

Chapter 2

Drug-Induced Cholestasis

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Background

Cholestatic liver disease has a wide variety of causes which often requires radiological examination to rule out extrahepatic and intrahepatic causes. Drug-induced cholestasis is frequent among the differential diagnoses in patients with cholestasis and normal hepatobiliary imaging. Cholestasis is mostly defined by a biochemical pattern with predominant increase in alkaline phosphatase (AlkPhos) in comparison with aminotransferases, whereas the hepatocellular pattern is evident when elevation in aminotransferases is more prominent than the AlkPhos [1, 2]. The understanding of the pathophysiology of hepatocellular type of liver injury is scarce whereas advances in the understanding of the pathogenesis of cholestatic liver disease have increased in recent years. It has become clear that drugs or metabolites of drugs interfere in many cases with the hepatobiliary transport systems found at the basolateral and canalicular membranes of hepatocytes.

Patients who present with cholestatic liver test abnormalities can have many differential diagnoses. In some cases the diagnosis is straightforward, such as in a patient recently treated with an antibiotic with known hepatotoxicity. However, in other patients with systemic illness, who are often treated with multiple drugs, it can be very difficult to establish the diagnosis of DILI. It is not common that a diagnosis of DILI is proven. Thus, in most cases DILI is suspected and is labeled as highly probable, probable, or possible. However, if a rechallenge with the same drug results in identical liver test abnormalities as previously observed, the diagnosis of DILI can be established. Rechallenge nowadays usually occurs inadvertently and the diagnosis DILI is often based on circumstantial evidence and exclusion of competing etiologies. The extent of diagnostic workup such as serological tests and radiological

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imaging relies heavily on the clinical context. Although symptomatic cholestatic DILI can cause considerable morbidity and lead to hospitalizations and investigational costs, the long-term prognosis is favorable in most cases. Although liver test abnormalities will reverse with the cessation of the suspected offending drug, this can lead in rare circumstances to vanishing bile duct syndrome (VBDS) [3, 4], a condition that may or may not be reversible. Furthermore, in the worst case scenario this may lead to biliary fibrosis and cirrhosis with decompensated liver disease [3].

Incidence and Outcome

Incidence

The true incidence of hepatic adverse drug reactions has previously been largely unknown. Except within clinical trials which give reliable information about development of abnormal liver tests, great uncertainty exists about the occurrence of DILI associated with the clinical use of drugs. Only two studies have been undertaken to investigate the incidence of DILI in the general population [5, 6]. These studies were prospective and based on careful search for DILI in a defined population and probably underestimate rather than overestimate the incidence of DILI.

A retrospective population based case-control study in the General Practice Research Database in the UK identified patients referred or hospitalized for a liver related diagnosis [7]. In this study cholestatic drug reactions were the most common manifestations of DILI. The strongest associated hepatotoxicity was observed for chlorpromazine, amoxicillin-clavulanic acid, flucloxacillin, and macrolides among other drugs [7]. The highest crude incidence rates were found for chlorpromazine, azathioprine (AZA), and sulfasalazine (approximately 1 per 1,000 users). A dose effect was observed for diclofenac, amoxicillin-clavulanic acid, and flucloxacillin and higher risk associated with longer duration of drug treatment observed for sulfasalazine, flucloxacillin, and diclofenac [7].

Hepatotoxicity due to drugs has been reported to occur in 2–10 % of patients hospitalized for jaundice [8–12]. Thus, DILI is not a common cause of jaundice. However, the majority of patients with jaundice have obvious etiology such as hepatobiliary malignancy, alcoholic liver disease, gallstone disease, and a much higher proportion of DILI is found among those without obvious etiology [11]. In several large retrospective DILI studies, cholestatic pattern has been found in 20–40 % of patients, mixed pattern in 12–20 %, and hepatocellular in 48–58 % [13–16] (Table 2.1). Limited data exists on the incidence of DILI with cholestatic reactions in the general population. The first population-based study on the incidence of DILI was undertaken in France in a defined population and revealed an incidence of 13.9 cases per 100,000 per year [5]. A total of 33 % of cases had a cholestatic or mixed pattern [5]. Another population-based study from Iceland, with an incidence of 19 cases per 100,000, showed that 32 % of the patients had a cholestatic and 26 %

Table 2.1 Type of liver injury in several large DILI studies

	Cholestatic (%)	Mixed (%)	Hepatocellular (%)
Bjornsson and Olsson [13]	26	22	52
De Valle et al. [16]	40	12	48
Andrade et al. [14]	20	22	58
Chalasani et al. [15]	23	20	56

Table 2.2 Types of liver injury and mortality rates in the largest studies on DILI

	Cholestatic pattern (%)	Mixed pattern (%)	Hepatocellular pattern (%)
Bjornsson and Olsson [13]	8	2	13
Andrade et al. [14]	5	2	7
Chalasani et al. [15]	14	2	8

mixed type of liver injury, whereas the rest had a hepatocellular type [6]. Patients with a cholestatic/mixed type of injury were older than those with a hepatocellular type, 60 years vs. 46 years of age ($P=0.004$), which is in line with the results from other studies [5, 13–16].

Outcome

Drug-induced jaundice has been associated with a poor prognosis and a severe drug liver reaction was found by Dr. Hy Zimmerman to lead to at least 10 % mortality [17]. This has been named Hy’s law and was later validated in a large series of patients with DILI showing a mortality/liver transplantation rate of 9–12 % [13–15] (Table 2.2). Originally, this association was thought to be true only for hepatocellular jaundice, and the prognosis of those with cholestatic injury was mainly related to comorbidities and age [4].

In recent series, cholestatic DILI has also been associated with mortality of 5–14 % [13–15]. However, in general the prognosis in patients with hepatocellular liver injury due to drugs is worse than in those with cholestatic/mixed pattern [13–15]. In the Drug Induced Liver Injury Network (DILIN) study, not all these patients had a liver related mortality [15]. Mortality and liver transplantation among patients with different patterns of liver injury is shown in Table 2.2.

Vanishing Bile Duct Syndrome

DILI of cholestatic type has been associated with a chronic intrahepatic cholestatic pattern called the vanishing bile duct syndrome [4]. Although well documented, VBDS is a very rare syndrome and has been considered to be only 0.5 % of all cases

of small duct biliary disease [18]. The liver histology can mimic that of PBC with granulomatous duct injury [4]. In a minority of patients progressive ductopenia occurs, which can lead to near complete absence of ducts with variable amounts of inflammation [19]. This is mainly observed in patients with prolonged cholestasis for months or years, often with jaundice. This can in rare cases lead to cirrhosis [3, 4, 19–23]. The prototype of drugs leading to this syndrome is chlorpromazine [3]. Many other drugs have been implicated and ductopenia has been associated with more than 40 drugs [21, 24]. Ductopenia can also be progressive, without resolution of jaundice and lead to fibrosis and biliary cirrhosis [3, 20, 25–28]. Inability of bile duct ductular proliferation is the likely explanation, leading to prolonged and occasionally irreversible changes resulting in death from cholestatic cirrhosis [28]. However, VBDS has been shown to be reversible in some cases with disappearance of jaundice during long-term follow-up [29, 30]. Animal experiments have demonstrated neoductular proliferation accompanied by improved biliary drainage [31]. Reversal of the vanishing bile duct syndrome due to drugs has been reported [30]. A sequence of changes documented with repeated liver biopsies demonstrating restoration of bile ducts has been nicely illustrated [30]. This is most likely due to regeneration of the terminal branches of the biliary tree from a progenitor cell compartment located at the interface of bile ducts with hepatic parenchyma [30].

Chronic Evolution During Long-Term Follow-Up

A prospective follow-up of patients from the Spanish Hepatotoxicity Registry revealed development of chronic liver injury in approximately 6 % of patients [32]. Chronic liver injury was defined differently in different types of DILI: hepatocellular pattern of damage was defined as chronic if liver tests showed persistent abnormality more than 3 months after stopping the drug therapy and in case of cholestatic/mixed type of injury, if abnormality was present for more than 6 months following drug discontinuation [32]. The most frequent drug associated with chronicity was amoxicillin–clavulanate. Patients with cholestatic liver injury were more likely to develop chronic liver injury [32]. Ductal lesions developed in three patients in the cholestatic/mixed group [32]. Similarly, a single center study from Sweden also found 6 % of patients previously diagnosed with DILI with persistently abnormal liver biochemistries at follow-up [33]. The rate of chronic liver injury at 6 months was 13.6 % in the first 300 cases enrolled in the DILIN study [15]. Features of the implicated agent, pattern of DILI or patient age were not associated with chronicity [15]. However, long-term outcome of these patients is unknown, as these patients were followed for 20 months [32], 48 months [33] and 6 months [15]. A follow-up study of DILI patients who originally all had DILI and concomitant jaundice with a mean follow-up of 10 years revealed that development of a clinically important liver disease after severe DILI was rare [34]. A total of 23/685 (3.4 %) DILI patients who had survived acute DILI were hospitalized for liver disease during the study period

and five had liver-related mortality [34]. Among these patients five out of eight with cirrhosis did not have an identifiable cause of cirrhosis, in which DILI might have played a role for this development and two of these had cholestatic liver injury. A significantly longer duration of drug therapy prior to the detection of DILI was observed in those who developed liver-related morbidity and mortality during follow-up [34]. Interestingly, the most common cause of hospitalization for DILI during follow-up was a protracted course of the DILI. Most patients with protracted courses (86 %) were of cholestatic/mixed type and had a mean follow-up of 13 years. In this subgroup of patients, all patients except one (with 6 years follow-up) normalized their liver tests at last follow-up and remained free of liver morbidity thereafter [34].

Diagnostic Workup

Definitions

Cholestasis is defined biochemically as an increase in AlkPhos $>2\times$ the upper limit of normal (ULN) and/or with an ALT/AlkPhos ratio <2 [1, 2]. Mixed liver injury is the intermediate between cholestatic and hepatocellular injury with an ALT/AlkPhos ratio greater than 2 and less than 5. Mixed injury is considered to have more in common with cholestatic than hepatocellular injury and cholestatic and mixed patterns are sometimes taken together as one condition [13–15]. The traditional classification of cholestasis has been into acute and prolonged cholestasis. Furthermore, drug-induced cholestasis is often classified into: (1) acute pure (“bland”) cholestasis, defined histologically as features of cholestasis such as hepatocyte cholestasis and canalicular dilatation often with bile plugs without occurrence of significant inflammation; (2) acute drug-induced cholestatic hepatitis characterized histologically by cholestasis with concomitant inflammatory reaction and sometimes hepatocyte necrosis; (3) drug-induced cholestasis with bile duct injury, ductular, cholangiolar, or cholangiolytic with minimal parenchymal liver cell injury; and (4) vanishing bile duct syndrome (see section “Outcomes”).

Symptoms and Signs

The clinical presentation of cholestatic liver disease is very variable. Asymptomatic elevation of liver enzymes can be observed with dominating increase in AlkPhos but jaundice with or without pruritus is a common presentation. Some patients present with fever and abdominal pain that can simulate gallstone disease. As some patients can have stones in the gallbladder, this can lead to unnecessary cholecystectomies.

Clinical information about the patient is very important to establish the diagnosis of the cholestatic reaction. Abdominal pain can occur as part of a cholestatic hepatitis due to drugs but abdominal discomfort is probably more prevalent. Painless jaundice is also a frequent presentation of DILI. If abdominal pain dominates the picture it argues against a drug as the etiology. In these cases, even though a suspicion of a drug etiology has been raised it may be necessary to do an MRCP or ERCP despite a normal abdominal ultrasound. In all types of alcoholic liver disease, cholestasis can be a prominent feature both biochemically and histologically [35]. Thus, alcohol abuse needs to be ruled out in the workup of suspected cholestatic injury due to drugs.

Different medical conditions such as sepsis [36] and cardiac failure [37] can be associated with pure cholestasis and it is of great importance to distinguish these conditions from a suspected cholestatic DILI. Although infectious hepatitis presents most often with hepatocellular pattern, a biochemical cholestatic pattern can occur in infectious hepatitis such as hepatitis A [38] and Epstein-Barr virus [39]. Other infections such as acute Q fever due to *Coxiella burnetii* [40] and typhoid fever [41] can present with cholestasis. In the appropriate clinical setting, rare infectious diseases have to be ruled out before the diagnosis of DILI can be established. Jaundice and cholestatic hepatitis due to hyperthyroidism has been reported [42]. Thus, the number of serological tests and the extent of radiological imaging to exclude other competing etiologies rely entirely on the clinical context.

Causality Assessment

At the current time, no marker of hepatotoxicity exists that is completely reliable and specific for DILI. A reasonable suspicion of a drug etiology and thorough exclusion of other potential causes is necessary to make a diagnosis of DILI. In clinical research on DILI the most common causality assessment method that has been used is the Roussel Uclaf Assessment model (RUCAM) [1, 2]. RUCAM is based on factors that are important to consider when taking a history in a patient with suspected DILI. These factors include the time from initial drug intake until start of the reaction, course of the liver injury after termination of the suspected drug, risk factors for DILI, concomitant drugs, exclusion of other causes, documented hepatotoxicity of this particular drug and if available the results of rechallenge. In most DILI cases a rapid biochemical and clinical improvement is observed after discontinuation of the implicated drug, that is positive dechallenge. However, for some drugs causing hepatotoxicity liver injury may worsen initially for days or sometimes weeks between discontinuation of the drug and clinical presentation of liver injury. It has been well documented that the regression of cholestasis is slower than in those with hepatocellular injury and the RUCAM instrument takes that into the equation. Some drugs have a “signature pattern,” that is, they tend to give similar type of liver injury and liver injury develops following a similar duration of drug intake.

A common cause of cholestatic hepatitis is associated with amoxicillin–clavulanate and liver injury can be difficult to recognize, as there can be a considerable delay, sometimes 3–4 weeks, between discontinuation of drug intake and symptoms of the liver injury such as itching and jaundice [43]. Thus, knowledge of the known hepatotoxicity of various drugs is important for establishing a correct diagnosis. Recently a comprehensive Web site on the documentation of liver injury for a wide range of drugs has been established, which can be of great help for physicians who wonder about the known hepatotoxicity of a particular drug [44].

Risk Factors

To predict the susceptibility for DILI in an individual patient is almost impossible. If the patient has already experienced a liver injury from a particular drug, there is a great risk that this will happen again in the same subject. Also a past history of DILI from one drug has been shown to be a predictor of future DILI [2, 34]. Genetic variability in the hepatic metabolism of drugs has been considered to be the most important risk factor for DILI but clinical utility of genetic testing in this context is not available at the current time.

Genetic Studies

One of the most common drugs leading to DILI is amoxicillin–clavulanate [13–15], which is mostly associated with cholestatic or mixed injury. One of the first HLA haplotypes associated with DILI, HLA B1*1501-DRB5*0101-DQB1*0602,149 was found in 57 % of patients with amoxicillin/clavulanate-induced DILI, but in only 12 % of controls [45]. Another study confirmed the association between HLA DRB1*15 and liver injury from amoxicillin–clavulanate [46]. Patients with amoxicillin–clavulanate-associated DILI had a significantly higher prevalence of HLA-DQR1*06 than controls [46]. A study from the Spanish Hepatotoxicity Registry revealed that those with cholestatic/mixed DILI had a significantly higher frequency of HLA-DRB1*15 and HLADQB1*06 alleles and a lower frequency of DRB1*07 and DQB1*02 alleles [47].

Results of genome-wide association studies of flucloxacillin induced liver injury, a drug mostly associated with cholestasis, showed an association peak in the major histocompatibility complex region with the strongest association observed for rs2395029, a marker in complete linkage disequilibrium with HLA B*570.1 [48]. Direct genotyping for HLA-B*5701 in 51 cases and 63 drug-exposed controls revealed a very strong relationship between this allele and flucloxacillin-induced liver injury with an odds ratio of 80. Increased susceptibility of cholestatic injury due to contraceptives has been reported to be associated with BSEP 1331T to C polymorphism [49].

