Review Article

A Review on Drug Interactions in Oral Hypoglycemic Drugs by Mechanism of Cytochrome P450 Enzyme Inhibition

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ABSTRACT

Purpose: Drug interaction is a phenomenon that has to be thoroughly investigated in order to avoid adverse effects. This review article highlights the drug interaction of oral hypoglycemics by mechanism of cytochrome P450 enzyme inhibition.

Approach: Published articles from PubMed and other sources were used to review and compile these drug interaction studies.

Findings: Drug interaction in oral hypoglycemics by mechanism of cytochrome P450 enzyme inhibition can increase the risk of hypoglycemia in diabetic patients and hence dose adjustments may be required.

Conclusion: These drug interaction studies are essential for patients suffering from diabetes mellitus as it prevents the risk of occurrence of hypoglycemia. This information is also important for the prescribing physicians as dose alteration or alternate drugs need to administered in case of concomitant administration of drugs in case of polypharmacy.

Keywords: Drug interaction; CYP450 enzyme; Oral hypoglycemics; Food-drug interaction.

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INTRODUCTION

Drug interaction maybe defined as the situation in which a substance - concomitant drugs, food or lifestyle that can effect/alter the pharmacokinetic and pharmacodynamic profile of a drug.[1] Drug interaction is a challenging concept, since the consumption of food and other herbal drugs is not documented in a patients profile. Thus it is necessary to study drug interaction as the synergism or loss of therapeutic activity of drug could lead to poor treatment and potentially be dangerous to the patient due to adverse drug reactions .

Diabetes mellitus is a common metabolic disorder and oral hypoglycemic drugs are common method of treatment.[2] Oral hypoglycemic drugs are primarily metabolized by CYP2C9 and CYP3A4.[3-7] Thus inhibition or induction of the same enzymes could lead to potential drug interaction.

This review highlights the various drug interactions of oral hypoglycemic drugs by mechanisms of cytochrome P450 enzyme inhibition and also throws light on the various types of drug interactions.

TYPES OF DRUG INTERACTIONS

This section will focus on the various types of drug interaction by different mechanisms.[8]

Drug interaction in absorption-

Not only drugs but food substances may have a profound effect on the

absorption of drugs in the gastrointestinal tract. Complex/chelate formation, the solubility and pH dependability can greatly alter the absorption of a drug. Drugs and ingestion of food that affect gastric emptying rate affects the dissolution rate and passage into small intestine may change the rate of absorption. Inhibition of some transporters like P-glycoprotein may influence the rate of absorption.[9]

Drug interaction in tissue distribution-

Drugs with high plasma protein binding more than 90% with a narrow therapeutic range tend to exhibit drug interaction. Drugs selectively bind with the receptors, proteins, or lipids in the tissue. As a result of competition for binding, the concentration of unbound drug in tissue may change which may result in drug interaction. Transporters also seem to play a role in the distribution of drug to liver, kidneys, and brain which can cause a change in the unbound drug concentration in tissue and can influence the effect and side effects of the drug.[10]

Drug interaction in drug metabolism-

This review mainly focuses on the interactions based on this mechanism. P450 has many known isoforms, such as CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP33A4. As the substrate specificity of this enzyme is broad, competitive inhibition occurs between drugs that are metabolized by the same enzyme isoforms. The enzyme responsible for the metabolism of a drug may not be the isoform inhibited by the drug. Drug interaction studies with experimental animals are often done to derive a relationship between the *invitro* and *invivo* studies based on the degree of interaction. These results are useful to predict to predict the *invivo* drug interactions in humans based from the *invitro* data. This procedure is applicable only in the case where the metabolism of the investigational drug is inhibited in a similar manner in terms of the CYP450 isoforms involved, type and degree of inhibition.

Drug interaction by method of induction of CYP450 generally results in decreased therapeutic effect due to increased rate of metabolism of the drug. The receding effect of induction by the abrupt cessation of concomitant drug administration can also prove to be hazardous due to rise in plasma levels.

Other enzyme systems like di-hydropyrimidine dehydrogenase,[11] aldehyde dehydrogenase,[12] glutathione transferase[13] and glucuronosyl transferase[14] are also responsible can also be responsible for drug interactions. But such cases are rarely reported.[15]

Drug interactions in excretion-

Most drugs are excreted by urine and in case of drugs a high reabsorption rate concomitant administration may change their urinary excretion by affecting the urinary pH. Patients with renal disorders taking renal-clearance dependent drugs have to be closely monitored for possible side effects due to interaction.

