Comparison of Inhibition of CYP1A2, 2C9 and 3A4 using Human Liver Microsomes and Hepatocytes

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ABSTRACT

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Introduction

Drug-drug interactions (DDIs) are of particular concern for regulatory agencies and the pharmaceutical industry, due to the possibility of serious drug interactions. The plasma levels of a drug may be increased or decreased by the ingestion of other drugs. The pharmacological effects of drugs are often modulated by the liver enzyme system (CYP) and hence, the actions of a particular drug may be altered when it is taken concomitantly with another drug. There are several types of drug-drug interactions that may occur, including competitive inhibition, non-competitive inhibition, and metabolic inhibition. The type of interaction depends on the specific enzymes involved and the mechanisms by which they interact.

Materials and Methods

Inhibitor Solution Preparation: Twelve percent solutions of each inhibitor were prepared in ethanol (100%) before dilution using PBS. The final concentration of each inhibitor was determined using a spectrophotometer.

Data Analysis and Statistic: The IC50 values were calculated using a non-linear regression model with Graphpad Prism 5 (Graphpad.com) by a four-parameter model. The data were analyzed for statistical significance using one-way ANOVA followed by Dunnett’s test for multiple comparisons. The significance level was set at p < 0.05.

Results and Discussion: In the present study, we have investigated the inhibition of CYP1A2, 2C9, and 3A4 using human liver microsomes and hepatocytes. The results showed that the inhibition of CYP1A2, 2C9, and 3A4 was significantly different between microsomal and hepatocytic derived data. Further, a study from Brown denoted direct interplay of transporters and altered Ki which highlights the benefits of using hepatocytes for in vitro DDI studies. The IC50 values of various inhibitory compounds were determined using a luciferase mediated assay system. The results showed that the inhibition of CYP1A2, 2C9, and 3A4 was significantly different between microsomal and hepatocytic derived data. Further, a study from Brown denoted direct interplay of transporters and altered Ki which highlights the benefits of using hepatocytes for in vitro DDI studies.

Conclusions: Overall, the results of this study indicate that the use of hepatocytes is preferred over microsomes for the study of DDIs. Hepatocytes provide a more accurate model for predicting drug interactions and are more representative of the human liver. However, further studies are needed to develop a more comprehensive understanding of the mechanisms underlying DDIs.

References: