The endothelin receptor antagonists (ERA’s), bosentan and ambrisentan are two novel pharmacologic agents indicated for the treatment of pulmonary arterial hypertension (PAH). PAH is characterised by elevated plasma and tissue levels of endothelin, causing vasoconstriction and induction of smooth muscle proliferation. ERA’s have proven beneficial effects on exercise capacity, haemodynamics and time to clinical worsening.

Bosentan and to lesser extent ambrisentan are implicated in a number of drug-drug interactions. Identification of these interactions allows clinicians to prevent avoidable harm to patients, as well as optimise efficacy. Some important interactions will be discussed here, in particular interactions with agents that are frequently prescribed to patients with PAH.

The cytochrome P450 (CYP450) enzyme system, particularly the CYP3A4 and CYP2C9 isoenzyme, is responsible for the oxidative metabolism of the ERA’s. Concomitant use of CYP450 inhibitors, such as theazole antifungals (e.g. voriconazole, posaconazole, fluconazole, ketoconazole), macrolides (e.g. clarithromycin), protease inhibitors (e.g. ritonavir) and amiodarone results in increased plasma concentrations of the ERA’s. Co-administration with CYP450 inducers (eg. rifampicin, phenytoin, carbamazepine) will result in decreased plasma concentrations.

Treatment of PAH also targets nitric oxide and prostacyclin pathways and combinations with ERA’s are utilised to provide possible synergistic benefits. Although no known interactions with ERA’s and prostanoids have been reported, high doses of sildenafil increase peak plasma bosentan concentration by 42%. Sildenafil reduces the hepatic uptake and elimination of bosentan via inhibition of the organic anion-transporting polypeptides (OATP). In contrast, bosentan has been reported to reduce sildenafil plasma levels by up to 50%, via induction of CYP3A4. When sildenafil is prescribed at the usual recommended dose of 20mg three times daily, plasma concentrations are expected to be too low to elicit an effect on the pharmacokinetics of bosentan. The combination is therefore well tolerated in clinical practice and appears to be effective. Ambrisentan has no reported effect on CYP450 isoenzymes, but appears to be a substrate of OATP, although the clinical significance of this has yet to be determined.

Anticoagulation with warfarin is commonly administered to patients with PAH to reduce the risk of thromboembolism. Warfarin is metabolised by the CYP450 and bosentan mediated induction of CYP2C9 up-regulates warfarin’s metabolism, necessitating higher doses to maintain target INR. Ambrisentan has no clinically relevant effect on the pharmacokinetics of warfarin.
ERA's are potent teratogens, therefore women of child bearing potential require contraception. Bosentan, but not ambrisentan may reduce the systemic levels and efficacy of hormonal contraceptives via induction of CYP3A4/5, potentially resulting in contraceptive failure. Ambrisentan may be prescribed as a safe alternative.

Infrequently cyclosporine may be prescribed to patients with PAH associated connective tissue disease or PAH patients undergoing a solid organ transplant. The co-administration of cyclosporine and bosentan is contraindicated as increases of up to 40 fold in bosentan trough levels and up to 50% reduction in cyclosporine levels have been reported. The interaction is mediated through OATP inhibition by cyclosporine and CYP3A4 induction by bosentan. Ambrisentan may be prescribed at a reduced dose of 5mg daily as only a two fold increase in cyclosporine concentration has been reported.

PAH can occur in up to 0.5% of patients with HIV and bosentan has demonstrated efficacy in HIV associated PAH. There are however a number of clinically significant interactions with anti-retroviral therapy. Boosted protease inhibitor (PI), lopinavir/ritonavir has been reported to increase bosentan concentrations by up to 48 fold primarily via inhibition of OATP. Bosentan, via induction of CYP3A4/5 can decrease lopinavir and ropinavir concentrations, but this is not clinically significant. The co-administration of a boosted PI with bosentan requires temporary cessation of bosentan and reintroduction at half the recommended dose. Close monitoring of bosentan tolerability, clinical symptoms and haemodynamics of PAH and HIV viral load is required. Unboosted atazanavir is also reduced by bosentan's induction of CYP3A4/5, contraindicating co-administration. There are no reported interactions with ambrisentan and anti-retroviral therapy.

ERA’s are an established class of therapeutic agents for the treatment of PAH. As treatment shifts towards combination therapy and more treatment options emerge, careful consideration of potential drug interactions is required to ensure maximum clinical benefit and to avoid risk of harm to patients. Ambrisentan offers some pharmacokinetic advantages compared to bosentan, with only one known clinically relevant drug-drug interaction.

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References: