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Invitro Tests for Predicting Drug-Drug Interaction

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ABSTRACT

Adverse drug-drug interactions represent a major challenge for the pharmaceutical industry. Recently, in vitro approaches for the evaluation of metabolism-related drug-drug interactions have been developed. These in vitro approaches are found to be useful in the assessment of clinical drug-drug interaction potential of new chemical entities and to aid the understanding of clinically significant drug-drug interactions observed with existing drugs. The general methods for the evaluation of drug-drug interactions using in vitro experimental systems are described and critically reviewed.

Key words: Adverse drug-drug interactions; Metabolism-related drug-drug interactions; *invitro* approach

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INTRODUCTION

Many studies have confirmed poly pharmacy as one of the major risk factors in precipitation of potential drug-drug interactions. The elderly populations are at increased risk because of decreased functioning of the systems, more the number of medications due to co-morbidities, and complicated drug regimens. Medication safety is an important issue for the physician, pharmacist and other health care professionals. As drug therapy becomes more complex and because many patients are being treated with two or more drugs, the ability to predict the magnitude of a specific action of given drug diminishes [1]. An adverse drug interaction is defined as an interaction between two or more co-administered medications that results in the alteration of the effectiveness or toxicity of any of the co- administered medications. Combination therapies are commonly used and this co-administration may increase the risk for significant drug–drug interactions. When two drugs are concomitantly administered through oral route, the dissolution pattern of one drug may affect the dissolution of the other. Changes in the gastric environment, degree of ionization of drug in stomach pH may get altered, which affects the disintegration and dissolution of tablet dosage forms. Also, many drugs acting on central nervous system have narrow therapeutic window and when these drugs are concomitantly administered to patients, drug interaction may occur, resulting in altered therapeutic efficiency. When the combination of migraine prophylaxis drugs and analgesics are administered concurrently through the oral route, due to the changes in gastric environment one drug may alter the absorption of another. This consequently might alter the plasma concentration of the concurrently administered drugs which might alter the therapeutic benefits of the drugs. Hence it is necessary to study the drug interactions *in vitro* and *in vivo*. In order to determine the drug concentrations in the drug interaction study, the development of sensitive and simple analytical and bio-analytical methods is essential.

DRUG-DRUG INTERACTION

We speak of drug interactions when the efficacy or toxicity of a medication is changed by administration of another compound. The latter can be another drug, an environmental pollutant, or an ingredient or additive present in the diet. As more drugs become available and are used concomitantly, the potential for drug

interactions increases. Recently, newly marketed drugs have been withdrawn from the market because of unacceptable interaction profiles. Drug interactions in patients receiving multiple-drug regimens are a constant concern for the clinician. According to certain sources, drug-drug interactions could be responsible for a hundred thousand deaths each year among patients. This, however, is very hard to objective, since official death statistics seldom identify and clearly document fatal outcomes that may be related to drug interactions. Understanding and anticipating drug interactions is a necessary part of rational therapeutics. The clinical importance of any drug interaction depends on several factors, including the condition of the patient, the drugs administered, the route of administration, the environment, the therapeutic index, the timing of administration of two or several drugs etc. This leads to considerable inter individual variations [2]

CAUSES OF DRUG-DRUG INTERACTION

- Competition for gastrointestinal absorption.
- Interaction during membrane crossing (blood vessels, hepatic, renal).
- Binding to plasma proteins.
- Binding to transport proteins and p-glycoproteins.
- Pharmaco-dynamic interactions at receptor level.
- Inhibition of metabolism
- Induction of metabolism.
- Competition for active renal excretion

Impairment of drug metabolism due to interactions with another. Compound has obvious clinical implications, including toxicity due to increased bio- availability and de-creased clearance. Oxidative metabolism, particularly oxidation by cytochrome P450 enzymes, is the major elimination route for many drugs. Hence, modification of the activity of these enzymes is one of the main causes of drug interactions. Although other enzymes and namely glucuronyl transferases may be involved in drug-drug interactions (Liston et al. 2001), the present review will focus on drug-drug interactions linked to cytochrome-P450-catalysed reactions.

