ABSTRACT

Prescribing drugs in hepatic impairment is an important and challenging aspect of clinical practice and effects of liver disease on pharmacokinetics and pharmacodynamics are highly variable and affect the plasma protein binding, in turn effects distribution and elimination of many drugs. HIV patients treated with combinations of antiretroviral therapy (HAART) regimens responsible to significant diminution in HIV viral load and increased CD$_{4+}$ lymphocytes numbers, there by slows the disease progression and improving patient survival. Protease inhibitors (PIs) based therapy has metabolic complications including insulin resistance, glucose intolerance and diabetes mellitus. HIV treatment on long term therapy causes impaired hepatic dysfunction in HIV patients. One of the most challenging issues facing by the health care providers treating with HIV infection is a complex problem of drug interactions associated with highly active antiretroviral therapy (HAART) in hepatic dysfunction. This requires an understanding of the drug-drug interactions between anti-HIV drugs and drugs used in the treatment of Diabetes mellitus in hepatic dysfunction. This thesis explored the drug-drug interactions of protease inhibitors (PIs) and repaglinide in hepatic dysfunction model. The present thesis was aimed to study the pharmacokinetic and pharmacodynamic DDIs interactions between the protease inhibitors (Ritonavir, Atazanavir and Indinavir) and repaglinide in normal, diabetic and hepatic impaired rats. The pharmacokinetic parameters and blood glucose levels of repaglinide were determined in rats after oral (0.5 mg/kg.b.w) of repaglinide and protease inhibitors at 20 mg/kg ritonavir, 36 mg/kg atazanavir and 72 mg/kg b.w Indinavir were administered orally to the respective groups. Compared to the repaglinide alone (control) group, protease inhibitors (Ritonavir, Atazanavir and Indinavir) significantly increased C$_{max}$, AUC and decreased the total body clearance of repaglinide, this increases the bioavailability of repaglinide which precipitates the hypoglycemic effect. Among three protease inhibitors the indinavir was a potent inhibitor of CYP 3A4 enzyme and P-gp transporter followed by atazanavir and ritonavir. The present study concluded the selected protease inhibitors (Ritonavir, Atazanavir and Indinavir) were altered the pharmacokinetics and pharmacodynamics of repaglinide in normal, diabetic and hepatic impaired rats, this current study has
raised awareness the potential drug-drug interactions by co-administration of repaglinide with protease inhibitors (PIs). These drug-drug interactions between the selected antiretroviral drugs and repaglinide might help the physicians or pharmacist to understand and to adjust the dose in the hepatic dysfunction patients.