Preface: Drug-induced Hepatotoxicity...A Topic Where We Don’t Know Enough!  xiii
Vinod K. Rustgi

Drug Metabolism in the Liver  1
Omar Abdulhameed Almazroo, Mohammad Kowser Miah, and Raman Venkataramanan

Metabolism is a biotransformation process, where endogenous and exogenous compounds are converted to more polar products to facilitate their elimination from the body. The process of metabolism is divided into 3 phases. Phase I metabolism involves functionalization reactions. Phase II drug metabolism is a conjugation reaction. Phase III refers to transporter-mediated elimination of drug and/or metabolites from body normally via liver, gut, kidney, or lung. This review presents basic information on drug-metabolizing enzymes and potential factors that might affect the metabolic capacities of the enzyme or alter drug response or drug-mediated toxicities.

Drug-Induced Liver Disease: Clinical Course  21
Hemamala Saithanyamurthi and Alison Jazwinski Faust

Drug-induced liver injury (DILI) is a term used to describe a spectrum of clinical presentations and severity that ranges from mild elevation of liver enzymes on routine blood work to acute liver failure and death. Approximately 10% of all patients with DILI develop acute liver failure resulting in death or liver transplantation. DILI may be prolonged with persistence of elevated liver enzymes for longer than 6 months in approximately 5% to 20% of cases. Cirrhosis and long-term liver-related morbidity and mortality have also been described but are rare, occurring in 1% to 3% of cases.

Mechanisms of Drug-Induced Hepatotoxicity  35
Amina Ibrahim Shehu, Xiaochao Ma, and Raman Venkataramanan

Drug-induced hepatotoxicity (DIH) is a significant cause of acute liver failure and liver transplantation. Diagnosis is challenging due to the idiosyncratic nature, its presentation in the form of other liver disease, and the lack of a definite diagnostic criteria. Generation of reactive metabolites, oxidative stress, and mitochondrial dysfunction are common mechanisms involved in DIH. Certain risk factors associated with a drug and within an individual further predispose patients to DIH.

Epidemiology and Genetic Risk Factors of Drug Hepatotoxicity  55
Jawad Ahmad and Joseph A. Odin

Idiosyncratic drug-induced liver injury (DILI) from prescription medications and herbal and dietary supplements has an annual incidence rate of
approximately 20 cases per 100,000 per year. However, the risk of DILI varies greatly according to the drug. In the United States and Europe, antimicrobials are the commonest implicated agents, with amoxicillin/clavulanate the most common, whereas in Asian countries, herbal and dietary supplements predominate. Genetic analysis of DILI is currently limited, but multiple polymorphisms of human leukocyte antigen genes and genes involved in drug metabolism and transport have been identified as risk factors for DILI.

Adverse Drug Reactions: Type A (Intrinsic) or Type B (Idiosyncratic) 73
Carlo J. Iasella, Heather J. Johnson, and Michael A. Dunn

Hepatotoxic adverse drug reactions are associated with significant morbidity and mortality and are the leading cause of postmarketing regulatory action in the United States. They are classified as Type A (intrinsic) or Type B (idiosyncratic). Type A are predictable, dose-related toxicities, often identified in preclinical or clinical trials, and usually occur in overdose settings or with pre-existing hepatic impairment. Type B are not clearly related to increasing dose and are associated with drug-specific and patient-specific characteristics and environmental risks. Rare Type B reactions are often identified postmarketing. Identification and management, including electronic resources, has evolved.

Phenotypes and Pathology of Drug-Induced Liver Disease 89
Zachary D. Goodman

Drug hepatotoxicity can simulate nearly any clinical syndrome or pathologic lesion that may occur in the liver, so clinical and histopathologic diagnosis of drug-induced liver injury may be difficult. Nevertheless, most drugs that are known to idiosyncratic liver injury tend to cause patterns of injury that produce characteristic phenotypes. Recognition of these patterns or phenotypes in liver biopsy material is helpful in evaluation of clinical cases of suspected drug-induced liver injury.

Drug Hepatotoxicity: Environmental Factors 103
Jonathan G. Stine and Naga P. Chalasani

Drug-induced liver injury presents as various forms of acute and chronic liver disease. There is wide geographic variation in the most commonly implicated agents. Smoking can induce cytochrome P450 enzymes but this does not necessarily translate into clinically relevant drug-induced liver injury. Excessive alcohol consumption is a clear risk factor for intrinsic hepatotoxicity from acetaminophen and may predispose to injury from antituberculosis medications. Understanding of the role of infection, proinflammatory states, disorders of coagulation, and the hepatic clock in predisposing patients to drug-induced liver injury is evolving. More study focusing specifically on environmental risk factors predisposing patients to drug-induced liver injury is needed.

Drug Hepatotoxicity: Newer Agents 115
Chalermrat Bunchorntavakul and K. Rajender Reddy

Idiosyncratic hepatotoxicity is one of the most common reasons for an approved drug being restricted. This article focuses on hepatotoxicity of
selected and recently introduced agents, such as, tyrosine kinase inhibitors, monoclonal antibodies, novel oral anticoagulants, newer antiplatelets, antibiotics, anti-diabetics, anti-epileptics, anti-depressants, anti-psychotics and anti-retrovirals. Overall, the incidence of clinically relevant hepatotoxicity from newer agents seems to be lower than that of the older agents. Nevertheless, cases of severe hepatotoxicity have been reported due to some of these newer agents, including, trastuzumab, ipilimumab, infliximab, imatinib, bosutinib, dasatinib, gefitinib, erlotinib, sunitinib, ponatinib, lapatinib, vemurafenib, dabigatran, rivaroxaban, felbamate, lamotrigine, levetiracetam, venlafaxine, duloxetine, darunavir, and maraviroc.

Herbal and Dietary Supplement–Induced Liver Injury

Ynto S. de Boer and Averell H. Sherker

The increase in the use of herbal and dietary supplements (HDSs) over the last decades has been accompanied by an increase in the reports of HDS-associated hepatotoxicity. The spectrum of HDS-induced liver injury is diverse and the outcome may vary from transient liver test increases to fulminant hepatic failure resulting in death or requiring liver transplant. There are no validated standardized tools to establish the diagnosis, but some HDS products have a typical clinical signature that may help to identify HDS-induced liver injury.

Drug-Induced Acute Liver Failure

Shahid Habib and Obaid S. Shaikh

Drug-induced acute liver failure (ALF) disproportionately affects women and nonwhites. It is most frequently caused by antimicrobials and to a lesser extent by complementary and alternative medications, antiepileptics, antimetabolites, nonsteroidals, and statins. Most drug-induced liver injury ALF patients have hepatocellular injury pattern. Cerebral edema and intracranial hypertension are the most serious complications of ALF. Other complications include coagulopathy, sepsis, metabolic derangements, and renal, circulatory, and respiratory dysfunction. Although advances in intensive care have improved outcome, ALF has significant mortality without liver transplantation. Liver-assist devices may provide a bridge to transplant or to spontaneous recovery.

Management of Acute Hepatotoxicity Including Medical Agents and Liver Support Systems

Humberto C. Gonzalez, Syed-Mohammed Jafri, and Stuart C. Gordon

Drug-induced liver injury (DILI) can be predictable or idiosyncratic and has an estimated incidence of approximately 20 cases per 100,000 persons per year. DILI is a common cause of acute liver failure in the United States. No accurate tests for diagnosing DILI exist, and its diagnosis is based on exclusion of other conditions. Managing DILI includes discontinuing the suspected causative agent and in selected cases administering an antidote. Liver support systems are used for long-term support or as a bridge to transplantation and are effective for improving encephalopathy, hyperbilirubinemia, and other liver-related conditions, but whether they improve survival remains uncertain.
Drug Metabolism, Drug Interactions, and Drug-Induced Liver Injury in Living Donor Liver Transplant Patients
Swaytha Ganesh, Omar Abdulhameed Almazroo, Amit Tevar, Abhinav Humar, and Raman Venkataramanan

Living donor liver transplant (LDLT) fills a critically needed gap in the number of livers available for transplant. However, little is known about the functional recovery of the liver in the donor and in the recipient after surgery. Given that both donor and recipients are treated with several drugs, it is important to characterize the time course of recovery of hepatic synthetic, metabolic, and excretory function in these patients. In the absence of data from LDLT, information on the effect of liver disease on the pharmacokinetics of medications can be used as guidance for drug dosing in LDLT patients.

Evolution of Experimental Models of the Liver to Predict Human Drug Hepatotoxicity and Efficacy
Lawrence A. Vernetti, Andreas Vogt, Albert Gough, and D. Lansing Taylor

In this article, we review the past applications of in vitro models in identifying human hepatotoxins and then focus on the use of multiscale experimental models in drug development, including the use of zebrafish and human cell-based, 3-dimensional, microfluidic systems of liver functions as key components in applying Quantitative Systems Pharmacology (QSP). We have implemented QSP as a platform to improve the rate of success in the process of drug discovery and development of therapeutics.