DETERMINATION OF *INVITRO* DRUG-DRUG INTERACTION

Because drug-drug interactions can cause serious adverse effects, it is important to take them into account during drug development. The interaction potential of any new com-pound must be assessed carefully in the course of development. It is not practicable to conduct formal in vivo studies of all possible drug interactions.

In the past, drug interactions were investigated quite late in the development process, during phase II and III clinical trials, according to the likelihood that two or more drugs would be used concurrently. Predicting the fates and interactions of drugs in man on the basis of animal experiments remains difficult and some-times misleading, notably because of the considerable inter-species differences in drug metabolizing pathways and enzyme activities. With the development of better in vitro models over the last ten years and with our better under-standing of drug metabolism, in vitro systems have become widely used as screening tools and for the study of the mechanisms of drug-drug interactions.The availability of human tissues and recombinant human CYP enzymes has greatly contributed to the development of in vitro screening tools for predicting potential in vivo drug interactions [3].

Drug-drug interactions studies can be performed at different stages of drug development and with different objectives. Since drug interactions are normally considered undesirable in drugs under development, their occurrence must be documented much earlier in the development process, if possible, during the selection phase (Lin 1998). At later stages of development, the aim of drug-drug interactions studies is to predict as accurately as possible the clinical consequences of such interactions. Economically, it is particularly advantageous to eliminate every early during development new drug candidates with a high interaction potential. Therefore, in vitro studies are particularly indicated for rapidly investigating all possible drug interactions of a new drug candidate. Because oxidative metabolism is a major elimination route for many drugs, CYPs are particularly sensitive sites for drug-drug interactions and the principal targets of these studies. Recently, drug regulators have encouraged the use of in-vitro methods in clinical interaction studies. Both the effects of a new drug on pharmacokinetic parameters of other drugs and the effects of common drugs on the new one should be tested (Fuhr et al.1996). Predictive models for in vitro-to-in vivo scaling of pharmacokinetic drug interactions can be constructed from a combination of laboratory and theoretical components. Many of the components are based on well-establish ed principles, while others are hypotheses and assumptions.Usually, a well-balanced link between in vitro and a limited number of in vivo investigations makes it possible to as the potential of a new drug to cause clinically relevant pharmacokinetic drug-drug interactions, but quantitative prediction of in-vivo drug interactions from in vitro data remains quite controversial because of the complex association of factors involved in drug interactions. Numerous technical problems inherent in estimating pharmacokinetic parameters from in vitro studies remain unsolved.

ANALYTICAL CONSIDERATIONS *IN INVITRO* DRUG- DRUG INTERACTION

In vitro drug-drug interaction studies can be performed using both radiolabeled and non- radiolabeled substrates/ test compounds. If non-radiolabeled compounds are used in the experiments, quantitation of metabolite or substrate should be done using standard bio-analytical methods (e.g., LC/MS). Standard assay procedures should include a defined standard curve range, a blank standard to ensure no assay interference by endogenous components of the assay matrix (blanks from multiple individuals should not be necessary), and quality control standards to verify the accuracy and precision of the assay. Special assurance should be provided that the substrate or inhibitor (or its metabolites) does not interfere in the analysis of the substrate metabolite. Long-term storage stability, a hallmark of method validation for analysis of blood or urine samples, is not as necessary for analytical methods designed to measure in vitro samples since it is not common to store such samples for extended periods. However, stability of the analyte, through the length of time and under conditions that in vitro samples are stored and maintained, needs to be ascertained. If authentic standards of metabolites are not available but radiolabeled investigational compound is, a quantitative high-performance liquid chromatography (HPLC)–radiometric approach can be used in the analysis of in vitro reactions. In this approach, recovery of the radiolabel from the incubation should be assessed. Standard curves for metabolite quantitation are not used; rather, quantitation is done based on percentages that each metabolite peak comprises the total radioactivity in the chromatogram. This is the same way by which metabolites are quantitatively assessed in radiolabeled excretion studies. The radio chemicals used must be of high purity and should not interfere with quantification of the metabolites. The lower limit of quantitation will be defined by a lower limit signal to-noise ratio rather than a lower limit defined by a standard curve. Upper limits of quantitation will not be reached if the scientist uses appropriate "as low as reasonably achievable" (ALARA) radiochemical practices [4].

