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Hepatic safety of antibiotics used in primary care

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Antibiotics used by general practitioners frequently appear in adverse-event reports of drug-induced hepatotoxicity. Most cases are idiosyncratic (the adverse reaction cannot be predicted from the drug's pharmacological profile or from pre-clinical toxicology tests) and occur via an immunological reaction or in response to the presence of hepatotoxic metabolites. With the exception of trovafloxacin and telithromycin (now severely restricted), hepatotoxicity crude incidence remains globally low but variable. Thus, amoxicillin/clavulanate and co-trimoxazole, as well as flucloxacillin, cause hepatotoxic reactions at rates that make them visible in general practice (cases are often isolated, may have a delayed onset, sometimes appear only after cessation of therapy and can produce an array of hepatic lesions that mirror hepatobiliary disease, making causality often difficult to establish). Conversely, hepatotoxic reactions related to macrolides, tetracyclines and fluoroquinolones (in that order, from high to low) are much rarer, and are identifiable only through large-scale studies or worldwide pharmacovigilance reporting. For antibiotics specifically used for tuberculosis, adverse effects range from asymptomatic increases in liver enzymes to acute hepatitis and fulminant hepatic failure. Yet, it is difficult to single out individual drugs, as treatment always entails associations. Patients at risk are mainly those with previous experience of hepatotoxic reaction to antibiotics, the aged or those with impaired hepatic function in the absence of close monitoring, making it important to carefully balance potential risks with expected benefits in primary care. Pharmacogenetic testing using the new genome-wide association studies approach holds promise for better understanding the mechanism(s) underlying hepatotoxicity.

Keywords: idiosyncratic, adverse event, clavulanic acid, co-trimoxazole, flucloxacillin

Introduction

Antibiotics are considered as a common cause of drug-induced liver injury (DILI).[1–3] Although the frequency of serious antibiotic-induced hepatotoxicity is low compared with the amounts prescribed each year—population-based estimates suggest that it occurs in <5 per 100 000 population[4]—it remains a main reason for antibiotic withdrawal after product launch. Antibiotic-induced hepatotoxicity is usually asymptomatic, transient and associated with only mild hepatic impairment.[5] In rare cases, however, significant morbidity,[6,7] the need for liver transplantation[7,8] and death from acute liver failure[7–9] have been reported. In recent years, the European Medicines Agency (EMA) and the US FDA have addressed these issues by putting emphasis on both pre-clinical (to detect signals) and clinical studies.[10] Nonetheless, predicting what hepatotoxicity will be after approval based on data assembled during drug development remains a risky exercise.

Public awareness of antibiotic-induced hepatotoxicity has, however, increased over recent years (following actions of regulatory bodies targeting specific antibiotics),[11,12] making it essential for the primary care physician to better identify and minimize the risk of serious liver damage with existing agents.[2,5] In the present review, we describe the adverse hepatic effects of antibiotics, including their frequency, severity and clinicopathological features, and discuss these observations within the context of the primary care setting. Indeed, this is not only where antibiotic consumption is greatest[13–15] but also where risks are highest, given the inherent difficulties of rapid access to in-depth biological investigations for prompt diagnosis. As a source of information, we first searched electronically the online version of the US National Library of Medicine (Bethesda, MD, USA; http://www.pubmed.com) for original research papers, case reports and reviews published until the end of February 2011. For antibiotics used primarily for non-tuberculosis

indications, the search terms were 'hepatic adverse event OR hepatotoxicity AND <each of the following terms>': 'beta-lactam*'; 'macrolid*'; '(sulfonamide OR sulphonamide)'; 'tetracyclin*'; 'fluoroquinolon*'; 'amoxycillin*'; 'clavulanic'; 'telithromycin'; 'clarithromycin'; 'azithromycin'; 'erythromycin'; 'levofloxacin'; 'moxifloxacin'; 'gatifloxacin'; and 'trovafloxacin', with restriction to papers dealing with antibiotic-induced hepatotoxicity. For hepatotoxicity related to antibiotics used for the treatment of tuberculosis, the search terms were 'hepatotoxicity AND <each of the following terms>': 'anti-tuberculosis agents'; 'ethambutol'; 'isoniazid'; 'pyrazinamide'; '(rifampicin OR rifampin)'; and 'streptomycin', with focus on papers published within the last 10 years. Reference lists from review papers were examined for additional relevant articles. Current prescribing information and regulatory documents from both the FDA and the EMA were also systematically retrieved and examined.

Identifying antibiotic-induced liver injury

Signs and symptoms of hepatotoxic reactions

Most cases of antibiotic-induced hepatotoxicity are idiosyncratic (the adverse reaction occurs in a very small proportion of patients, cannot be predicted either from the drug's pharmacology or from pre-clinical toxicology tests and is host dependent).[2,4,16] It is thought to occur either via an immunological reaction, including concomitant liver inflammation associated with viral or bacterial infection of liver or inflammatory disease,[17] in response to hepatotoxic metabolites,[18] or, as more recently suggested, when the drug synergizes with lipopolysaccharide-induced inflammatory cytokine signalling to cause acute hepatocyte death.[17,19] Symptoms are similar to those of other liver diseases, and include jaundice, malaise, abdominal pain, unexplained nausea and anorexia.[2] Because antibiotic-induced hepatotoxicity mimics other liver diseases, diagnosis is necessarily one of elimination and is usually based on a high degree of clinical suspicion following exclusion of competing aetiologies, such as viral hepatitis or biliary disease.[18] Clues suggestive of drug allergy include rash, fever or eosinophilia, duration of exposure of 1–5 weeks and an often rapid response following re-administration of the antibiotic.[2,18,20]

Risk factors and early detection

In cases of suspected liver reactions, it is essential to obtain a detailed drug history that includes awareness of the drug's hepatotoxic potential, the timing of drug administration in relation to the emergence of symptoms, previous administration of the antibiotic in question and concomitant drug use (including alternative or herbal medications).[18,20,21] Antibiotic-induced hepatotoxicity can often be detected early from elevations in serum alanine aminotransferase (ALT) levels,[18] where these exceed twice the upper limit of normal (ULN).[20,22–24] Clinically significant rises in ALT accompanied by jaundice (bilirubin level $\geq 2\times$ULN) suggest a worse prognosis compared with elevated ALT alone,[9] with the combination of hepatocellular injury (ALT $>3\times$ULN) and jaundice (bilirubin $>2\times$ULN) being associated with ~10% mortality (Hy's Law).[7,25] Because of the short-term nature of protocols in clinical trials of antibiotics, these changes may remain unseen for a drug later proven to be hepatotoxic.[26]

Several factors, however, complicate the picture. First, host factors such as age, pre-existing liver disease, concurrent medications and excessive alcohol consumption may all increase susceptibility to drug-induced hepatotoxicity,[20] although the nature of their interaction with antibiotics to increase the risk of hepatotoxicity is uncertain. General practitioners should be aware that while age is often considered a risk factor, children and adolescents may also be affected by the same drugs as adults.[27] Predisposing factors, including the concomitant use of acetaminophen (paracetamol), may affect biochemical tests, while infection, especially sepsis, may cause liver toxicity usually in the form of cholestasis. Second, hepatotoxicity seems often related to the administration of large doses of any drug, with 77% of DILI cases included in the Swedish registry occurring with drugs administered at dosages of >50 mg/day.[28] In the context of antibiotics, this means that the large daily dosages that may be essential today to keep pace with the decreased susceptibility of the main target organisms (e.g. *Streptococcus pneumoniae* versus amoxicillin) will increase the risk in a non-specific fashion, dependent on the local epidemiology and guidelines. Third, initial liver injury, as detected by an increase in transaminases, may be transient despite continued treatment, unless the patient has additional factors that will cause mild toxicity to turn into severe hepatic dysfunction.[29] Fourth, cases of frank liver failures caused by antibiotics, excluding telithromycin and trovafloxacin (see hereunder), remain very rare and their number appears to be balanced with the large use of these drugs on the one hand, and the rate of idiopathic liver failure seen in normal adults (~1 case for 1 million adults/year) on the other hand.[19]

Lastly, the retrospective analysis of DILI cases and drug-causality assessment remains a perilous exercise, because of the inherently subjective nature of this approach and potential observer biases. While instruments have been devised for a more objective approach (the most familiar and comprehensive being the Roussel-Uclaf Causality Assessment Method),[22,23] the results obtained may often fit rather poorly with those of the evaluations made by the regulatory authorities,[30] creating some confusion among professionals as well as the public. In this context, rechallenge, often considered as a 'gold standard' to ascertain causality,[31] seems to us impractical and probably unethical with outpatients, not only because of its inherent dangers, but also because the original infection itself (which cannot be recreated) may be an important component in the onset of the toxic reaction.

Timing and treatment of antibiotic-induced liver injury

The interval between drug administration and the onset of hepatic dysfunction is variable: adverse effects may develop almost immediately, late in the course of prolonged antibiotic treatment or several months after the cessation of therapy.[5,32] This is frequently observed with amoxicillin/clavulanate and tetracycline,[32] and was reported for trovafloxacin,[33] although rapid onset is also seen.[33,34] Cholelithiasis associated with ceftriaxone–calcium precipitates typically occurs only after 9–11 days of treatment.[32] Physicians should therefore alert patients to the warning signs of antibiotic-induced hepatotoxicity and advise them to seek medical attention, even if symptoms appear sometime after completing their treatment.

For all cases of immediate or rapid onset, prompt withdrawal of the suspected antibiotic is indicated.[4,5,35] Most patients will then make a full recovery, but chronic liver injury is not infrequent.[32,35] Thus, antibiotics were the third most common cause of chronic liver damage in a large, long-term, follow-up registry set up in Spain.[35]

Frequency and characteristics of antibiotic-induced hepatotoxicity

Clinical studies are generally underpowered to identify trends in hepatotoxicity, while studies undertaken to assess hepatic signals are often complicated by numerous variables. With few prospective population-based studies, case histories and registries of spontaneous reports of adverse drug reactions are actually the main source of toxicity data.[36] As shown in Figure 1, the incidence and inherent risk of hepatotoxicity varies widely between antibiotics. Table 1 summarizes the classes of antibiotics implicated in hepatotoxic reactions. The clinico-pathological picture can include acute hepatocellular, cholestatic and mixed hepatocellular-cholestatic injury, as well as chronic hepatitis, chronic cholestatic injury, granulomas, and, in the case of intravenous tetracycline, steatosis and steatohepatitis.[4]

In the next sections, we will review what is known about the hepatotoxicity of the main antimicrobials in current clinical use. At the end of each subsection, we will also briefly comment on those antibiotics that were withdrawn because of major hepatotoxic reactions. This may be instructive for a correct assessment of the risks associated with the other molecules in each pharmacological class, and indicate what should be looked for when dealing with drugs that are newly introduced and are therefore less thoroughly investigated.

β-Lactams

Penicillins

Frequency

Liver injury is extremely rare with ampicillin, and rare with benzylpenicillin (penicillin G) and phenoxymethylpenicillin (penicillin V). Amoxicillin has little hepatotoxic potential if administered alone (see hereunder for amoxicillin/clavulanate). Transient increases in ALT have been reported with oxacillin, carbenicillin and ticarcillin.[37] Isolated cases of Stevens–Johnson syndrome and chronic cholestasis[38] as well as recurrent cholestasis after repeated treatment[39] have been described, but these were reversible. In the UK, reported rates of hepatic reactions to amoxicillin vary from 0.1–0.2[5] to 3 per 100 000 prescriptions.[40] Severe reactions include cholestasis[41] and acute liver failure, but cases are rare, and deaths due to acute liver failure have not been reported.[42] The crude incidence of flucloxacillin-associated acute liver injury has been estimated as 1.8 per 100 000 prescriptions, or 2.6 per 100 000 users,[43] and that of flucloxacillin-associated jaundice as 3.6 per 100 000 prescriptions.[44]

