Interaction of Lopinavir with efflux proteins: MDR1, MRP1,2 and 3

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POREUSE

• To test whether Lopinavir (Lop/LVR), a protease inhibitor used currently in the anti-HIV therapy, is a substrate for efflux proteins MDR1, MRP1,2,3 which might contribute to its low oral and brain bioavailability.
• To devise methods to bypass this efflux if it exists, and try to get increased oral and brain bioavailability of Lopinavir.

RATIONALE

• HIV protease inhibitors (PIs) have revolutionized the treatment of HIV infection by inhibiting the viral enzyme and preventing viral replication.
• The oral bioavailability of some HIV protease inhibitors (Lopinavir, nelfinavir, and amprenavir) are low and/or variable, with limited penetration into the central nervous system (CNS).
• Subtherapeutic concentrations of PIs in the brain are a likely cause for the development of treatment-resistant viral strains in the brain.
• It is possible that the low oral bioavailability of Lopinavir might be due to an interaction with one or more transporter proteins.

LORPINAIVR

Lopinavir (LVR) is a novel protease inhibitor (PI) developed from Ritonavir. It is the brand name for this combination in Kaletra, Abbott Laboratories.

• The molecular formula is: C₃₇H₄₈N₄O₅, and its molecular weight is 628.80.
• Lopinavir is given along with Ritonavir and the brand name for this combination is Kaletra, Abbott Laboratories.
• Lopinavir, the active component of this combination, is extensively metabolized by CYP3A4 and produces low systemic concentrations when used alone. Ritonavir potently inhibits CYP3A4 and is used to enhance the systemic exposure of Lopinavir.
• In a study where the kinetic and thermodynamic characterisation of different HIV-1 PIs was studied, Lopinavir had low affinity, a high dissociation constant (Kd) and a low substrate efficacy.
• Lopinavir is a substrate for P-glycoprotein (P-gp) and MRP1, which are ATP-dependent P-gp inhibitors.

MDR1

• MDR1 Polycypermorphonuclear (PMN) cells are drug-resistant to antineoplastic agents (e.g., doxorubicin (Dox), cisplatin, and vincristine (Vcr)) in vitro, due to the overexpression of P-gp.
• P-gp is a membrane protein that is present in the apical membrane of the gut, liver, lungs, and brain and is responsible for the efflux of drugs from the cell.
• P-gp is present in the apical membrane of the gut, liver, lungs, and brain and is responsible for the efflux of drugs back into the lumen of these organs.
• P-gp transport involves ATP hydrolysis.
• P-gp is a key player in the multidrug resistance of cancer cells.
• P-gp is present in the apical membrane of the gut, liver, lungs, and brain and is responsible for the efflux of drugs back into the lumen of these organs.

MRP1

• The expression and localization of MRP1 makes it extremely important to study the efflux of therapeutic drugs with these proteins.
• MRP1 is a widely expressed transporter that, when present in epithelial cells, is found in the apical membrane.
• MRP1 transport involves ATP hydrolysis.
• MRP1 is present in the epithelium of the choral pouch.
• MRP1 is able to confer resistance to anthracyclines, vinca alkaloids, cyclophosphamide and methot extremist.

MRP2

• MRP2 family transporters were selectively inhibited with MK-571, a specific leukotriene D₄ (LTD₄) receptor antagonist.
• MRP2 is selective for P-gp/P-gp mediated efflux.
• Fumitremorgin-C (FC) is a selective inhibitor of the ABCB1 protein.
• Lopinavir has at least the same or higher anti-viral activity when compared with the parent drug.

MRP3

• Both MRP3 and MRP5 localize basolaterally in renal proximal tubules, gut enterocytes, syncytiotrophoblast cells of the placenta, and possibly the brain capillaries.
• Therefore, they are functional similar to Pgp in their involvement in the terminal elimination of compounds and its role as a barrier to gut and placenta.
• In rats, MRP2 contributes to hepatobiliary, intestinal and renal drug excretion and to the reduction of oral availability of its substrates.
• It is now known that PIs are transported by MRP2.

INHIBITORS USED

• Efflux ratios for 3H Lopinavir transport and efflux with cold Lopinavir and inhibitors in MDCK-II-MRP2 cell line

DISCUSSION AND CONCLUSION

• Lopinavir efflux was directional and was completely inhibited by 500 µM MK-571 and P-gp4008 respectively.
• The MDR1-MRP1 cells have a reduced intracellular accumulation of Lopinavir.
• Drug-drug interactions may occur since drugs could be lost to the gut wall, where they would be absorbed and transported back into the circulation, leading to a reduction in the oral bioavailability of Lopinavir.
• Therefore, it is desirable to modify Lopinavir in a way that it will be metabolized by CYP3A4 and produce lower concentrations when used alone.
• Ritonavir potently inhibits CYP3A4 and is used to enhance the systemic exposure of Lopinavir.
• Therefore, it is desirable to modify Lopinavir in a way that it will be metabolized by CYP3A4 and produce lower concentrations when used alone.

FUTURE WORK

• Our strategy to bypass the efflux of Lop would be to synthesize produgs of Lop which will:
• evade the efflux pumps substantially
• be taken by the intestinal and brain cells with the help of nutrient influx transporters like peptide transporters (Pyr11 and 2) or vitamin transporters (MVT or Folate or Biotin)
• have lesser protein binding as compared to Lop.
• have atleast the same or higher anti-viral activity when compared with the parent drug.
• we also want to check for interaction of Lop with other efflux proteins like MRP2 and BCRP which might play an important role in the low oral bioavailability of Lop.