Effects of AMBRISENTAN, Darusentan, Bosentan, and Sitaxsentan on Human Hepatic Uptake and EFFLUX TRANSPORTERS

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Four endothelin receptor antagonists (ERAs) were examined for substrate activity and potential inhibition of selected hepatic uptake and efflux transporters using sandwich cultured human hepatocytes. ERA substrate activity for respective transporters (i) was evaluated using ritonavir (OATP, BSEP), bromosulphalein (OATP), Na+ depleted (NTCP), and erythromycin (Pgp). ERA transporter (i) inhibition was examined using substrates E2-17betaG (OATP), taurocholate uptake (NTCP), taurocholate efflux (BSEP), and DPDPE (MRP2). Each ERA was tested for substrate activity at 2uM and inhibition at 2, 20, 100uM. Sitaxsentan and bosentan demonstrated greater hepatic uptake (5-30 fold) than that of ambrisentan and darusentan. Decreases in influx of all 4 ERAs with co-administration of ritonavir, bromosulphalein, or probenecid suggested that OATPs contribute to uptake. Darusentan influx was the least altered by those agents (84-100% of control), whereas bosentan was the most (32-58%). The absence of Na+, reduced uptake of ERAs (bosentan>darusentan>sitaxsentan>ambrisentan) demonstrated the relative contribution of NTCP to influx, Ritonavir did not change the biliary excretion index (BEI) of ambrisentan, suggesting no effect on BSEP mediated efflux. Darusentan and bosentan showed increased BEI with ritonavir, whereas parent sitaxsentan was not excreted. Erythromycin did not change the BEI for ambrisentan, but reduced efflux for darusentan (64% of control) and bosentan (72%), demonstrating that Pgp contributes to the excretion of the latter drugs. No concentrations of ambrisentan nor darusentan significantly reduced OATP, NTCP, BSEP, or MRP2 transport. Bosentan (100uM; 33% of control) and sitaxsentan (20 and 100uM; 19 and 2%) significantly attenuated NTCP transport. Only sitaxsentan (100uM) significantly decreased OATP transport to 52% of control. BSEP transport was reduced by 100 uM bosentan (78% of control) and sitaxsentan (85%). Neither bosentan nor sitaxsentan significantly altered MRP2 transport. These results indicate that ERAs are hepatic transport substrates, and suggest that bosentan and sitaxsentan, but not ambrisentan and darusentan inhibit human hepatic transport.