CHAPTER-6

DISCUSSION OF RESULTS

6.1 PHARMACOKINETIC AND PHARMACODYNAMICS OF REPAGLINIDE IN THE ABSENCE AND IN THE PRESENCE OF RITONAVIR IN NORMAL, DIABETIC AND HEPATIC IMPAIRED RATS

CYP P450 enzymes are accountable for the drug metabolism in human liver and CYP 3A4 enzyme is culpable through which repaglinide metabolism happens in human liver. When repaglinide was administered in normal, diabetic, and hepatic impaired rats as single dose with ritonavir, it was found that repaglinide plasma concentrations were increased as marked by its pharmacokinetic parameters (AUC, C<sub>max</sub>, t<sub>1/2</sub> and Cl). During the first pass metabolism it was noticed that peak plasma concentration of repaglinide was increased when co-administered with ritonavir this may be due to inhibition of CYP3A4-mediated biotransformation of repaglinide. CYP3A4 is present in appreciable quantities in the small intestine mucosa, and the intestine and CYP3A4 has been demonstrated to play a major role in drug interactions with CYP3A4 inhibitors. A more significant increase in plasma concentrations of repaglinide was noticed in hepatic impaired rats as compared with normal and diabetic rats. This entail that the inhibition of 3A4 and 2C8 along with the OATP would have a major effect on altered pharmacokinetics of repaglinide.

The increased bioavailability (AUC and C<sub>max</sub>) of repaglinide when administered with ritonavir increased the plasma concentration of repaglinide, and slower elimination (as reflected from its clearance and half life) may result in enhanced blood glucose lowering activity which may further trigger hypoglycemic activity. The blood glucose levels were decreased significantly when repaglinide is given in combination with ritonavir in normal, diabetic and hepatic impaired groups. Statistically significant increased the area under curve AUC and C<sub>max</sub> values indicated improved bioavailability of repaglinide in the presence of ritonavir. This may be due to the interaction of ritonavir with repaglinide metabolism and OATP transporter that is ritonavir reduces the hepatic
metabolism; thus, the hypoglycemic effect of repaglinide gets enhanced. The repaglinide metabolism was inhibited by the ritonavir so; that the concentration of repaglinide was increased in plasma due to this clearance of repaglinide was decreased.

6.2 PHARMACOKINETIC AND PHARMACODYNAMICS OF REPAGLINIDE IN THE ABSENCE AND IN THE PRESENCE OF ATAZANAVIR IN NORMAL, DIABETIC AND HEPATIC IMPAIRED RATS

Repaglinide metabolism happens mainly with hepatic cytochrome P450 enzyme system with CYP 3A4. The repaglinide pharmacokinetics was further convoluted because of active hepatic uptake of repaglinide by OATP uptake transporter and it is a substrate for the OATP transporter and it also act as a substrate for P-glycoprotein which can significantly contribute to potential drug-drug interactions with other P-gp substrate or inhibitors. HIV protease inhibitors (PIs) have identified as a substrates, inhibitors or inducers of CYP3A4, OATP and P-gp in vitro and in vivo studies. Atazanavir is broadly metabolized by Cytochrome P450 enzyme system which have capable of altering both P-gp and CYP 3A4 activity in-vitro system. Atazanavir inhibits P-gp mediated transport and acts as a potent mechanism based inhibitor of CYP3A4 and it also inhibit the OATP transport particularly OATP1B1, OATP1B3 and OATP2B1 mediated transport in liver. The pharmacokinetics (Cmax, AUC0-t, AUCt-∞, t1/2, clearance) and pharmacodynamics (percent blood glucose reduction) of repaglinide was significantly altered in the atazanavir treated normal, diabetic and hepatic impaired rats. The significant improvement of Cmax and AUC of repaglinide in normal, diabetic and hepatic impaired rats could be due to CYP3A4 enzyme and P-gp inhibition during the first pass metabolism. Compared to the control group the atazanavir significantly decrease the clearance of repaglinide in normal, diabetic and hepatic impaired rats, this could be due to the inhibition of CYP3A4 and OATP transporter in the liver. The degree in change in the exposure of repaglinide is more in hepatic impaired rats could be due to the synergistic effect of both OATP inhibition by atazanavir and liver dysfunction in the rats. The clearance of repaglinide was statistically significant decreased in normal and diabetic rats was due to inhibition of CYP3A4 and OATP,P-gp transport by atazanavir, but in
hepatic impaired rats the magnitude change in the exposure of repaglinide is more in this
could be due to the synergistic effect of OATP inhibition by atazanavir and liver
dysfunction in rats. In hepatic impaired rats $t_{1/2}$ of repaglinide was increased significantly
when compared to the repaglinide alone control group due to decrease in clearance of
repaglinide.

The blood glucose levels were decreased significantly when repaglinide is given in
combination with atazanavir in normal, diabetic and hepatic impaired groups. The
increased bioavailability (AUC and Cmax) of repaglinide when administered with
atazanavir increases the plasma levels of repaglinide and decreases elimination which
results in embellish mean blood glucose percentage which may further expedite
hypoglycemic action.

6.3 PHARMACOKINETIC AND PHARMACODYNAMICS OF REPAGLINIDE
IN THE ABSENCE AND IN THE PRESENCE OF INDINAVIR IN NORMAL,
DIABETIC AND HEPATIC IMPAIRED RATS

When indinavir was co-administered with repaglinide there was significant increase in
plasma concentration and alteration in pharmacokinetic parameters like( $C_{\text{max}}$, $T_{\text{max}}$, $AUC$
$0 \to t$, $AUC_{0\text{-total}}$, $t_{1/2}$ and clearance ) and pharmacodynamic parameter ( percent blood
glucose reduction) of repaglinide were observed in normal, diabetic and hepatic impaired
rats. Increase in peak plasma concentration of repaglinide in indinavir pretreated normal,
diabetic and hepatic impaired rats was observed when compared to repaglinide alone
treated control group.

Indinavir is an inhibitor of P-gp in intestine and as it inhibits the CYP3A4 mediated
biotransformation in liver and in intestine. The $AUC_{0\text{-}t}$ and $AUC_{0\text{-total}}$ was significantly
increased in the presence of indinavir in normal, diabetic and hepatic impaired rats. There
was an increase in $C_{\text{max}}$ and $AUC$ revealed improved in bioavailability of repaglinide in
the presence of indinavir, this suggest that the indinavir inhibit the CYP3A4 mediated
biotransformation in liver and in intestine.  Indinavir also act as an inhibitor of P-gp in
the intestine. Repaglinide elimination was reduced in normal, diabetic and hepatic
impaired rats, this was reflected in the decreased in clearance and increased in half life of the repaglinide in normal, diabetic and hepatic impaired rats when compared to the repaglinide alone (control) group.