INVITRO DRUG-DRUG INTERACTION THROUGH CYTOCHROME P450 INHIBITOR

In Vitro Test Systems

A majority of drugs are cleared via CYP-mediated metabolism; therefore, the inhibition of CYP enzymes can lead to serious clinical drug interactions. The potential for such interactions is highest when concomitant drugs are metabolized by the same CYP enzyme. In addition, many compounds can also be strong inhibitors of CYP enzymes, which are not directly involved in the clearance of the drug, and could greatly affect the metabolism of co-administered drugs. The information from enzyme inhibition studies is extremely valuable as it could allow extrapolation of the data to other compounds and of drug interactions in organs other than liver (e.g., the intestine), depending on the degree of metabolism by the specific organ. The availability of human liver tissue, cDNA-expressed CYP enzymes, and specific probe substrates have been valuable tools in the assessment of a drug's potential to inhibit different CYP enzymes in vitro. Inhibition of CYP activity by drugs is most frequently examined in human liver microsomal preparations. For inhibition of enzyme selective activities, it is sufficient to use tissue from individual donors as long as the activity for the reaction is sufficiently present. Alternately, recombinant CYPs can be used when a specific enzyme is to be investigated. Microsomes and recombinant CYP enzymes are the preferred test system as they are more readily available than human hepatocytes, and CYP kinetic measurements are not confounded with other metabolic processes or cellular uptake. A disadvantage of microsomes or recombinant enzymes is that they do not represent the true physiological environment (e.g., not all Phase II enzymes are present).

INVITRO DRUG-DRUG INTERACTIONS THROUGH DISSOLUTION TEST

In vitro dissolution is a test used to characterize the dissolution properties of the active drug from a dosage formulation. Drug is administered orally in solid dosage forms, such as tablet or capsules, must dissolve in the contents of the gastrointestinal tract before drug absorption can occur. Therefore, if it is important to achieve high peak blood levels of a drug, it will usually obtain rapid drug dissolution from the dosage form. So, dissolution rate per minute is very important for better absorption and better therapeutic activity. In vitro dissolution may be relevant to the prediction of *in vivo* performance. DDI can determine from the in vitro dissolution studies, the dissolution rate can vary when drug- drug interaction occurred [5].

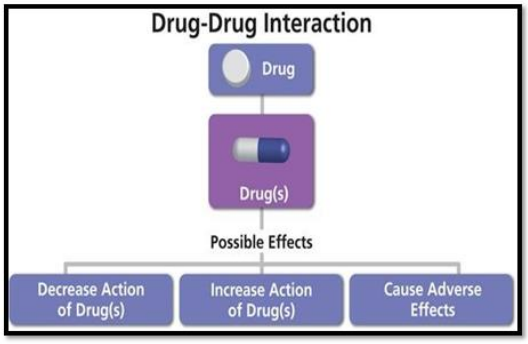

Figure 1: Drug – Drug Interaction

CONCLUSION

This review represents a view of participating cytochromes P450 (CYPs) for the conduct of in vitro drug-drug interaction (DDI) studies. In vitro CYP release and hazard identification assays to evaluate the potential of a biologic drug to cause a DDI. The CYP enzyme has greatly contributed to the development of in vitro screening tools for predicting potential in vivo drug interactions. In vitro dissolution may be relevant to the prediction of in vivo performance. So, DDI can determine from the in vitro dissolution studies, the dissolution rate can vary when drug- drug interaction occurred. This final guidance is intended to help drug developers plan and evaluate studies to determine the DDI potential of an investigational drug product.

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