An Updated Review on Drug-Induced Cholestasis: Mechanisms and Investigation of Physicochemical Properties and Pharmacokinetic Parameters

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ABSTRACT: Drug-induced cholestasis is an important form of acquired liver disease and is associated with significant morbidity and mortality. Bile acids are key signaling molecules, but they can exert toxic responses when they accumulate in hepatocytes. This review focuses on the physiological mechanisms of drug-induced cholestasis associated with altered bile acid homeostasis due to direct (e.g., bile acid transporter inhibition) or indirect (e.g., activation of nuclear receptors, altered function/expression of bile acid transporters) processes. Mechanistic information about the effects of a drug on bile acid homeostasis is important when evaluating the cholestatic potential of a compound, but experimental data often are not available. The relationship between physicochemical properties, pharmacokinetic parameters, and inhibition of the bile salt export pump among 77 cholestatic drugs with different pathophysiological mechanisms of cholestasis (i.e., impaired formation of bile vs. physical obstruction of bile flow) was investigated. The utility of *in silico* models to obtain mechanistic information about the impact of compounds on bile acid homeostasis to aid in predicting the cholestatic potential of drugs is highlighted. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3037–3057, 2013

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INTRODUCTION

The liver is the major organ responsible for the metabolism and excretion of endogenous and exogenous compounds, including drugs. The liver is predisposed to drug toxicity because of its anatomical location and the expression of uptake transporters that facilitate accumulation of drugs in hepatocytes. Drug-induced liver injury (DILI) is the most common cause of acute liver failure,[1] and is one of the primary reasons for the failure of pharmaceutical agents during drug development. Unfortunately, current *in vitro* screening approaches or *in vivo* preclinical studies do not adequately predict the likelihood of DILI. Even Phase III clinical trials that involve a few thousand patients often fail to detect DILI. In some cases, instances of severe liver injury and death only were observed after drug approval and administration to tens or hundreds of thousands of patients. These unexpected findings led to blackbox warnings, or in severe cases, withdrawal of the drug from the market. Recent examples include troglitazone and bromfenac (withdrawn), and bosentan and diclofenac (blackbox warnings).

DILI is classified into hepatocellular, mixed, or cholestatic injury based on the major underlying mechanism.[2] Among 784 DILI cases reviewed by the Swedish adverse drug reactions advisory committee between 1970 and 2004, almost one-half of the cases had either cholestatic or mixed cholestatic hepatic toxicity.[3] Acute cholestatic injury comprised approximately 16% of all hepatic adverse drug reactions in a

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Danish study of 1100 DILI cases from 1978 to 1987.[4] In the United States, drugs were responsible for approximately 20% of cases of jaundice in the elderly population.[5] However, reported reactions are thought to be only a small fraction of all the instances of drug-related cholestasis in the community because drug-induced cholestasis can present with asymptomatic disease where the only clinical manifestation is an elevation in liver enzymes, which often is not detected or reported. Therefore, the actual number of cases and medical costs associated with drug-induced cholestasis could exceed what has either been reported or estimated. In the present paper, the clinical presentation and mechanisms of bile acid-mediated drug-induced cholestasis are reviewed. In addition, we investigated whether the physicochemical properties or pharmacokinetic parameters of selected drugs, or the ability of these compounds to inhibit BSEP, influence the type of cholestatic liver injury (impaired bile formation vs. obstruction of bile flow). Furthermore, existing *in silico* models developed to predict drug effects on bile acid transporters and nuclear receptors that are involved in bile acid homeostasis are reviewed.

CLINICAL FEATURES OF DRUG-INDUCED CHOLESTASIS

Diagnosis

Biochemical tests (liver function tests) typically are used to define drug-induced cholestasis. The Council of International Organizations of Medical Sciences defines cholestatic injury as an elevation of serum alkaline phosphatase (AP) to greater than 2× the upper limit of normal (ULN) combined with a major elevation of γ-glutamyl transpeptiase (GGT) in the presence of a normal alanine transaminase (ALT) value. Alternatively, cholestasis is thought to be present when there is an increase in both ALT and AP, but with an ALT/AP ratio of < 2. In severe cases of cholestasis, an increase in serum-conjugated bilirubin also is observed. Mixed hepatocellular/cholestatic injury is defined as an ALT/AP ratio of 2–5, whereas hepatocellular injury is defined as ALT $> 2\times$ ULN or ALT/AP ≥ 5.[6] An accurate diagnosis of DILI also requires careful causality assessment, interpretation of clinical features, and laboratory tests including liver biopsy findings, if available, and the exclusion of other potential causes for liver injury.

Clinical Presentation

Drug-induced cholestasis may present as an acute illness that promptly diminishes after withdrawal of the offending drug. Drug-induced cholestasis may present with or without jaundice, and symptoms may occur weeks or months after the start of treatment. Nonspecific symptoms such as nausea, malaise, anorexia, and fatigue may be elicited due to parenchymal liver injury. For some drugs (e.g., amoxicillin-clavulanate, erythromycin), abdominal pain or discomfort has been reported.[7] Chronic drug-induced cholestasis can result in the development of xanthomas, pruritus, and melanoderma. Symptoms often resolve following withdrawal of the offending drug, but in some cases, if there is significant loss of the interlobular bile ducts, chronic liver disease may develop and even progress to liver failure.[8] Rarely, drugs can induce cholelithiasis (gall stones) or mimic large duct sclerosing cholangitis, resulting in extrahepatic obstruction.[9] Drug-induced cholestasis can be classified into the following categories.

Acute Drug-Induced Cholestasis without Hepatitis (Bland Cholestasis)

This is a rare type of drug-induced cholestasis that typically is produced by estrogens or anabolic steroids, and manifests histologically as pure canalicular cholestasis. Bland cholestasis causes abnormal biliary secretions without hepatocellular damage.

Acute Drug-Induced Cholestasis with Hepatitis (Cholestatic Hepatitis)

This type of drug-induced cholestasis is associated with concomitant hepatic parenchymal damage. Cholestatic hepatitis is characterized by portal inflammation and varying degrees of hepatocyte injury and necrosis.

Acute Drug-Induced Cholestasis with Bile Duct Injury

This type of drug-induced cholestasis involves bile duct injury (ductular, cholangiolar, or cholangiolytic) but minimal parenchymal liver cell injury.

Chronic Drug-Induced Cholangiopathies

These drug-induced cholestatic disorders vary from mild, nonspecific bile duct injury (mild elevation in AP or GGT) to vanishing bile duct syndrome (VBDS), sclerosing cholangitis, and cholelithiasis.[10]

PHYSIOLOGY OF BILE ACID HOMEOSTASIS

Cholestasis may occur if there is impaired formation of bile or if there is a physical obstruction to the flow of bile after it has been secreted from hepatocytes. To understand the pathogenesis of cholestasis, it is important to understand the physiological principles involved in bile flow.

Synthesis and Conjugation

Primary bile acids are synthesized from cholesterol in hepatocytes. Approximately 16 enzymes are involved in this process; the rate-limiting step is 7α-hydroxylation by Cytochrome P450 7A1