Abstract

Evaluation of potent drug-drug interactions (DDIs) have become an integral approach in drug development as well as health care to provide rational therapy. This thesis concerns to explore the possible DDIs of selected antiretroviral drugs (Protease Inhibitors: indinavir, ritonavir, and atazanavir; Non-nucleoside reverse transcriptase inhibitors: efavirenz and nevirapine) with gliclazide (antidiabetic drug) in animal models. This study was aimed i) to investigate the safety and efficacy of the combination of selected antiretroviral drugs with gliclazide by conducting pharmacodynamic (PD) interaction studies in rats (normal and alloxan-induced diabetic) and rabbits, and pharmacokinetic (PK) interactions studies in rabbits, ii) information about the mechanism of interaction(s), if occurs and iii) to determine whether the glucose disorders associated with protease inhibitors are either class specific or drug specific. DDIs of selected antiretroviral drugs with gliclazide were evaluated i) by conducting in two dissimilar species (rodent – normal and diabetic rat; non-rodent - rabbit) so as to identify, validate and conclude the results with clinical perspective, ii) by extrapolating the human therapeutic oral doses of experimental drugs based on animal body surface area which underscores the clinical relevance, iii) to conduct PD and PK studies concurrently in a same rabbit group in order to establish a clear association between PD-PK and to explore the possible mechanism of DDIs, iv) to determine primary PD parameters (glucose by GOD/POD method and insulin by radioimmunoassay) and secondary PD
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parameters (insulin resistance and β-cell function by homeostasis model assessment) at specified time intervals in order to emphasize the clinical relevance considering glucose-insulin homeostasis, and v) to conduct single- and multiple-dose PK/PD interaction studies in order to provide valuable information on the time course and magnitude of antiretroviral drug interactions with gliclazide with respect to clinical prospective. The PD results showed a good correlation with PK results in animal models. The results were treated statistically (Student's paired t-test) and it was concluded that i) there is a significant ($P < 0.05$) pharmacodynamic interaction of indinavir with gliclazide and hence this combination should be contraindicated in a clinical situation, ii) there is a significant ($P < 0.05$) pharmacokinetic interaction of ritonavir, atazanavir and efavirenz with gliclazide at metabolic level by CYP3A4 inhibition (ritonavir), CYP2C9 & CYP3A4 inhibition (atazanavir), and CYP3A4 induction (efavirenz), and hence these combinations needs dose adjustment and care should be taken, and iii) there is no significant ($P < 0.05$) interaction of nevirapine with gliclazide and hence proved to be a safe combination. Moreover, the results obtained in this study made us to arrive at a conclusion that, the glucose disorders associated with protease inhibitors are drug specific, but not class specific. These results might serve as an aid to the physicians, pharmacologists and pharmacists to understand the mechanisms of drug interactions associated with antiretroviral drugs and antidiabetic drugs, and in the selection of drug combinations with respect to safety and efficacy.