Pathology

Hepatotoxicity associated with penicillins is predominantly hepatocellular,[37] although cases of cholestasis with ductopenia have been described.[38,39,41] It may frequently be confused with viral hepatitis.[45] Phenoxymethylpenicillin has been associated with increased serum alkaline phosphatase activity and mild intrahepatic cholestasis,[46] as well as acute hepatitis with elevated ALT.[47] Severe and prolonged cholestasis has been reported with benzylpenicillin,[48] including following treatment with cloxacillin,[49] and with ampicillin in combination with the β-lactamase inhibitor sulbactam, from which recovery took several months.[50] Cholestatic hepatitis is more characteristic of the semi-synthetic penicillinase-resistant oxypenicillins oxacillin, cloxacillin, dicloxacillin and, most notably, flucloxacillin.[4,5] Case reports of severe and prolonged cholestasis with ductopenia[41,51,52] are supported by epidemiological data.[40]

Risk factors

Older patients and those receiving >2 weeks of treatment appear at significantly increased risk of flucloxacillin-associated jaundice.[53] There is also recent evidence to suggest a genetic predisposition to flucloxacillin-associated hepatotoxicity. A genome-wide association study using 866 399 markers in 51 cases of flucloxacillin DILI and 282 controls, which were matched for sex and ancestry, showed an association peak in the major histocompatibility complex (MHC) regions that are part of an extended MHC 57.1 haplotype present in <4% of Europeans.[54]

Amoxicillin/clavulanate

Frequency

Primary care physicians must be aware that the combination of the β-lactamase inhibitor clavulanic acid with amoxicillin

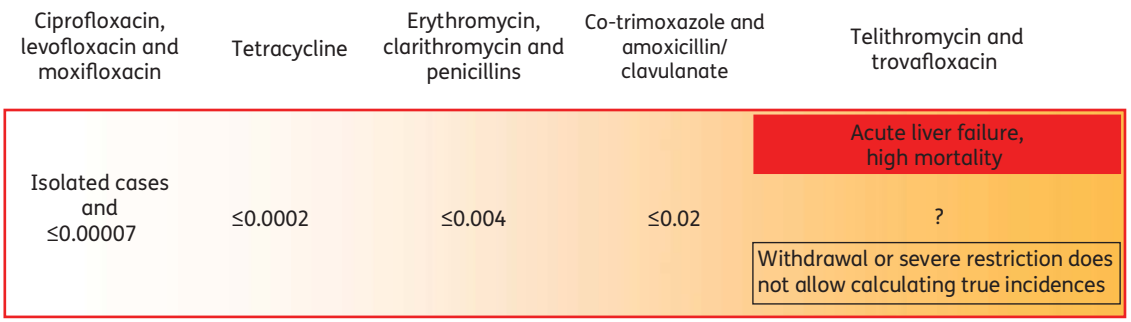

Figure 1. Hepatotoxicity risk of antibiotics (percentage of prescriptions for antibiotics with main indications for use in the community setting). Derived from references 32, 37, 40, 42, 44, 73, 89, 96 and 108. Excluding antibiotics used mainly for the treatment of tuberculosis.

Table 1. Frequency and characteristics of hepatotoxicity induced by antibiotics with indications for infections commonly handled initially by general practitioners and/or used for the treatment of tuberculosis

Antibiotic	Incidence	Liver injury	Onset	Time to recovery	Risk factors	Comments	References
Antibiotics mainly used for non-tuberculosis indications							
β-Lactams							
penicillins	range from 1 per 2 million to 3 per 100000 prescriptions	primarily hepatocellular				severe and fatal reactions extremely rare but have been reported	5,37,40,42
oxypenicillins	1.8 per 100000 prescriptions	primarily cholestatic hepatitis	both early (1–9 weeks) after the start of treatment but also delayed following treatment cessation	within 12 weeks of cessation of therapy but up to 30% patients have protracted course	older age (>55 years), female sex, longer duration of treatment	flucloxacillin most hepatotoxic	5,32,43,51,53
amoxicillin/clavulanate	1–17 per 100000 prescriptions	hepatocellular, cholestatic or mixed hepatocellular-cholestatic hepatitis	within 4 weeks of the start of therapy but typically after drug discontinuation	within 16 weeks of cessation of therapy but some patients have protracted course	older age (>65 years), female sex, prolonged and repeated courses	hepatotoxicity associated with clavulanic acid moiety; although usually benign, fatalities have been reported	32,40,42,43,56,59,61
cephalosporins (ceftriaxone)	up to 25% of adult patients and ~40% of paediatric patients	cholelithiasis from ceftriaxone–calcium precipitate (so-called biliary sludge)	after 9–11 days of treatment	within 2–3 weeks of treatment cessation	paediatric patients, prolonged treatment	may mirror acute cholecystitis	32,210
Macrolides/ketolides							
erythromycin	<4 cases per 100000 prescriptions	cholestatic pattern of injury with evidence of portal and bullous inflammation, eosinophilia and mild hepatocellular necrosis	within 10–20 days of treatment	within 8 weeks of treatment cessation but some patients have protracted course		clarithromycin has similar profile and incidence; prognosis generally good with fatalities extremely rare	32,43,72,73,210
telithromycin	unknown	hepatocellular and canalicular bile cholestasis	within a few days of the start of treatment (median 10 days)	significant numbers of affected patients develop severe liver injury, some of which prove fatal	male sex	no published incidence data but risk of hepatotoxicity estimated 82% greater than with other drugs	88,89,95
Fluoroquinolones							
ciprofloxacin	isolated cases	hepatocellular and cholestatic hepatitis				serious cases including fatalities reported, though very rare	100,102,103,211
levofloxacin	<1 case per 5 million prescriptions	hepatocellular and cholestatic hepatitis				serious cases including fatalities reported, though very rare	107–110
moxifloxacin	isolated cases	hepatocellular and cholestatic hepatitis	within 3–10 days of starting treatment, although delayed onset up to 30 days after cessation of therapy has also been observed			serious cases including fatalities reported, though very rare	122
trovafloxacin		hepatic necrosis leading to liver failure	variable but rapid onset within 2 days of the start of treatment seen in some patients		re-exposure	restricted use or market withdrawal due to serious hepatotoxicity	32,33,128,129

Sulphonamides							
sulfasalazine	1 per 1000 prescriptions	cholestatic or mixed hepatocellular-cholestatic injury	within the first 4 weeks of treatment	within a few weeks of treatment discontinuation		severe cases of hepatic injury described including fulminant liver failure	4,43
trimethoprim/ sulfamethoxazole	<2 per 10000 prescriptions	cholestatic or mixed hepatocellular-cholestatic injury		within a few weeks of treatment discontinuation	female sex, HIV positive, older age (≥75 years)	sulphonamide component responsible for most side effects	32,135
sulfadimethoxine		necrosis and granulomatous hepatitis	rapid after administration of 2 g				138
sulfadoxine+pyrimethamine		granulamatous hepatitis			female sex, older age (>65 years)	sulphonamide component of sulfadoxine+pyrimethamine treatment responsible for most side effects	139
Tetracyclines							
tetracycline	1 per 18 million daily doses	microvesicular steatosis (acute fatty liver); cholestatic, ductopenia	long latency period		female sex, pregnancy, large (≥1.5 g daily) intravenous dose, renal disease		32,143,144
doxycycline	lower than tetracycline	cholestatic liver injury	long latency period of over a year	variable with most patients recovering on cessation of therapy but serious and occasionally fatal cases reported	re-exposure leads to recurrence	risk lower than with tetracycline	145
minocycline		microvesicular steatosis (acute fatty liver), autoimmune hepatitis					32,146,147
Antibiotics mainly used for tuberculosis							
Ethambutol	isolated cases but increases in combination with isoniazid (6%), rifampicin (30%) and pyrazinamide (50%)	cholestatic hepatitis	within 3–16 weeks of treatment	within a few weeks of treatment cessation	older age (>60 years), female sex, malnutrition	rarely used alone, with most hepatotoxicity attributed to concomitantly administered drugs	154,182,184
Isoniazid	1%–10% of patients	hepatocellular necrosis	within a few days of treatment	may resolve with continued treatment	older age (>60 years), female sex, malnutrition, slow acetylator status	hepatotoxicity is exacerbated with concomitant rifampicin administration	178,181,191
Pyrazinamide	6%–20% of patients	centrolobular cirrhosis and cholestasis	within first 5 weeks but may be delayed (>30 days)	gradual decline in serum transaminase levels after prompt cessation of treatment	older age (>60 years), female sex, malnutrition, chronic viral hepatitis	data inconsistent on dose-related hepatotoxicity	179,181,193–195
Rifampicin	<2% of patients	cholestatic hepatitis	within 3–12 weeks	gradual decline in serum transaminase levels after prompt cessation of treatment	rarely used alone, therefore as for other agents	potential to exacerbate hepatotoxicity of co-administered agents	199,200,203
Streptomycin	no hepatotoxic potential					liver disease is a risk factor for nephrotoxicity	212

markedly increases the risk of hepatotoxicity.[43,55] Thus, amoxicillin/clavulanate is responsible for 13%–23% of drug-induced hepatotoxicity cases[7,56,57] and is the leading cause of hospitalization for adverse hepatic events.[7] Because symptom onset is usually delayed,[58] early diagnosis is difficult.

Hepatotoxicity is clearly linked to the clavulanic acid moiety, with a 5- to 9-fold increase for the combination versus amoxicillin alone.[40,59,60] While amoxicillin alone only slightly increases the risk of DILI compared with non-use (adjusted odds ratio, 1.7), the amoxicillin/clavulanate adjusted odds ratio versus non-use reaches 31.9 with recent use and 94.8 with current use.[43] A recent retrospective case analysis of 800 patients with drug-induced jaundice suggested that amoxicillin/clavulanate was responsible for 32% of cases, giving an estimated incidence rate of 9.91 cases of jaundice per 100000 prescriptions.[44]

Hepatotoxicity associated with amoxicillin/clavulanate usually follows a benign course, with symptoms resolving over several weeks. Some patients, however, have a protracted course that can lead to acute liver failure and death.[42] A prospective registry study reported an unfavourable outcome (persistence of liver injury, liver transplantation or death) in 7% of the 69 patients who suffered amoxicillin/clavulanate hepatotoxicity.[56]

Pathology

Hepatotoxicity associated with amoxicillin/clavulanate is usually characterized by delayed cholestatic or mixed hepatocellular-cholestatic injury.[40,59,61] This 'hepatotoxic signature' has, however, been challenged with evidence to suggest that while common in older patients, younger patients are more likely to develop hepatocellular injury than cholestatic or mixed injury.[56]

Risk factors

Prolonged or repeated courses or being >65 years of age increases the risk of developing hepatotoxicity,[40,56] and the presence of both can increase the risk of acute liver injury to 1 per 1000 users,[40] an incidence that can be detected by primary care physicians in everyday practice. Female sex and age >65 years predispose individuals to amoxicillin/clavulanate-associated jaundice.[44] A significant association between the *DRB1*1501-DRB5*0101-DQB1*0602* haplotype and cholestatic hepatitis related to amoxicillin/clavulanate was reported in a pioneering Belgian study,[62] and was recently confirmed by the DILIGEN group from the UK.[63] A wide genome analysis in this population is underway.

Cephalosporins

Cephalosporins are only rarely implicated in hepatotoxic reactions.[64–67] Cholestasis featured in all documented cases of cephalosporin-associated hepatotoxicity, with symptoms manifesting within a few days of treatment. With the exception of ceftriaxone, for which a specific mechanism has been identified, hepatotoxicity appears to be immunologically mediated.[68] A recent report of cefdinir-induced hepatotoxicity describes jaundice, mild cholestasis with portal and lobular mixed inflammation, and focal bile duct injury.[69]

Macrolides (including azalides and ketolides)

Erythromycin

Frequency

Erythromycin-related hepatotoxicity, documented >40 years ago, occurs with all ester derivatives.[4,5,70] According to Westphal *et al.*,[45] its incidence should be considered as high; elevation of serum aminotransferases is seen in up to 15% of cases and overt hepatitis in ~2% of patients if treated for >2 weeks.[71,72] More recent reports, however, suggest that it remains much lower[73] and similar to that of penicillin V.[74] A retrospective cohort study using the UK General Practice Research Database (GPRD) estimated the risk of cholestatic hepatitis as 3.6 cases per 100000 users.[73] Hospitalization for symptomatic acute hepatitis is rare (a US study reported 2.28 cases for every 1 million patients receiving a 10 day course of erythromycin).[75] To our knowledge, there has been only one documented fatal outcome with erythromycin, which occurred in an elderly male patient treated with intravenous erythromycin lactobionate.[76]

Pathology

Erythromycin-induced hepatotoxicity probably arises from a combination of intrinsic hepatotoxic effects and the hypersensitivity reactions that characterize most cases of liver injury. A cholestatic pattern of injury is typical, but most cases also have evidence of hepatocellular injury.[72] Prognosis is generally good, with symptoms and biochemical abnormalities resolving within 2–5 weeks of treatment discontinuation; very occasionally, cholestasis persists for 3–6 months.[4] Actually, all 32 patients with erythromycin-associated hepatocellular injury in the Swedish registry survived, compared with the 40% mortality in halothane- and naproxen-induced hepatocellular damage.[25]

Clarithromycin

The hepatotoxic profile of clarithromycin appears similar to that of erythromycin.[43] The first report of cholestatic hepatitis[77] was followed by a brief report of reversible cholestatic hepatitis in 5 of 14 elderly patients taking high-dose clarithromycin.[78] Two cases of fulminant hepatic failure have been associated with clarithromycin, one of which required liver transplantation,[79] while the second, a fatal case, was attributed to an interaction between clarithromycin and concomitant disulfiram.[80] However, infrequent severe hepatic dysfunction and liver failure resulting in death appear in the US labelling for clarithromycin.[81]

Azithromycin

Adverse hepatic events associated with azithromycin (an azalide closely related to the macrolides but with a considerably longer half-life and extended tissue accumulation) are rare. Reversible azithromycin-related intrahepatic cholestasis has recently been reported in isolated cases,[82–85] while association between azithromycin and asymptomatic elevated liver enzymes in treated children is well documented.[86]

Telithromycin

Telithromycin is the first, and so far the only, ketolide approved for clinical use. It was primarily designed for activity against macrolide-resistant *S. pneumoniae*[87] and, in this context, should have perhaps been restricted to situations where this would have conferred a decisive advantage, i.e. for severe infections in regions where resistance to macrolides is high. In Phase III trials, mild-to-moderate increases in ALT were observed at a higher frequency than in the placebo arm. Subsequent to commercial launch in the USA, three cases of serious liver injury with jaundice and significantly elevated liver enzymes (>10×ULN in one case) occurred in patients having received telithromycin for minor upper respiratory tract infections. One patient spontaneously recovered, while the second required liver transplantation and the third died.[88] An initial analysis of 12 cases provided evidence for a rare, unusual form of hepatotoxicity characterized by short latency, systemic symptoms and, in some cases, significant ascites.[89] The FDA then issued a warning about the potential for serious liver toxicity, a drastically restricted indication (sole use in community-acquired pneumonia)[11] and a boxed warning in the US product labelling.[90] This decision has been reinforced by additional case reports to the FDA's Medwatch.[21,96] In parallel, the EMA introduced 'alterations in hepatic enzymes, cases of severe hepatitis, and liver failure' in the 'Special warnings' section of the 'Summary of Product Characteristics' (SPC), but maintained indications for both community-acquired pneumonia and acute exacerbation of chronic bronchitis (for the latter, however, only if the infection is caused by known or suspected β-lactam- and/or macrolide-resistant strains).[91–93]

Frequency

The warnings discussed above have resulted in a marked reduction in the prescription of telithromycin, making epidemiological studies difficult. Analysis of the FDA post-marketing database indicates a reporting rate of 167 cases of acute liver failure per 1 million person-years of telithromycin use (versus an expected value of 1 case per 1 million person-years).[94] The manufacturer reports an incidence of 7 cases of telithromycin-induced hepatitis per 10000 people treated.[90] The FDA Adverse Event Reporting System shows that the risk of hepatotoxicity is 82% greater with telithromycin than with other agents.[95] The EMA mentions that an increase in liver enzymes is common, hepatitis uncommon and cholestatic jaundice rare, while the frequency of severe hepatitis and liver failure cannot be estimated from the available data[91] (EMA categorizes adverse effects as common, uncommon, rare and very rare based on frequencies of ≥1/100 to <1/10, ≥1/1000 to <1/100, ≥1/10000 to <1/1000 and <1/10000 of treated patients, respectively).

Pathology

Telithromycin-related liver injury is characterized by rapid onset of symptoms (consistent with rapid-onset hypersensitivity), including jaundice, fever, abdominal pain and, on occasion, ascites.[21,96,97] Of 42 cases of telithromycin-induced hepatotoxicity recently described, 25 developed jaundice and met criteria for Hy's Law, 32 were hospitalized, 14 had severe liver injury (grade 4 and 5), 1 required transplantation, and 4 died.[96] Re-exposure to telithromycin caused recurrent acute hepatitis in a patient who had experienced adverse hepatic effects with a previous course.[97]

Fluoroquinolones

Fluoroquinolones achieve high concentrations in bile, which makes them well suited to the treatment of bacterial cholecystitis and cholangitis. Modest increases in serum ALT levels can be considered as a fluoroquinolone class effect. More severe liver injury remains rare (but see below for information on trovafloxacin). In fact, there have been only few reports of significant hepatotoxicity, even when used in patients with advanced liver disease.[5,98] Fluoroquinolones, such as moxifloxacin and levofloxacin, are used off-label as alternative drugs in antituberculosis regimens, but neither drug appears to cause additional hepatotoxicity in this patient population.[99]

Ciprofloxacin

The literature remains scanty over the potential hepatotoxicity of ciprofloxacin, and the incidence of ciprofloxacin-induced hepatotoxicity is considered very low,[4,5] although two fatal cases of acute liver failure in elderly men have been documented.[100,101] Cases of hepatocellular injury ($n=51$) and cholestatic hepatitis, with or without ductopenia,[102,103] have been described following treatment with ciprofloxacin. A recent report also highlights a case of simultaneous acute cholestatic liver injury and renal failure, which resolved within 5 months of discontinuing treatment.[104] The recently harmonized European SPC of ciprofloxacin[105] mentions only cases of severe hepatotoxicity in the 'Special warnings' section, which needs to be seen in the context of a very large use of this drug worldwide. The SPC further mentions that an increase in transaminases and bilirubin is uncommon, hepatic impairment, cholestatic icterus and hepatitis rare, and liver necrosis (very rarely progressing to life-threatening hepatic failure) very rare, based on both oral and intravenous administration of ciprofloxacin.

Levofloxacin

The incidence of adverse hepatic effects associated with levofloxacin, an extended-spectrum fluoroquinolone, is also low. Abnormal liver function occurred in <1% of patients in clinical trials,[106] while post-marketing surveillance revealed rates of severe liver injuries (hepatitis, necrosis and hepatic failure) of <1 case per 5 million prescriptions.[107] Nonetheless, cases of levofloxacin-related liver injury have been reported, including cases of hepatic failure.[108–113] The US prescribing information mentions that severe, and sometimes fatal, hepatotoxicity not associated with hypersensitivity has been reported.[114]

Moxifloxacin

Frequency

Reviews of clinical trials and post-marketing surveillance studies indicate minimal incidence of hepatic injury, though liver function tests may be abnormal in ~1%–5% of patients.[115,116]

While no index case of moxifloxacin-related liver injury has emerged in either clinical trials or post-marketing surveillance, and published data have remained scanty for many years,[117,118] there have been spontaneous reports of hepatocellular injury. These include eight deaths due to hepatic failure where a link to moxifloxacin could not be excluded[119] and a more recent case where it was considered to be idiosyncratic.[120] This has been introduced as an amendment by the EMA in the European SPC,[121] but such fatal cases should be seen in the context of 85 million treatments with moxifloxacin worldwide at that time.[122] The current, revised SPC mentions elevation of transaminases as being common, hepatic alteration uncommon, and icterus and hepatitis rare. Moxifloxacin is not included in the list of drugs identified in at least five adjudicated cases of DILI.[123] Moxifloxacin, as for levofloxacin, was also found to cause no additional hepatotoxicity when used by patients with hepatitis induced by first-line antituberculosis drugs.[99]

Pathology

Liver injuries induced by moxifloxacin are typically cholestatic or mixed hepatocellular-cholestatic rather than hepatocellular. Symptoms are usually evident within 3–10 days of starting moxifloxacin, although delayed onset of up to 30 days after cessation of therapy has also been observed. A case of moxifloxacin-associated drug hypersensitivity syndrome with toxic epidermal necrolysis and fulminant fatal hepatic failure has been described.[124]

Gemifloxacin, gatifloxacin and trovafloxacin

Gemifloxacin is approved in the USA and a few other countries, but not in Europe. To date, there has been no report of hepatocellular injury with gemifloxacin, but this may reflect its very limited patient exposure.[125] Gatifloxacin was approved in the USA and other countries, but not in Europe. It has been recently withdrawn, mainly for adverse glycaemic effects. Gatifloxacin, however, was also implicated in several cases of hepatotoxicity, with 27 occurrences reported to the FDA (cited in 11 cases as the most probable cause of death).[126] Trovafloxacin was approved in the USA in 1998, but post-marketing surveillance quickly revealed significant, serious hepatotoxicity,[127] with clear signs of eosinophilic infiltration, hepatocellular vacuolar degeneration and necrosis.[128] Thus, within 2 years (with only 2.5 million patient exposures), 140 cases of serious hepatic events, including 14 cases of acute liver failure, 4 cases requiring liver transplantation and 5 deaths, were reported.[127,129] The drug was, therefore, restricted to serious and life- or limb-threatening infections.[127,129,130] Although approved in Europe, the drug was quickly withdrawn by its registration holder before its actual commercial launch. The greater hepatotoxic potential of trovafloxacin may be due to its difluorophenyl side chain (shared with temafloxacin, also withdrawn for adverse hepatic effects[33]), but the cyclopropylamine moiety (specific to trovafloxacin) could also play an important role.[131] Trovafloxacin was also shown to sensitize hepatocytes to TNF-α-induced death,[132] an effect not seen with levofloxacin in comparative studies.[133] These clear structural relationships imply that the hepatotoxicity of trovafloxacin is unlikely to be the extreme of a fluoroquinolone class effect.

Sulphonamides

The hepatotoxicity of the sulphonamides, the oldest class of antibiotics, is well documented.[134] This class includes sulfamethoxazole, sulfasalazine, sulfamethizole and sulfamethoxypyridazine, as well as the combinations trimethoprim/sulfamethoxazole and pyrimethamine/sulfadoxine.

Frequency

Sulfasalazine emerged as one of the most hepatotoxic drugs in a recent population-based case–control study using the UK-based GPRD, with an incidence approaching 1 per 1000 users,[43] i.e. similar to amoxicillin/clavulanate. Sulfasalazine hepatotoxicity is frequent enough to be detected at the primary care level. Most cases of sulphonamide-induced hepatotoxicity are mild and patients usually recover within a few weeks of treatment discontinuation,[2] but severe cases, including fulminant liver failure, have been described for the combination trimethoprim/sulfamethoxazole.[135,136]

Pathology

Sulphonamides most often induce cholestatic or mixed hepatocellular-cholestatic injury,[2,137] although cases of necrosis and granulomatous hepatitis have also been described.[135,138,139] The sulphonamide component is thought to be responsible for most hepatic side effects with trimethoprim/sulfamethoxazole. The underlying mechanism, explaining the idiosyncratic character of the toxicity, could be its slow acetylation in some patients, preventing its normal elimination and allowing it to enter into other catabolic pathways related to toxicity.[139a] A case of jaundice and acute liver failure occurred in a patient receiving trimethoprim/sulfamethoxazole for a urinary tract infection; however, liver function returned to normal over a 2 month period, without intervention.[140]

Tetracyclines

Frequency

Tetracycline hepatotoxicity, first described >50 years ago,[141] seems related to the use of large doses[142] and, contrary to most other antibiotics, is predictable and reproducible in animal models.[45] With normal, low, oral doses, tetracyclines only rarely cause liver injury (~1 case per 18 million daily doses according to early estimates,[143] and 3.7 cases per 100000 users or 1.5 cases per 100000 prescriptions in more recent surveys), representing one of the lowest rates for which a significant association of liver injury and antibiotic use has been established.[43] Early reports (including one death) of an association between tetracycline hepatotoxicity and pregnancy all related to high-dose intravenous treatment.[144] A later survey suggested that female sex was not a risk factor with low-dose oral tetracycline therapy and, importantly, did not increase the risk of death due to hepatic side effects.[143]

Doxycycline is less hepatotoxic than tetracycline, with no increased risk compared with controls in a retrospective study (current use odds ratio, 1.49; 95% confidence interval, 0.61–3.62).[145] A recent fatal case has been described,[113] but

after exposure to levofloxacin and in association with naproxen. Rarely, minocycline-associated hepatotoxicity has necessitated liver transplantation or proved fatal.[5,146] No public report of tigecycline-related DILI has been identified to date.

Pathology

Microvesicular steatosis was the characteristic feature of treatment with intravenous or large oral doses of tetracycline,[142] whereas cholestasis was the predominant clinico-pathological pattern with oxytetracycline and minocycline.[43] Long-term minocycline use as a treatment for acne has also been associated with autoimmune hepatitis, characterized by antinuclear autoantibodies, a lupus-like syndrome, fatigue, rash and arthralgia,[96] and hypersensitivity syndrome.[147]

Linezolid

Linezolid treatment is most often initiated in the hospital, but, because of its excellent bioavailability in its oral form, linezolid treatment is often extended to home therapy after discharge and, therefore, is under the control of the general practitioner. Prolonged treatment with linezolid has been associated with severe liver failure and lactic acidosis, with liver biopsy showing microvesicular steatosis.[148] These alterations were related to the known mitochondrial dysfunction induced by linezolid,[149] but no further details have been disclosed so far. In two recently published studies from Japan, chronic liver disorders (liver cirrhosis and hepatitis),[150] on the one hand, and high pre-treatment levels of total bilirubin and transaminases and coexistence of chronic liver disease (CLD), on the other hand,[151] were found to be significant risk factors for the development of thrombocytopenia, a well-known side effect of linezolid that most commonly develops after ≥14 days of treatment.[150] As thrombocytopenia is itself a common complication in patients with CLD,[152] it is possible that some sort of synergistic effect and/or an enhancement of linezolid toxicity is occurring due to a reduction in its metabolism.[151] Although there is evidence that linezolid accumulates in bile,[153] there are insufficient data to provide specific recommendations about potential side effects at this time.

Antituberculosis drugs

Although prescribed by specialist practitioners, antituberculosis drugs are most often used today in outpatients. Thus, primary care physicians are among the first professionals to see potential side effects, including liver damage.

First-line treatment of adult respiratory tuberculosis entails 8 weeks of combination therapy with isoniazid, pyrazinamide and rifampicin, followed by 16 weeks of isoniazid and rifampicin, to which ethambutol is usually added. Streptomycin is used in cases of retreatment,[154] with fluoroquinolones reserved for second-line use in drug-resistant tuberculosis or as substitutes in patients unable to tolerate first-line agents.[99,155] These drugs have been used for many years, and have known and well-documented adverse effects on the liver that range from asymptomatic increases in liver enzymes to acute hepatitis and fulminant hepatic failure.[156] Most commonly associated with isoniazid, pyrazinamide and rifampicin, they usually occur within the first few weeks of the intensive phase of therapy,[154,155,157] are among the most common of all adverse events,[158] and are responsible for most premature discontinuations due to adverse events.[159] The hepatotoxicity of antituberculosis drugs has already been the subject of several recent reviews[154,155,160] and will, therefore, be covered here only briefly. Because treatment of active tuberculosis entails concomitant use of more than one drug, it is difficult to identify the hepatotoxic effect of any individual drug in the combination regimen. Thus, we will first review the general risk factors identified in patients receiving antituberculosis treatment and then briefly review each drug individually.

General risk factors

Older age (>60 years), female sex and malnutrition (low body mass index) are widely accepted risk factors for drug-induced hepatotoxicity among tuberculosis patients.[154,157,161–166] Pre-existing liver disease, such as chronic viral hepatitis, would seem a likely risk factor and has been identified in some,[154,167] but not all,[168,169] studies. Similarly, inconsistent findings have been reported for co-infection with HIV.[154,170–172] Acetylator status may predispose to an increased risk of drug-induced hepatotoxicity, with several studies showing increased risk in slow versus fast acetylators,[173–177] although contradictory but less recent results have also been reported.[178,179] In addition to the *N*-acetyltransferase 2 slow acetylator genotype, other potential risk genotypes for hepatotoxicity include CYP2E1 polymorphisms.[176,177] Excess alcohol consumption is thought to predispose to an increased risk of drug-induced hepatotoxicity and, in one study, was found to exacerbate hepatotoxicity in patients with chronic hepatitis C infection.[167] Lastly, concomitant administration of other hepatotoxic drugs, such as acetaminophen (paracetamol), can also increase the risk of hepatotoxicity.[180]

Ethambutol

Frequency

Ethambutol-associated hepatotoxicity is considered rare.[181] A recent study, in which ethambutol alone or in combination with fluoroquinolones and streptomycin was used to manage hepatotoxicity secondary to standard first-line drugs, showed no additional drug-induced hepatotoxicity.[99] Previous studies suggest that the incidence is lowest when ethambutol is combined with streptomycin and isoniazid,[182,183] whereas in one small series, 50% of patients experienced drug-induced hepatotoxicity when ethambutol was combined with pyrazinamide.[184]

Pathology

Ethambutol is not considered hepatotoxic, although a few isolated cases of hepatic injury and one of cholestatic hepatitis have been described.[181]

Isoniazid

Frequency

Isoniazid, used for both active treatment and prophylaxis of latent tuberculosis, has known hepatotoxic potential that has

been attributed to various metabolites, including hydrazine.[154,185] About 10% of patients experience increases in serum transaminase levels during treatment, with ~1%–2% developing symptomatic hepatitis.[178,181] Significantly higher rates of symptomatic hepatitis have been described in comparison with rifampicin (1.8% versus 0.08%, $P<0.001$; 4% versus 0.7%, $P=0.003$) as well as lower rates of treatment completion due to poorer tolerability.[186,187] However, the frequency of severe hepatotoxicity appears significantly less common with isoniazid than with rifampicin in combination with pyrazinamide.[188,189] Similarly, rates of hepatotoxicity are reportedly higher when isoniazid is co-administered with rifampicin[181] (as a potent inducer of the hepatic CYP450 system, rifampicin can increase production of reactive metabolites of isoniazid and thereby increase the risk of hepatotoxicity[154,190,191]).

Pathology

Liver injury is characterized by hepatocellular necrosis and degeneration, such as hepatocyte ballooning, as well as mild inflammatory infiltrates within the portal tracts and, less commonly, cholestasis.[181] In six cases of fulminant hepatitis following isoniazid/rifampicin combination therapy, centrilobular necrosis was the principal hepatic lesion.[190]

Pyrazinamide

Frequency

Introduced into clinical practice in the 1950s, pyrazinamide has known hepatotoxic potential; increases in serum transaminase levels and symptomatic hepatitis occur in 10%–20% of patients.[181] Originally attributed to high initial dosage regimens, the relationship between pyrazinamide dosage and frequency of hepatotoxicity remains controversial. Early reports of no association between higher dosage and increased hepatotoxicity[192] have been supported by a recent meta-analysis[193] and a case–control study of dosing schedules.[194] While this issue remains unresolved, several studies point to a higher frequency of hepatotoxicity in regimens containing pyrazinamide than in those containing only isoniazid and rifampicin.[179,195,196] In one series, drug-induced hepatotoxicity was almost twice as frequent with pyrazinamide as compared with non-pyrazinamide regimens.[179] In another study, the estimated risk of hepatotoxicity was 2.8% for pyrazinamide-based regimens, compared with 0.8% for concomitant isoniazid and rifampicin therapy.[196] The inclusion of pyrazinamide in retreatment regimens also appears to increase the risk of hepatotoxicity, with rates of 24% in one series as compared with none in the isoniazid, rifampicin, ethambutol and streptomycin treatment arm.[197]

Pathology

Extensive centrolobular necrosis has been described in one case,[198] while the key pathological features in a case of fatal liver failure consisted of bridging necrosis, lymphocyte infiltration, focal cholestasis, increased fibrosis and micronodular cirrhosis.[154]

Rifampicin

Frequency

Compared with isoniazid and pyrazinamide, rifampicin has a lower propensity to cause hepatotoxicity,[181] with <2% of patients experiencing increased serum transaminase levels in a recent study.[199] This is consistent with earlier data, in which the incidence of hepatotoxicity was 1.5% for rifampicin versus 4% and 5% for isoniazid and pyrazinamide, respectively.[200] In a meta-analysis of pooled data on >3500 patients, severe hepatotoxicity occurred in 0%–0.7% of patients treated with rifampicin versus 1.4%–5.2% of isoniazid-treated patients.[201] Although hepatotoxicity attributed to rifampicin itself is rare, it may contribute to increased hepatotoxicity when co-administered with isoniazid and, especially, pyrazinamide.[202] In one study, rifampicin in combination with pyrazinamide significantly increased rates of treatment interruption for hepatotoxicity as compared with isoniazid alone (10% versus 2.5%; $P=0.007$).[203] In another study, mild hepatotoxicity (grade 1 or 2) was more frequent in patients receiving a higher dose of rifampicin in combination with pyrazinamide than with the standard dose (46% versus 20%; $P=0.054$).[204]

Pathology

The histopathological picture is one of spotty-to-diffuse hepatocellular necrosis primarily associated with cholestasis.[154,181] In some cases it can lead to liver failure.[205]

Streptomycin

Frequency

Of the current first-line drugs, streptomycin has little or no hepatotoxic potential; however, it can cause nephrotoxicity,[181] as is the case for all aminoglycosides.[206] Patients with liver disease are more susceptible to aminoglycoside-induced nephrotoxicity,[212] meaning that acute renal failure is prognostic for acute liver failure (in this setting, acute renal failure may precipitate hepatic encephalopathy). Potentially, the inclusion of streptomycin in antituberculosis regimens may alter the course, if not the frequency, of fulminant hepatitis due to isoniazid- or pyrazinamide-induced hepatotoxicity.[181]

Conclusions

Antibiotic-induced hepatotoxicity produces an array of hepatic lesions that are often clinically indistinguishable from those of hepatobiliary diseases, making causality difficult to establish. While the temporal relationship between drug administration and onset of hepatic symptoms and exclusion of competing aetiologies may help, in most cases diagnosis is largely circumstantial. Delayed onset of hepatic dysfunction after cessation of therapy, which has been reported with several antibiotics, complicates the picture further, especially in cases of fatal liver failure. It is also difficult to determine cause and effect when there are only a few isolated spontaneous reports. Amoxicillin/clavulanate (due to the clavulanic acid component), co-trimoxazole (due to the sulphonamide component) and flucloxacillin appear as the most frequently involved drugs among

those in current clinical use by primary care physicians. Conversely, no other currently approved antibiotic that is in use in general practice, except for telithromycin, can be singled out to be overly hepatotoxic.

Antibiotics are a vital weapon in combating serious bacterial infections. To maximize the benefit-to-risk ratio of antibiotic therapy, it is vital to ensure that the appropriate patients are treated with the most suitable drugs. In this respect, it is critical to be vigilant for potential risk factors that may increase the likelihood of a patient experiencing adverse hepatic events, namely the choice of the drug (see above) and patient factors. The latter mainly include a previous experience of hepatic dysfunction with the same antibiotic drug, the co-administration of other drugs known to cause hepatotoxic reactions, a pre-existing hepatic insufficiency without close monitoring of the hepatic function and, depending on the drug, one of several other risk factors, as listed in the paper and summarized in Table 1. Although antibiotic-induced hepatotoxicity is a rare event, and serious events are exceptionally rare, it is important to understand that most antibiotics can cause idiosyncratic hepatotoxic reactions. Both physicians and patients need to be aware of, and monitor for, potential symptoms and take prompt action if signs of hepatotoxicity emerge. This remains probably the only and most effective course of action until pharmacogenetic testing, which several organizations are working on[29,207,208] and which already shows promise for a few other drugs,[209] becomes available on an 'easy-to-use' basis for prospectively identifying those patients susceptible to antibiotic-induced liver injury in daily clinical practice.

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