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Title: Pharmacokinetic interactions of imatinib with bosentan and sildenafil for treatment of severe pulmonary arterial hypertension

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Body: Introduction: Pulmonary arterial hypertension (PAH) is a progressive disease causing incremental pulmonary vasculopathy, and resulting in premature death. Current therapeutic interventions primarily target pulmonary vasodilatation and have limited efficacy in improving pulmonary hemodynamics. Imatinib is a tyrosine kinase inhibitor, which may have efficacy in treatment of PAH. Here, we present results from a phase III randomized study evaluating the pharmacokinetic interactions between imatinib and 2 co-medications, sildenafil and bosentan, which are commonly used for PAH treatment. Method: Adult patients (N=202) with severe PAH were randomized to receive imatinib (n=103) or placebo (n=99). Imatinib 200 mg was initiated for 2 weeks, followed by 400 mg, up to 24 weeks if tolerated. Concentrations of each drug (imatinib, sildenafil, or bosentan) at Days 14, 28, and 168 were log-transformed and analyzed using linear mixed models to assess the impact of concomitant administration of the other drugs. Result: Sildenafil concentrations (95% CI) increased by 64% in the presence of imatinib and decreased by 44% in the presence of bosentan. Bosentan concentrations (95% CI) increased by 51% in the presence of imatinib and by 53% in the presence of sildenafil. Imatinib concentrations (95% CI) decreased by 33% in the presence of bosentan and did not change in the presence of sildenafil. Conclusion: Concentrations of bosentan and sildenafil were elevated on co-administration with imatinib while bosentan decreased imatinib concentration. Sildenafil had no effect on imatinib concentration. This study further supports the known interaction between sildenafil and bosentan.