The incidence of echo-derived pulmonary arterial hypertension (PAH) in patients undergoing renal or liver transplantation is reported as high as 30%-60% and 25%, respectively. Not all of these patients will continue to have the diagnosis of PAH or require treatment following the organ transplant. However, if therapy is warranted, the medical team will need to be mindful of the potential drug–drug interactions with the currently available agents to treat PAH and medications used following transplantation (immunosuppression, antifungal agents, etc). The 2 types of drug–drug interactions important to PAH medications and agents used following transplantation are pharmacokinetic or pharmacodynamic interactions. Pharmacokinetic drug interactions are those in which one or more medications interfere with the metabolism or clearance of another agent, leading to either an increase or decrease in plasma concentration. Pharmacodynamic interactions consist of the effect of the drug on the body, including adverse reactions, and may be enhanced when used in combination with other of medications.

At this time, the 3 different classes of drugs approved for the treatment of PAH are prostacyclin derivatives, endothelin antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors. There are very few pharmacokinetic drug interactions encountered with epoprostenol, treprostinil, or iloprost. Treprostinil is substantially metabolized by the liver, mostly via the cytochrome (CYP) P450 2C8 enzymatic pathway, leading to the potential for an increase in treprostinil concentrations when combined with gemfibrozil or a decrease in treprostinil concentrations when given with rifampin. The main concern with prostacyclin derivatives is the risk of bleeding and interactions with medications that affect platelet aggregation.

Both commercially available ERAs are metabolized by the liver, but they have significantly different potentials for pharmacokinetic drug interactions. Bosentan’s elimination is dependent on hepatic metabolism via CYP3A4, CYP2C9, and CYP2C19. This drug is both a substrate and an inducer for these enzymatic pathways and therefore significantly increases its own metabolism with repeated administration, leading to a reduction in plasma concentrations. Combining bosentan with inhibitors of CYP enzymes often used in a transplant population like antifungal azoles (eg, voriconazole, itraconazole, posaconazole, ketoconazole), clarithromycin, erythromycin, protease inhibitors, and diltiazem may lead to an increase in plasma concentrations. Conversely, CYP inducers such as rifampicin, phenytoin, and carbamazepine may cause a decrease in plasma concentrations.

Bosentan is also a substrate of the human organic anion transporting polypeptides (OATPs) OATP1B1 and OATP1B3, found in the liver, and is responsible for hepatic uptake of many drugs. Induction or inhibition of this transporter system will effectively alter the rate of metabolism and plasma concentration of drugs. Cyclosporine is an inhibitor of OATP1B1 and when combined with bosentan can result in a significant and potentially dangerous increase in plasma concentrations of bosentan, making the combination of these 2 drugs contraindicated. Clarithromycin and erythromycin are inhibitors of OATP1B1 and should be used with caution with bosentan.

Ambrisentan is metabolized via the liver by uridine diphosphate glucuronosyltransferases (UGTs). The CYP3A4 and 2C19 pathways are responsible for 20% or less of its metabolism, and since ambrisentan is only a substrate for these pathways, it does not interfere with its own metabolism or that of other drugs. As seen with bosentan, OATPs are involved in the hepatic uptake of ambrisentan and caution is advised when administering with agents that inhibit this pathway. A small study evaluating the effects of cyclosporine on ambrisentan pharmacokinetics revealed a marked elevation in ambrisentan plasma concentrations, accompanied by an increase in reported side effects such as hypotension and gastrointestinal complaints. Therefore, the dose of ambrisentan should not exceed 5 mg daily when prescribed in combination with cyclosporine.

Sildenafil and tadalafil are the PDE5 inhibitors currently used in the treatment of PAH. Both agents are metabolized via the CYP3A4 pathway and are subject to many drug–drug interactions by medications that either induce or inhibit this pathway. For example, when used in

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combination with bosentan, a CYP3A4 inducer, both sildenafil and tadalafil concentrations are decreased by about 50%. Drugs like phenytoin and rifampin may decrease the drug effectiveness due to an increase in clearance, whereas agents like cyclosporine, azoles, and clarithromycin may increase PDE5 inhibitors’ concentration and lead to more side effects. There is some evidence that sildenafil inhibits the OATP1B transporters and therefore may have more drug-drug interactions than tadalafil, which does not appear to affect these transporters.  

In the solid organ transplant, addition of therapy to treat PAH must be done with careful consideration of the current medical regimen and pharmacokinetic profiles of the currently available PAH medications. Close monitoring for side effects encountered with an increase in drug exposure and therefore a potential for an increase in vasodilation (hypotension, gastrointestinal effects, headache) or for a decrease in drug exposure and potentially worsening PAH symptoms (volume overload, edema, shortness of breath) is warranted.

References