level of the drug.[46] A randomized controlled trial exploring the pharmacokinetic interaction between bosentan 125 mg given twice daily and glyburide 2.5 mg given twice daily showed that when given together, both drugs reduce the C_{max} and AUC_t of each other. This is likely due to the fact that both drugs induce CYP3A4, which is the major enzyme involved in the metabolism of the 2 drugs.[47] Bosentan and glyburide when given together can also cause marked elevation in the liver enzymes, and hence the combination is contraindicated.[47] In addition to being an inducer of CYP3A4, bosentan is also an inducer of CYP2C9 and a substrate of CYP3A4 and CYP2C9. Hence, concurrent administration of inhibitors of CYP3A4 (ketoconazole, itraconazole, amprenavir, erythromycin, fluconazole, diltiazem, fluoxetine, fluvoxamine) and CYP2C9 (fluconazole, amiodarone) is not recommended as it may increase exposure to bosentan.[48] Conversely, administration of inducers of CYP3A4 (phenobarbital, phenytoin, rifampin) and CYP2C9 (carbamazepine, rifampin) has the potential to reduce exposure to bosentan.[13] Bosentan can also cause interactions with substrates of CYP3A4 (simvastatin, *R*-warfarin, glyburide, cyclosporine) and CYP2C9 (*S*-warfarin, glyburide).[49] A randomized, double-blind, placebo-controlled trial showed that administration of bosentan 500 mg twice daily for 10 days reduced the plasma concentration of both *R* and *S* enantiomers of warfarin significantly (38% and 29%, respectively).[50] In a trial evaluating the interaction between bosentan and ketoconazole, coadministration of these drugs was shown to significantly increase the C_{max} and AUC_t of bosentan compared with bosentan alone.[47] Dose reduction may be needed when bosentan is coadministered with lopinavir/ritonavir given the latter is a strong inhibitor of CYP3A. Bosentan can reduce plasma levels of simvastatin and hence cholesterol levels need to be monitored when patients are on both therapies concomitantly.[51] This interaction is important to note as statins are very commonly prescribed medications in the aging PAH population for the control of hypercholesterolemia. Similarly, it can also reduce plasma levels of ethinyl estradiol due to CYP3A4 induction.[52] This can occur with any form of contraception including oral, patch, injectable, as well as implantable forms.[45] It is a well-known fact that

pregnancy in PAH is associated with a maternal mortality of 30% to 50%.[53] It is crucial that women of childbearing potential utilize hormonal and/or mechanical contraception to avoid pregnancy. Additional forms of contraception should be considered in women with childbearing potential who are on bosentan, given the drug interaction.[45] Bosentan, when coadministered with sildenafil, can cause increase in serum levels of bosentan and decrease in sildenafil levels although no dosage adjustment is recommended as this interaction has not proven to be significant clinically.[54,55]

Macitentan

Macitentan is a novel nonselective ERA.[5] It is metabolized primarily by CYP3A4, but other enzymes involved in its metabolism include CYP2C8, CYP2C9, and CYP2C19.[14,56] It has an active metabolite, ACT-132577.[57] Macitentan has a more favorable profile among ERAs with respect to drug interactions. Concomitant administration of cyclosporine (CYP3A4 inhibitor) with macitentan has not shown to have any clinically relevant effect on pharmacokinetics of macitentan.[57] In a study by Bruderer et al, rifampin (CYP3A4 inducer) reduced dose interval AUC_t of macitentan by 79% when coadministered with it but exposure to the active metabolite of macitentan (ACT-132577) was not significantly affected.[57] Manufacturers recommend against using macitentan concomitantly in patients who are receiving strong CYP3A4 inhibitors (ketoconazole, ritonavir) or inducers (rifampin). A randomized, open-label, crossover study assessing the pharmacokinetic and pharmacodynamic effects of macitentan on a single 25 mg dose of warfarin showed that there was no change in the mean international normalized ratio or factor VII activity. Similarly, warfarin did not affect the plasma concentrations of macitentan or its active metabolite (ACT-132577).[58]

