RESULTS
DDI = Drug-drug interaction
DILI = Drug induced liver injury
OATP

ABSTRACT

The aim of this study was to develop and optimize an in vitro model for identifying liver specific toxicity.  The test compounds were applied to the culture wells (0, 1, 5, 10, 20 µM) with 5% CO2 for 24 hr.  Cell health was determined by membrane integrity using the MTT assay.  GSH and 8-Isoprostane (pg/ml) were measured using the EnzChek and ISO assays respectively.  Inhibition of UGT1A and BSEP were determined in a cell-free system.  Analysis of the data obtained demonstrates that unique biochemical profiles indicative of risk for liver toxicity can be identified for the drugs associated with adverse effects.  This model is capable of identifying drugs that may cause liver toxicity in humans.  When comparing the liver to the other organs, the primary hepatocytes in sandwich culture provide a more relevant model for assessing organ specific toxicity and are the best tissue culture model.  In conclusion, the LST panel described provides an excellent method for assessing risk for liver specific toxicity.

cell-specific toxicity.  The potential for drug-drug interactions (DDI) is a significant issue in clinical practice.  A number of factors contribute to this problem, including co-administration of drugs, drug metabolism, and drug transport.  The development of non-clinical models that can predict organ specific toxicity is a critical need.  However, these models must be carefully designed in order to define more subtle toxicity that may not be detected in animal safety studies.  Many times this post market toxicity is labeled as idiosyncratic and can result in the withdrawal of promising new drugs.  Therefore, it is critical that non-clinical benchmark toxicity procedures with high throughput and predictive value o

INTRODUCTION

Most early drug discovery efforts incorporate in vivo studies to identify and validate the risk of a new drug entity causing liver toxicity in preclinical safety studies.  In vitro approaches can rapidly identify severe chemical toxicity, however, these procedures do not provide a mechanism-based toxicology assessment or a means to determine the safety of a drug in the human population.  Presently, the only in vivo study that is labeled as hepatotoxic and can result in the withdrawal of promising new drugs.  Therefore, it is critical that non-clinical benchmark toxicity procedures with high throughput and predictive value o

METHODS

Cell Culture

Primary hepatocytes in sandwich culture were obtained from rat, dog, monkey, or human.  The test compounds were applied to the culture wells (0, 1, 5, 10, 20 µM) with 5% CO2 for 24 hr.  Cell health was determined by membrane integrity using the MTT assay.  GSH and 8-Isoprostane (pg/ml) were measured using the EnzChek and ISO assays respectively.  Inhibition of UGT1A and BSEP were determined in a cell-free system.  Analysis of the data obtained demonstrates that unique biochemical profiles indicative of risk for liver toxicity can be identified for the drugs associated with adverse effects.  This model is capable of identifying drugs that may cause liver toxicity in humans.  When comparing the liver to the other organs, the primary hepatocytes in sandwich culture provide a more relevant model for assessing organ specific toxicity and are the best tissue culture model.  In conclusion, the LST panel described provides an excellent method for assessing risk for liver specific toxicity.

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Summary

Safer Drugs

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