Drugs are often conjugated and excreted in bile. Drug interactions in the process of biliary excretion may affect the AUC and mean residence time of the unchanged drug in plasma. To predict interactions in the process of biliary and urinary excretion *in vitro* studies using human tissue-derived samples, cells expressing transporters and membrane vesicles may be useful.[16]

MECHANISM OF ACTION OF ORAL HYPOGLYCEMIC DRUGS:

It is necessary to know the mechanism of action oral hypoglycemics to understand its various interactions.[17] Classification and mechanism of action of oral hypoglycemic drugs are mentioned below (Table 1) .

VARIOUS DRUG INTERACTIONS OF ORAL HYPOGLYCEMICS BY CYP450 INHIBITION

Interaction with proton pump inhibitors-

Drugs such as rabeprazole and pantaprazole are known to weak inhibitors of CYP3A4, CYP2C9, CYP2C19 and CYP2D6 hence suggesting possibility of interaction.[26,27] The *in vivo* studies conducted on Alloxan induced diabetic albino wistar rats showed that there are no interactions at therapeutic doses but at higher doses it enhanced the anti-diabetic potential of sulfonylureas like glibenclamide and glipizide.[28] Since the PPI's *perse* did not influence the

Table 1: Classification and mechanism of action of oral hypoglycemic drugs

Class of Drug	Mechanism of action
Sulfonylureas	Blocking of ATP-regulated potassium channels causing depolarization that results in calcium influx and enhanced insulin release from pancreatic β-cells.[18]
Meglitinides	Similar to sulfonylureas inhibits potassium efflux causing depolarization and insulin release from pancreatic β-cells.[19]
Insulin sensitizers	Acts by decreasing the liver's production of glucose via activation of AMP-activated protein kinase. Other mechanism may include the inhibition of the breakdown of fatty acids used to produce glucose.[20]
α-glucosidase inhibitors	Acts by inhibiting the activity of enzymes required to break carbohydrates down into simple sugars.[21]
DPP-4 inhibitors	It acts as an inhibitor of dipeptidyl peptidase-4 a protease that degrades the incretin GLP-1.[22]
GLP-1 analogues	Acts by potentiation of glucose-mediated insulin secretion and suppression of postprandial glucagon release.[23]

blood glucose levels it can be concluded that the interaction is not of the pharmacodynamic type. Though sulfonylureas are mainly metabolized by CYP3A4 and CYP2C9, the weak inhibitory effect of the PPI's on the same enzyme shows significant interaction only at higher doses, but is safe to be administered concomitantly at therapeutic doses. Hence patients who are suffering from Zollinger-Ellison syndrome are administered high doses PPI need to be closely monitored in diabetic condition.[29]

Interaction with Anti-Hyperlipidemic Drugs-

HMG CoA reductase inhibitors such as pravastatin is mainly metabolized by CYP3A4 and CYP3A5 isozymes,[30,31] but it also as moderate inhibition on metabolizing enzymes like CYP2C9, CYP2D6 and CYP3A4.[32] Since these enzymes are responsible for the metabolism of oral hypoglycemic drugs like gliclazide there is possibility of interaction. The *in vivo* studies conducted on Alloxan induced diabetic albino wistar rats, normal rats and normal rabbits show pharmacokinetic interaction at metabolic and excretion levels. Since the interaction is observed in two dissimilar species it is likely to occur in humans also. Hence the concomitant administration of gliclazide and pravastatin should be contraindicated or dose must be altered to prevent hyperglycemia.[33]

Interaction with Anti-Arrhythmic Drugs-

The Anti-Arrhythmic drug Amiodarone is known to be weak inhibitor of CYP3A4, CYP2C9 and P-glycoprotein. CYP3A4 and CYP2C9 are responsible for the metabolism of the sulfonylureas - gliclazide. Hence indicating the possibility of interaction.[34] The *in vivo* studies conducted on Alloxan induced diabetic albino wistar rats, normal rats and normal rabbits showed increase in hypoglycemic effect of gliclazide when concomitantly administered. And since the effect was seen in two dissimilar species it was most likely to occur in humans as well. Though the combination was well tolerated and did not cause hypoglycemic shock in experimental animal, it is necessary to monitor the blood glucose levels when such drugs are concomitantly administered.[35]

Interaction with Antiretroviral drugs-

Antiretroviral drugs show inhibition and some seem to show induction of CYP450 enzymes. Gliclazide is a second generation sulfonylureas mainly metabolized by CYP3A4 and CYP2C9 and hence an interaction is expected. An *in vivo* study conducted Alloxan induced diabetic albino wistar rats, normal rats and normal rabbits for the interaction of antiretroviral drugs such as indinavir, ritonavir, atazanavir, efavirenz and nevirapine with a second generation sulfonylureas-gliclazide showed varied results.

