Hepatotoxicity of Antibacterials: Pathomechanisms and Clinical Data

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Abstract

Drug-induced hepatotoxicity is a frequent cause of liver disease and acute liver failure, particularly in patients treated with multiple drugs. Several antibacterial drugs have the potential to cause severe liver injury and failure. This article aims to increase the awareness and understanding of drug-induced liver injury (DILI) due to antibacterial drugs. It reviews the pattern of antibacterial DILI and provides details on molecular mechanisms and toxicogenomics, as well as clinical data based on epidemiology studies. Certain antibacterial drugs are more frequently linked to hepatotoxicity than others. Therefore, the hepatotoxic potential of tetracyclines, sulfonamides, tuberculostatic agents, macrolides, quinolones, and beta-lactams are discussed in more detail. Efforts to improve the early detection of DILI and the acquisition of high-quality epidemiological data are pivotal for increased patient safety.

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Introduction and Pathogenesis

Recent warnings concerning the hepatotoxic effects of quinolones drew attention to the hepatotoxicity of antibacterial drugs in general. The European Medicines Agency (EMEA) identified a need for non-clinical guidance on drug-induced liver injury (DILI) following the critical assessment of cases of hepatotoxicity that led to post-market withdrawal of approved drugs [1]. In contrast to nephrotoxicity, the potential hepatic side effects of antibacterial drugs are underestimated. Although the hepatotoxic potential varies widely, it concerns a very wide range of substances and substance groups and deserves greater attention by physicians to avoid deleterious effects on patients.

Due to the high rate of exposure, antibacterial agents are a frequent cause of DILI [2]. According to unpublished data from the Department of Hepatology at the University Hospital Graz (1997–2007), antibacterial drugs are the most common medication-based reason for liver biopsies (Zollner G, personal communication). Table 1 shows the spectrum of potential liver damage caused by medication.

In terms of pathogenesis, two forms of hepatotoxicity are distinguished: intrinsic and idiosyncratic [3]. Intrinsic hepatotoxicity (such as that caused by paracetamol) is dose-dependent and predictable to a certain degree [4]. The idiosyncratic form is not dose-dependent, unpredictable, and frequently requires a number of co-factors (such as gene polymorphisms of detoxification enzymes, human leukocyte antigen (HLA) association, simultaneous administration of other drugs) to develop. The idiosyncratic form can be further classified as a metabolic and an immunoallergic type [4, 5].

Antibacterial drugs and other substances can either stimulate (such as rifampicin, anti-epileptic agents, or alcohol) or inhibit (such as macrolides, anti-mycotic agents, or protease inhibitors) phase-I enzymes (cytochrome P450) of hepatic detoxification [6]. Both processes may lead to the accumulation of toxic metabolites which may induce direct metabolic or immunological liver damage. An example would be treatment with isoniazid [7, 8]. In 10–20% of the treated patients, an initial asymptomatic increase of ALT occurs. This increase is due to the fact that, in addition to the formation of a nontoxic metabolite, a small amount of the isoniazid is transformed into a toxic metabolite. In most cases, further treatment leads to metabolic adaptation and normalization of the liver parameters. In approximately 1% of patients, however, the production of the toxic metabolite rises further – for example, enhanced by CYP450 inductors such as rifampicin – and leads to hepatitis [8]. The molecular mechanisms of liver toxicity are listed in Table 2 [9, 10].

Antibacterial drugs may not only affect hepatocytes, but also cholangiocytes, which may present as non-inflammatory (e.g., due to fusidic acid) or inflammatory

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Table 1
Potential liver injury due to medications.

Pathology
Unspecific increase in alanine aminotransferase (ALT) and gamma-glutamyltransferase (gamma-GT)
Hepatitis
Cholestasis
Steatosis, non-alcoholic steatohepatitis (NASH)
Granulomas

cholestasis (e.g., by flucloxacillin, erythromycin, amoxicillin/clavulanic acid). Mechanisms inducing cholestasis may affect hepatocytes and the small or the large bile ducts [11, 12].