Underlying Condition

Rifampicin, a tuberculostatica later shown to be effective in the treatment of pruritus in primary biliary cirrhosis (PBC), has been shown to lead to cholestatic hepatitis [45]. Rifampicin seems to be associated with an increased risk for hepatotoxicity in patients with PBC. In two studies that tested rifampicin for treating pruritus in patients with primary biliary cirrhosis, a high frequency of hepatotoxicity was observed [50, 51] and much higher than previously reported.

Susceptibility to oral contraceptives or postmenopausal hormone replacement therapy appears to be increased in patients with intrahepatic cholestasis of pregnancy [52, 53]. These results support the concept of a genetically determined canalicular transporter deficiency as a common denominator. In general it is controversial whether preexisting liver disease is a risk factor the development of DILI.

Effect of Age

The cholestatic type of DILI is more common among the elderly, whereas hepatocellular DILI appears to be more common in younger individuals [6, 16, 54]. In one study older age was independently associated with cholestatic type of injury [54]. Advancing age has also been shown to be a risk factor for the development of amoxicillin–clavulanate cholestatic type of injury [54]. The reason for this age related susceptibility for cholestatic liver injury is unclear. It is conceivable that expression of hepatocellular transporters could be related to age. In a recent study, a significant inter-individual variability could be demonstrated in canalicular transporter proteins [55]. However, this variability in the susceptibility to develop drug-induced cholestasis was not related to age differences in baseline expression levels of these canalicular transporter proteins [55].

Drug Properties

Limited data exist on the risk of DILI associated with the chemical properties of drugs. Temafloxacin and Trovafloxacin known to be able to cause cholestasis have a unique difluorinated side chain that does not occur in other quinolones with much less hepatotoxicity [55]. Drugs given orally in a daily dose of more than 50 mg have recently been shown to be more likely to lead to DILI than those with a lower daily dose [56]. Among US prescription medicines, daily doses of oral medications were associated significantly with liver failure, liver transplantation, and death from DILI. In approximately one-third of cases the observed pattern was of cholestatic type [56]. These results were reproduced in a study of approximately 600 DILI cases from the Spanish Hepatotoxicity Registry, demonstrating that 77 % of patients

with DILI received medications with daily doses greater than 50 mg [54], 50 % having cholestatic or mixed pattern [54].

The same group of investigators also demonstrated that drugs with 50 % or greater hepatic metabolism caused a significantly higher frequency (compared with drugs with less hepatic metabolism) of hepatic adverse events [56]. Interestingly, compared with medications without biliary excretion, compounds with biliary excretion significantly increased the incidence of jaundice (74 % vs. 40 %; $P < 0.0001$) [56]. Cholestatic drug reactions per se were not further analyzed and need further study. Although some drugs are given in high doses and metabolized to a great extent in the liver they do not seem to be prone to lead to hepatotoxicity. Interestingly, a recent study demonstrated that apart from the high daily dose found to be important for the risk of DILI, the lipophilicity of drugs contributed significantly to the risk [57]. The dose and the lipophilicity of the drug, called by the authors as the “rule-of-two” seems to be able to better estimate the risk of DILI than the dose alone [57]. However, the hepatic metabolism of the drugs was not taken into this equation and needs further study.

Pathophysiology

Hepatic metabolism of drugs involves phase I reactions followed by phase II reactions or phase I alone or rarely only phase II [58]. Phase II reactions result in their anionic conjugates with sulfate, glucuronate or glutathione. These drug metabolites are transported across hepatocyte membranes by transporters (uptake or efflux transporters) on the apical or the canalicular membranes [59]. This hepatic drug transport has been shown to be involved in the pathophysiology of cholestatic adverse effects due to drugs [59, 60]. Transport at the apical membrane into hepatocytes involves the organic anion transporting polypeptide [59]. Little data exist on defects in these uptake transporters and risk for cholestatic liver injury [59]. Basolateral transport processes probably determine hepatic exposure to drugs and their metabolites, which reach the canalicular membrane [60, 61]. Inhibition of this basolateral transport does not seem to increase the risk of cholestasis due to drugs [62]. In contrast, inhibition of efflux proteins can lead to cholestatic liver injury caused by certain compounds or their metabolites [60, 61]. The efflux of drugs into bile involves canalicular transporters of the MRP family, includes certain glycoproteins of the MDR family and bile salt export pump (BSEP, ABCB11) [62]. The bile salt export pump (BSEP) has been shown to be a major transporter of bile salts and drug metabolites from hepatocytes into bile [62]. Drugs that inhibit export on the canalicular side through inhibition of BSEP can lead to cholestasis in susceptible subjects [62].

