Agent-Directed Tracing of Multi-Scale Drug Disposition Events within Normal and Diseased In Silico Livers

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ABSTRACT

Cirrhosis, a chronic liver disease, alters hepatic drug disposition; however, little is known about micro-mechanisms underpinning disease progression and how they contribute to changes in liver disposition properties. In this article, the authors present multilevel, agent-based and agent-directed In Silico Livers (ISLs) to probe plausible micro-mechanistic details for a cationic drug, diltiazem, in two different types of cirrhotic rat livers. Starting with ISLs that validated against diltiazem disposition data from normal livers, the authors systematically transformed ISL characteristics to achieve validation against perfusion outflow profiles from the two types of diseased livers. In this regard, the authors developed and implemented multilevel methods to trace each object representing diltiazem during simulated perfusion experiments. This enabled gaining heretofore-unavailable insight into plausible micro-mechanistic details from diltiazem’s perspective in normal and diseased livers. The authors posit that the presented ISL micro-mechanistic details may have disease caused counterparts during disposition.

Keywords: Cirrhosis, Drug Disposition, In Silico Liver, Multi-Scale Tracing, Simulation Experiment

INTRODUCTION

Cirrhosis includes chronic, advanced fibrosis (scarring) of liver, a major site of drug metabolism and clearance. It results from the perpetuation of the normal wound healing response and subsequent distortion of hepatic histoarchitecture. The disease complicates drug therapy management because it alters hepatic drug disposition, which, in turn, alters pharmacokinetic (PK) and/or pharmacodynamic characteristics. The nature of that alteration is dependent on the nature and the extent of disease. With some exceptions (Hung et al.,

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2002), little is known about exactly how the cirrhotic changes affect hepatic drug disposition. Improved, mechanistic insight is needed to enable rational drug therapy based on clinical measures of both type and extent of liver disease.

We have used a new strategy to achieve improved insight. It involves developing and experimenting on multi-scale In Silico Livers (ISLs) (Park, Ropella, Kim, Roberts, & Hunt, 2009). Key ISL and support components were represented as independent, interacting agents. In silico experiments were conducted using an automated, high-performance software environment capable of parallel computation. We started with ISLs that validated for drug and sucrose disposition profiles of normal rat livers in situ (Yan, Ropella, Park, Roberts, & Hunt, 2008). The models were then subjected to cycles of experimentation and iterative refinement to achieve simulated drug disposition profiles that were acceptably similar to those from two different types of diseased livers (Hung et al., 2002). The diseased ISLs were created independently: for each type, an increasing number of normal ISL characteristics were altered systematically until simulated drug disposition profiles were experimentally indistinguishable from the referent profiles.

Having achieved a degree of validation, we posit that the causative, mechanistic details occurring during ISL execution may have hepatic counterparts during disposition, as diagrammed in Figure 1. Differences in micro-mechanistic details between the normal and the two “diseased” ISLs are hypotheses about corresponding differences between the normal and diseased livers, and about differences between diseased livers. Achieving a degree of profile similarity is evidence supporting those hypotheses. The differences in dynamic, multilevel details during execution of the two diseased ISLs provide a plausible, physiologically based explanation of the disease-caused differences in hepatic drug disposition. With additional rounds of refinement and validation, future ISLs are expected to provide increasingly useful scientific predictions and deeper insight into mechanistic details of disease progression and its role in hepatic PK.

**BIOLOGY**

**Liver and Cirrhosis**

Liver is the largest glandular organ (~1.5 kg; human), which plays a central role in drug metabolism and clearance (Arias et al., 2009). Cells composing the liver are organized into roughly hexagonal units called lobules. Hepatocytes occupy the majority of lobular volume. Each lobule is organized around a central vein that drains blood into the hepatic vein. Along its periphery, a lobule is associated with hepatic portal vein and artery networks that deliver incoming blood. Vessels, lined by endothelial cells, branch among the hepatocytes, forming sinusoids into which the blood flows.

Cirrhosis distorts hepatic tissue architecture and vasculature (Schiff, Sorrell, & Maddrey, 2003). Loss of endothelial fenestrations and filling of the space of Disse, a permeable connective tissue interface between endothelia and hepatocytes, can be observed as disease progresses. Various factors such as chronic alcoholism and hepatitis contribute to cirrhotic development. Major clinical consequences include impaired hepatocyte (liver) function, alterations in drug disposition, and circulatory abnormalities. Currently available therapeutic treatments primarily focus on reducing complications and preventing further degeneration.

**In Situ Liver Perfusion**

The original single-pass perfusion experiments are summarized in Figure 2; full details are provided in (Hung et al., 2002). Normal livers and two types of cirrhotic liver were studied. Both diseased types followed a similar pretreatment protocol to induce cirrhotic changes: one was produced by chronic carbon tetrachloride (CCl₄) treatment; the other was by chronic alcohol (ethanol) treatment. Both treatments induced hepatic injury, but their histologies were different. Chronic CCl₄ treatment produced acute hepatocellular injury with centrilobular necrosis and stenosis, whereas alcohol treatment resulted in hepatocellular injury with inflam-
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