Classification and Definitions

As previously shown by the example of isoniazid, increased transaminase/gamma GT levels do not always imply liver damage, as they may be part of an adaptive response to a medication. According to the Council for International Organizations of Medical Sciences (CIOMS) classification, it is possible to distinguish between hepatocellular, cholestatic, and mixed DILI (Table 3) by the transaminase pattern.

Hepatocellular DILI may be caused by, among other factors, isoniazid, ketoconazole, pyrazinamide, rifampicin, tetracyclines, and trovafloxacin. Mixed DILI may be caused by clindamycin, nitrofurantoin, sulfonamides, and trimethoprim/sulfamethoxazole, while amoxicillin/clavulanic acid, erythromycin, and terbinafine may be reasons for cholestatic DILI [13] (Table 4).

The so-called Hy's rule for hepatocellular DILI is named after the pathologist Hyman Zimmermann and is also used by the Food and Drug Administration (FDA) [4]. It predicts mortality to be > 10% in patients if the combination of hepatocellular liver damage and jaundice occur in DILI in the absence of a bile duct obstruction. DILI is defined here as a simultaneous increase in ALT to more than threefold the upper limit of normal (ULN) and bilirubin to more than twofold the upper limit of normal [4].

A large review by Lee in 2003 [14] showed that DILI is responsible for more than 50% of all acute liver failures in the USA. Idiosyncratic reactions occur at a rate of between 1:1,000 and 1:100,000, usually with a latency of 5–90 days, and lead to liver transplantation or death in 75% of cases. The crucial measure is to immediately discontinue the medication.

Intrinsic, dose-dependent toxicities, on the other hand, are caused in a large percentage of cases by paracetamol. Women are affected by DILI much more frequently than men (73% of idiosyncratic reactions and 79% of paracetamol intoxications occur in women). It should also be noted that more than half of paracetamol intoxications are not due to suicidal intention [15].

In contrast, the most common causes of idiosyncratic DILI are antibacterial drugs (particularly tuberculostatic agents) and non-steroidal anti-inflammatory drugs (NSAIDs). However, medications with an idiosyncratic potential may frequently cause only mild and harmless increases in transaminases; about 15% of these extend beyond the threefold ULN.

All DILI patients with bilirubin levels beyond twofold the ULN between 1970 and 2004 were documented in a Swedish register [16]. It was found that mortality was highest for hepatocellular DILI at 12.7%, followed by 7.8% for cholestatic and 2.4% for mixed DILI. Predictors of lethality for hepatocellular DILI were age as well as the levels of ALT and bilirubin, while for the other two forms, only bilirubin levels were of predictive value.

Interestingly, in 300 patients enrolled in a prospective study of DILI in the United States starting in 2003 [17], death from cholestatic injury was more common than death from hepatocellular injury. However, in two large corresponding series from Europe (Spain [18] and Sweden [16]), hepatocellular fatality was more predominant. The proportion of antibacterials contributing to DILI was different in these studies, with the highest rate in the US. Although direct comparison is not possible due to different designs (prospective in the US and retrospective in EU), it seems that antibacterials lead to a greater risk of cholestatic injury-associated fatality. However, most of

Table 2
Molecular mechanisms of hepatotoxicity.

Mechanism	Effect
Binding of medications to intracellular proteins	Disordered enzyme function Reduced protein synthesis Adenosine triphosphate (ATP) degradation Disorder of the cytoskeleton, cell rupture
Mitochondrial damage	Disturbed fatty acid oxidation → steatosis
Medication/protein compound	Neoantigens: antibodies, T cell immune response
Apoptosis	Cell death
Disturbance of transport mechanisms	Disturbed bile secretion
Damage to cholangiocytes	Cholestasis, vanishing bile duct syndrome (VBDS)
Activation of stellate cells	→ fibrosis