Drug Interactions With Soluble Guanylate Cyclase Stimulator

Riociguat is a soluble guanylate cyclase stimulator which is Food and Drug Administration (FDA) approved for the treatment of both PAH and chronic thromboembolic PH.[15,59] It is metabolized primarily by the CYP1A1 and CYP3A4/5 isoenzymes of the CYP450 system and hence can have clinically significant drug interactions with inducers or inhibitors of these enzymes.[59] It is also a substrate of P-gp.[59] Riociguat should not be coadministered with nitrates or phosphodiesterase inhibitors (sildenafil, tadalafil, dipyridamole, theophylline) as they act on the same pathway (NO pathway) and can precipitate severe hypotension.[15] Riociguat is best absorbed under acidic conditions and drugs that alter the gastric pH can reduce its bioavailability.[60] A randomized, open-label, crossover study evaluating the effect of omeprazole and antacid aluminum/magnesium hydroxide (AlOH/MgOH) showed that AUC_t and C_{max} of riociguat were reduced by 26% and 35%, respectively, when coadministered with omeprazole and by 34% and 56%, respectively, when combined with AlOH/MgOH.[60] Antacids should not be administered within an hour of taking riociguat whereas no dosage adjustments are required when coadministering with proton pump inhibitors.[60] Dosage adjustments may be necessary when using riociguat concurrently with strong CYP3A4 inhibitors (dose reduction), P-gp inhibitors (dose reduction), or inducers (dose increase).[15] Concomitant exposure to riociguat and ketoconazole, which is a multipathway inhibitor of CYP1A1, CYP3A4, and P-gp, has been shown to increase the AUC_t and C_{max} of riociguat by 46% and 150%, respectively.[59,61] Initiating patients on a lower dose of 0.5 mg three times a day of riociguat should be considered in such situations.[59] Coadministration of riociguat with clarithromycin, which is a CYP3A4 and P-gp inhibitor, has also been shown to increase exposure to riociguat and its active metabolite M1 although no dosage adjustments are recommended.[61] Smoking induces the CYP1A1 isoenzyme which has a major role in the metabolism of riociguat.[62] Exposure to riociguat is reduced in smokers irrespective of hepatic or renal function and doses higher than 2.5 mg three times a day are recommended by the manufacturer although the safety and efficacy of higher doses are not well established.[15,63,64] All females of reproductive potential receiving riociguat need to be enrolled in the REMS program like with ERAs as riociguat is considered to be teratogenic.[15,59] No clinically significant drug interactions exist between riociguat and oral contraceptives like levonorgestrel and ethinyl estradiol.[64]

Drug Interactions With Prostanoids

Prostacyclin is a potent pulmonary and systemic vasodilator as well as an antithrombotic and antiproliferative agent.[5,65] Its effect on the pulmonary vasculature is mediated through the production of cyclic adenosine monophosphate.[65] Pulmonary arterial hypertension patients have a reduced levels of prostacyclin synthase and its metabolites.[5] Prostacyclin analogues include epoprostenol, iloprost, and treprostinil.

Epoprostenol

Epoprostenol has an ultrashort half-life of <5 minutes and is administered via a continuous intravenous infusion through an infusion pump.[5] Epoprostenol is not known to have any major drug interactions, but caution is advised when coadministered with certain drugs.[16,17] Coadministration with diuretics, antihypertensives, and vasodilators can cause hypotension. When administered with antiplatelets or anticoagulants, risk of bleeding may be increased.[16,17] A pharmacokinetic study evaluating the effect of epoprostenol on

digoxin showed that epoprostenol reduced the clearance of digoxin by 15% on the second day of therapy. This effect, though statistically significant, was not found to have any clinical significance. Potential still exists for digoxin toxicity when used concurrently with epoprostenol and caution is advised when using the 2 drugs together.[66] A similar study evaluating epoprostenol and furosemide showed that the clearance of furosemide was decreased by 13% when concomitantly administered with epoprostenol but this effect was neither statistically nor clinically significant.[67]