Indinavir seemed to show pharmacodynamic interaction due to the opposing effects of gliclazide and indinavir on glucose-insulin homeostasis and/or insulin resistance and/or tissue uptake of glucose. Since this interaction is observed in two dissimilar species it's most likely to occur in humans and the combination must be contraindicated.

Ritonavir and atazanavir showed significant pharmacokinetic interaction by altering the

metabolism of gliclazide by CYP3A4 and CYP2C9 inhibition.[36,37] Since such interaction is exhibited in two dissimilar species there is high possibility of interaction in humans. Thus dose adjustment and continuous monitoring of glucose levels is recommended on concomitant administration of the drugs.

Efavirenz showed pharmacokinetic interaction by CYP3A4 induction causing decreased potency of gliclazide.[38,39] Thus on concomitant administration dose adjustment maybe required and special precaution must be taken on this combined administration.[40]

Interaction with Sulfonamides-

Tolbutamide is mainly metabolized by CYP2C9 enzyme[41] and sulfonamides are reported to be inhibitors of the same CYP2C9 isozyme making drug interaction a possibility.[42] The *invitro* studies conducted for the inhibitory effect of sulfonamides like sulfadiazine, sulfamethizole, sulfisoxazole, sulfamethoxazole, sulfapyridine, sulfadimethoxine, and sulfamonomethoxine on tolbutamide was evaluated and it was reported that the co-administration of sulfonamides with relatively small ki and CYP2C9 substrates with a narrow therapeutic index like tolbutamide, warfarin and phenytoin must be carefully monitored.[43-45]

Interaction with fruits (food-drug interaction)-

Food drug interaction is a challenging concept as the food intake is not mentioned in the patient's profile. Some reports indicate that some fruit juices inhibit CYP2C9 and CYP3A4 activities and cause food-drug interactions.[46-48] An invitro study conducted on the inhibitory effect of citrus fruits such as hyuga-natsu, unshu mandarin, banpeiyu, hirami lemon, valencia orange, pomelo, grapefruit, lemon and lime, and tropical fruits such as melon, mango, litchi, pineapple, papaya, mangos teen, passion fruit and kiwi fruit on the activity of CYP450 2C9 showed that pineapple juice resulted in almost complete inhibition of CYP2C9 whereas other citrus fruits and tropical fruits have weak inhibitory effect. It was also concluded that pineapple juice causes irreversible inhibition of human CYP2C9 activity. The study also showed that pineapple juice potently inhibited the CYP2C9-mediated metabolism of tolbutamide *in vitro*. Thus further *in vivo* studies need to be conducted to confirm the possibility of interaction in humans.[49]

An *in vivo* study conducted on pomegranate juice and tolbutamide in wistar albino rats suggest pomegranate juice ingestion inhibits the intestinal metabolism of tolbutamide without inhibiting the hepatic metabolism in rats. Thus, it was discovered that pomegranate juice inhibited human CYP2C9 activity and furthermore increased tolbutamide bioavailability in rats. Hence patients on tolbutamide need to be cautious while taking pomegranate juice.[50]

Grapefruit juice is a potent CYP3A4 inhibitor and studies suggest that its interaction with repaglinide may cause hypoglycemia as repaglinide is metabolic substrate for the CYP3A4 isozyme.[51]

CONCLUSION

Evaluation of potent drug-drug interaction (DDIs) has become an integral part of drug development as well as useful in prevention of adverse effects. Polypharmacy is a very common practise for patients suffering with chronic diseases. Diabetes mellitus is a chronic disorder often associated with several diseases like cardiovascular diseases, immune disorders and hyperlipidemia. In this light of this perspective there is much need to focus on

the evaluation of possible DDIs associated with polypharmacy, and drugs used in treatment of diabetes mellitus and maintenance of normal blood glucose of the patient.

Several points has to be considered in the study of metabolic drug interactions-

Drug concentration and dose- The degree of inhibition of drug metabolism and induction of enzymes is strongly dependent on the inhibitor concentration, substrate concentration, dose, and dosing interval.

Inhibition and induction caused by metabolites- Metabolites may cause drug interactions depending on the amount produced and their enzyme inhibition strength.

Interaction of drugs demonstrating blood flow-dependent clearance in metabolism- Changes in hepatic blood flow cause changes in plasma concentration of drugs only when drugs demonstrating blood flow-dependent hepatic clearance are administered intravenously.

Genetic polymorphisms and drug interactions

Differences between drugs metabolized by a single enzyme and multiple enzymes.

Several studies indicate the interaction of oral hypoglycemic drugs with proton pump inhibitors, antihyperlipidemics, antiarrhythmics, antiretroviral drugs and also fruits by mechanism of inhibition or induction of CYP450 enzyme systems. But further studies in humans may be required to confirm the possibility of interaction.

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