Many cholestatic drug reactions result from a drug- or metabolite-mediated inhibition of hepatobiliary transporter systems [60, 61]. Cholestatic liver disease associated with rifampicin, troglitazone, glibenclamide, and bosentan has in animal experiments been related to inhibition of bile salt export pump function in cholestatic liver

disease [60, 61]. Cholestasis due to flucloxacillin, terbinafine, sulindac, and bosentan has been associated with inhibition of the canalicular BSEP [63–65]. Bosentan, a drug with well-known hepatotoxicity, has been shown to inhibit BSEP, leading to accumulation of toxic bile acids within the hepatocytes [66, 67]. Mutations that disturb BSEP function have been identified in patients with a history of cholestasis due to drugs [68]. Patients with mutations in genes that encode BSEP or MDR3 have a threefold increase in risk of cholestatic DILI from oral contraceptives, psychotropic drugs, proton pump inhibitors and certain antibiotics [68]. Other molecular mechanisms of cholestasis have been reported such as destruction of the cytoskeleton, impaired trafficking and disruption of the tight junction network, inhibition of ATP-dependent transporters and modulation of fluidity of the canalicular membrane [68].

Specific Agents

As the list of drugs associated with cholestatic injury is very long [44, 69] only the most important drugs and type of drugs will be covered.

Antibiotics are the most common type of drugs associated with DILI [13–16].

Penicillanase-Resistant Penicillins and Other Penicillins

Flucloxacillin-induced cholestasis is well documented [20, 22, 70, 71]. Flucloxacillin is on the market and commonly prescribed in Australia, Sweden, and UK, whereas this drug has never been marketed in the USA and many other countries. Flucloxacillin is the most common reason of *idiosyncratic* liver injury in Sweden, with 16 % of all DILI cases [13] and the second most common cause of drug-induced jaundice in the UK [72]. Female sex, age and high daily doses have been shown to be associated with higher risk of liver injury due to flucloxacillin [20, 71]. A total of 7/129 (5 %) who had reported flucloxacillin liver injury, in Sweden from 1970–2004, which is probably an underestimation as not all cases have been reported to the authorities [13]. Ductopenia [22] and cholestatic cirrhosis leading to liver transplantation has been reported [20, 70]. Also other semi-synthetic penicillanase resistant penicillins such as cloxacillin, dicloxacillins, and oxacillins have been shown to induce cholestatic hepatitis [15, 20, 70]. Treatment with penicillinase-sensitive penicillins very rarely causes liver damage [73], but a prolonged and severe cholestasis has been reported for benzylpenicillin [74].

Amoxicillin–Clavulanate

Amoxicillin–Clavulanate (A–C) is a commonly prescribed antibiotic in many countries and in most DILI studies it is among the most common antibiotics leading to DILI [14, 15]. One-third of drug-induced jaundice was associated with A–C

in a study from the UK [72] and the most common cause of DILI in Spain [14]. In the USA A–C was the most common antibiotic associated with DILI [15]. Liver injury can develop early in the course of treatment but also late in the course of prolonged treatment and furthermore following discontinuation of therapy [75]. Most cases of A–C induced liver injury have a cholestatic or mixed pattern. Liver injury is mainly related to the clavulanic acid component, as the incidence of DILI with A–C combination is markedly higher than that of amoxicillin alone [76]. Risk factors for hepatotoxicity are age over 65 years, female sex and repeated course of the antibiotic [75–77]. Most cases are mild but a protracted course is also possible and can in rare cases lead to acute liver failure or require transplantation [75, 77].

Tetracyclines

Tetracycline hepatotoxicity was originally associated with large doses that were often given intravenously and in pregnancy [78]. Incidence of hepatotoxicity associated with normal and low dose tetracyclines such as doxycycline, seems to be lower than most reported antibiotics leading to DILI with a generally favorable prognosis [79, 80]. The liver injury was designated as cholestatic, hepatocellular, and mixed, with similar frequencies [79]. No cases of death due to tetracyclines have been reported to the Swedish authorities by spontaneous reporting [13, 79].

Trimethoprim–Sulfamethoxazole

In most studies on DILI, this drug is commonly associated with DILI [13–16]. After A–C, nitrofurantoin and isoniazid, Trimethoprim–Sulfamethoxazole (T–S) was the fourth most common antibiotic inducing DILI in the North American DILIN study [15]. The sulphonamide component is considered to be responsible and sulfonamides mostly lead to cholestatic patterns [81]. Almost 60 % of reactions are of cholestatic nature [82]. In one study approximately 10 % of patients with jaundice due to T–S either died or underwent liver transplantation [13].

Macrolides

Erythromycin is a well-documented cause of cholestatic liver injury [73]. Erythromycin was the second most commonly reported antibiotic leading to DILI in Sweden [13]. In a collection of case reports from the literature, cholestatic injury was observed in 69 % of cases [82]. Prognosis is generally favorable and it has extremely rarely been reported to lead to acute liver failure and death [13, 82]. Clarithromycin and azithromycin have both been associated with cholestatic liver injury [83, 84].

Other Antibiotics

The antifungal Terbinafine has been shown to induce cholestatic injury that can be very severe and lead to acute liver failure and/or require liver transplantation [85, 86]. Terbinafine induced hepatotoxicity has been reported in a number of patients from previous studies on DILI [13, 15]. Other antibiotics in common use and shown to lead to cholestatic hepatitis are ciprofloxacin [87, 88] and cephalosporins [89, 90]. DILI due to cephalosporins has previously been considered to be extremely rare. However, a recent study from the DILIN network in the USA, described 32 out of a total of 655 cases (5 %) enrolled between 2004 and 2010 [90]. The majority demonstrated a cholestatic pattern and in several cases the toxicity occurred after therapy had been stopped; at least one fatal outcome was attributed to the cephalosporin-induced hepatotoxicity [90].

Immunosuppressive Agents

A number of cases of severe cholestatic hepatitis due to AZA have been reported in the literature [91–93]. Nodular regenerative liver hyperplasia (NRH) is a rare but potentially serious complication of treatment with AZA [94].

Most patients develop liver injury during the first 3 months of therapy [94]. The frequency of DILI associated with AZA is unclear. According to a systematic review, the mean prevalence of AZA or 6-mercaptopurine (MP)-induced liver injury in IBD was approximately 3 %, and the mean annual drug-induced liver disorder rate was only 1.4 % [95]. This low figure was based on retrospective studies and contrasts with an approximately 10 % incidence reported by a prospective study [94]. In this prospective study hepatotoxicity occurred in 16/161 (10 %) after a median of 85 days, but only in approximately one-third of cases azathioprine therapy had to be discontinued [94]. In a recent prospective study, as much as 1 out of 133 users of azathioprine developed liver injury [6], which is the highest frequency of idiosyncratic liver injury associated with drugs, reported so far.

Psychotropic Drugs

Chlorpromazine has been the prototype of cholestatic type of injury and can lead to cholestatic hepatitis, ductopenia and in rare cases to cholestatic cirrhosis [3]. Other antipsychotic drugs such as risperidone have also been reported to cause cholestatic liver injury [96, 97]. Cholestatic hepatitis has also been observed after tricyclic antidepressants such as imipramine and amitriptyline [44]. Duloxetine, a commonly used antidepressant, nowadays has recently been associated with cholestatic hepatitis [98].

Drugs Against HIV

Liver injury has been attributed to highly active antiretroviral therapy (HAART) [99]. DILI was the most likely cause in one-third of patients with AIDS and jaundice [100]. Among cases of suspected DILI reported to the WHO monitoring center, HIV drugs such as stavudine, didanosine, and nevirapine were among the top ten most common causes of fatal liver injury due to drugs [101]. Non-cirrhotic portal hypertension (NCPH) in HIV infected persons has been associated with antiretroviral therapy, particularly the drug didanosine [102–105]. Most patients present with cholestatic liver disease for months or years before signs manifestations of portal hypertension such as variceal bleeding and ascites became apparent [102, 104]. The prognosis seems to be favorable until symptoms and signs of portal hypertension develop [105]. Approximately one-fourth of patients with NCPH and esophageal varices had liver related mortality [105]. In multivariate analysis, the only independent predictor of NCPH was didanosine exposure [105].

Other Types of Drugs Associated With Cholestatic Liver Injury

Although cholestatic liver disease has been associated with oral contraceptives (OC) for many decades, less than 1 % of cases in Sweden, Spain, and the USA were attributed to OC [13–15]. The long-term use of OC has been associated with an increased risk of certain types of liver disease such as acute intrahepatic canalicular cholestasis, hepatic adenoma, focal nodular hyperplasia, hepatic vein thrombosis, and portal vein thrombosis [52, 106]. In a Swedish study on adverse liver reactions attributed to OC over 25 years, there was a sharp decline in the number of reports during the studied period, suggesting changes in reporting habits [107]. There was also a significantly lower incidence of reports for medium-compared to high-estrogen dose OC, and a further decrease in incidence with low-estrogen dose OC [107]. Cholestatic and hepatocellular liver enzyme patterns were equally frequent in patients with adverse reactions from low-dose estrogen OC and both types had favorable prognosis [107]. The duration of therapy until the hepatic reaction was detected ranged from 3 to 360 days (median of 60 days) [107]. Lower doses of estrogens and gestagens seem to lead to a decreased incidence of adverse liver reactions [107]. Anabolic steroids have a well-documented hepatotoxicity, mainly in the form of intrahepatic cholestasis [108]. Hepatotoxicity associated with dietary supplements containing anabolic steroids has been increasingly recognized in the USA [108, 109]. Several other dietary supplements have been associated with cholestasis, although for some reason hepatocellular pattern is more frequently observed associated with dietary supplements [109].

Management

Once DILI is suspected in a patient with new onset liver disease prompt discontinuation of the drug implicated is usually the first step in the management of these patients. At the same time it is also of major importance to assess the severity of the liver disease. Symptomatic patients with jaundice should be hospitalized. Once coagulopathy and/or encephalopathy develops an immediate contact should be taken with a transplant center if the patient does not have an obvious contraindication for liver transplantation. Patients with suspected DILI and concomitant jaundice should be carefully looked after and liver transplantation considered before they develop severe encephalopathy. Patients with DILI-related acute liver failure should be considered for liver transplantation early in the course of the disease as acute liver failure due to drugs has a generally poor prognosis without transplantation [110]. Transplantation free survival in non-acetaminophen-induced liver failure was better in patients receiving *N*-acetylcysteine (NAC) than those who were randomized to placebo [110]. Approximately one-fourth of these patients had drugs other than acetaminophen induced acute liver failure [110]. Other than NAC specific treatment options of the liver injury associated with drugs are very limited. Although ursodeoxycholic acid has been used in long-standing cholestatic drug reactions, no data is available that has documented its efficacy. Rechallenge with the suspected drug leading to DILI for diagnostic of therapeutic purposes is generally not recommended as there is usually a more severe reactions associated with rechallenge [111].

Summary

Cholestasis due to drugs is a diagnosis that needs to be considered in most patients presenting with a biochemical cholestatic pattern. Detailed information on the drug use, results of dechallenge, the documented hepatotoxicity of the drug, and exclusion of competing etiologies are important to support a diagnosis of DILI. Most cases of cholestatic DILI are mild but in rare cases, ductopenia and cholestatic cirrhosis can develop. Patients with cholestatic jaundice due to drugs can develop liver failure in approximately 10 % of cases.

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