Treprostinil

Treprostinil is available in 3 different formulations: Remodulin (subcutaneous and intravenous), Tyvaso (inhaled), and Orenitram (oral).[18-20] It is more stable and has a longer half-life compared with epoprostenol of about 4 hours.[20] Pharmacokinetic and pharmacodynamic interaction studies of subcutaneous and oral treprostinil have shown that concurrent administration with antihypertensive agents, diuretics, and other vasodilators may increase risk of symptomatic hypotension.[18,20] Coadministration with anticoagulants may increase bleeding risk due to the antiplatelet effects of treprostinil.[18,20,68] Gemfibrozil (CYP2C8 inhibitor) can increase levels of oral treprostinil by 2-fold; it is recommended that when coadministered with gemfibrozil, the starting dose of oral treprostinil be lowered to 0.125 mg twice daily and increased in increments of 0.125 mg twice daily. Similarly, rifampin (CYP2C8 inducer) decreases treprostinil exposure by 30% but no dosage adjustments are recommended by the manufacturer.[20,68]

Iloprost

Iloprost is administered in a nebulized form and requires multiple daily treatments.[5] No major interactions of iloprost have been seen in pharmacokinetic and pharmacodynamic studies; however, it can potentiate the hypotensive effects of other vasodilators and antihypertensive agents. It can also potentiate the effects of anticoagulants due to its effect on platelet aggregation.[21]

Drug Interactions With Prostacyclin Receptor Agonist

Selexipag is a selective prostacyclin receptor agonist which was approved by the US FDA in December 2015 for the treatment of PAH.[22] Selexipag is mainly metabolized by carboxylesterase 1 to its active metabolite ACT-333679, which is ~37 times more potent than selexipag.[22,69] Selexipag and its active metabolite also undergo oxidative metabolism by CYP2C8 and CYP3A4.[22] Other enzymes involved in the metabolism of ACT-333679 include uridine glucuronosyltransferase (UGT) enzymes, UGT1A3 and UGT2B7.[69] Coadministration of selexipag with gemfibrozil (strong CYP2C8 inhibitor) has been shown to increase the C_{max} and AUC_t of its active metabolite (ACT-333679) by 3.6-fold and 11-fold, respectively, in a study.[70] Hence, concomitant use of selexipag and gemfibrozil is contraindicated.[70] The same study also showed that coadministration of selexipag with rifampin (CYP2C8 inducer) reduced exposure to the active metabolite of selexipag by half.[70] It is recommended to double the dose of selexipag when using it in combination with rifampin. In a pharmacokinetic study assessing the interaction between selexipag 200 μg twice daily and clopidogrel 300 mg single dose or 75 mg daily, the AUC_t of the active metabolite of selexipag (ACT-333679) was increased significantly but there was no effect on the pharmacokinetics of selexipag.[71] Once a day dosing of selexipag is recommended when coadministered with clopidogrel, as this has shown to maintain the exposure to ACT-333679 within therapeutic range.[71] Lopinavir/ritonavir (strong CYP3A4 inhibitor) has been shown not to have any clinically relevant effects on the pharmacokinetics of selexipag.[72]

Conclusion

Patients with PAH commonly have multiple comorbidities, often requiring management with multiple medications. The landscape of PAH has continued to evolve with the development of newer advanced therapies targeting the underlying vasoconstriction and inflammation by causing pulmonary artery vasodilation. Combination therapy has now become standard of care for patients with PAH and this has increased the potential for drug-drug interactions. Advanced therapies for PAH can have multiple drug interactions and it is critical for the pharmacist to be knowledgeable about the dosing as well as the significant drug interactions to improve the efficacy of combination treatment in this population.

Pulmonary arterial hypertension pharmacotherapy may be subject to multiple pharmacokinetic and pharmacodynamic interactions. These interactions may be specific to individual agents or may be concern for an entire pharmacologic category of PAH treatment. If not properly addressed, drug interactions with PAH treatments may lead to treatment failure or even toxicity. To optimize clinical outcomes, clinicians must be up to date on all mediations their patients are taking. Drug interactions with PAH pharmacotherapy are important and manageable. Drug interaction monitoring is a multidisciplinary team responsibility where prescribers and pharmacists both perpetually review the medication regimen with a focus on drug interactions.

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ORCID iD

Shraddha Narechania https://orcid.org/0000-0002-5611-5304

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