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Adverse Effects of Drugs and Toxins on the Liver

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1. Introduction

More than 1000 drugs and toxins are suspected to induce liver damage, but only for a few are causality proven. Preclinical studies of drugs cannot predict hepatotoxicity due to the low incidence of such events, and postmarketing data are difficult to interpret. This is due to the fact that the clinical presentation of drug-induced liver injury is highly variable from asymptomatic, reversible elevation of liver enzymes to a fulminated hepatic failure. Furthermore, in most cases the clinical, biochemical and pathological pictures are indistinguishable from that seen with other causes of liver disease. Thus, suspected drug-induced hepatic injury is often a diagnosis made by exclusion of other causes. These include among others infectious, inflammatory and neoplastic diseases in the liver as well as complications in the organ due to systemic diseases. A common diagnostic challenge is a situation where patients who develop acute liver disease use several drugs, together with alcohol, recreational and illegal compounds. Moreover, even excipients present in drug formulations cannot always be ruled out as causative agents. Furthermore, due to the increasing popularity of complementary and alternative medicine, several new substances have been suspected of liver injury. These toxins are associated with ingredients of herbal medicine and nutritional-based therapies. The common belief that these substances and therapies are only beneficial to humans is challenged by an increasing number of reports of adverse effects including hepatic injury. As a general rule, drug- and toxin-induced liver injury is usually benign with full recovery after withdrawal of the offending agent. However, this implies that a drug or a toxin must be recognized as a possible causative agent. Furthermore, drug- and toxin-induced liver injury is a frequent cause of liver failure, and represents a health problem in our society. The present chapter summarizes the main principles of adverse effects of drugs and toxins on the liver, in particular examples of adverse effects of herbal medicine and nutritional-based therapies in the literature as well as cases submitted to drug information centres and pharmacovigilance units in Norway.

1.1 Epidemiology and demographics of drug-induced liver injury

The risk of serious liver damage is small compared to the number of patients who use drugs, but drug-induced hepatic injury is currently one of the most important reasons for

exclusion of drugs for further clinical development, and withdrawal of drugs from the market (Bakke et al., 1995). Furthermore, prescribed drugs have been shown to account for about 30-50% of cases of acute liver failure with risk of death or liver transplantation (Ostapowicz et al., 2002; Larrey & Pageaux 2005). The true incidence of drug-induced liver injury is not known because most of the data comes from retrospective studies. An important exception is single prospective study of the incidence of drug-induced adverse effects in the liver for a general population, performed over 3 years in France (Sgro et al., 2002). It was found to be 14/100 000 persons, and this incidence is 16 times higher than that collected by pharmacovigilance centres. Thus, spontaneously reported cases analysed in a retrospective fashion are not useful to predict or compare hepatotoxic potential of various drugs. A retrospective study from the UK showed that among 800 jaundiced patients referred to a single centre, 3.5% had drug-induced liver injury. The annual incidence rate of drug-induced liver injury in this study was estimated to 1.27 per 100 000 inhabitants per annum (Hussaini et al., 2007). A Swiss study found that approximately 1 in 100 patients developed drug-induced liver injury during hospitalisation in a department of medicine. Incidences were highest for antineoplastic agents and tuberculostatics (Meier et al., 2005).

Demographic data have suggested several risk or host factors for drug-induced liver injury. Typical examples are female sex, old age, use of alcohol, genetic factors, comorbidities, large body mass index, and several others. However, susceptibility of an individual varies with the drug in question, and drug properties (chemical structure) represent a separate risk factor (Lucena et al., 2008). Although drug-induced liver injury is in general rare in children, salicylates and valproic acid are associated with hepatic damage in this population. Chronic liver disease is thought to be of minor importance as a risk factor, but liver injury to isoniazid is seen in patients with viral hepatitis or Human Immunodeficiency Virus (HIV). Furthemore, chronic alcohol ingestion, fasting and malnutrition can increase the risk of serious paracetamol (acetaminophen) toxicity (Metha et al., 2010). Data on the risk of liver injury for specific drugs is not known. Although asymptomatic rises in liver enzymes are common for several drugs, the more clinically relevant forms of liver damage are thought to occur with a frequency between 1 in 1000 and 1 in 10,000. Liver injury associated with overdose is frequently due to ingestion of paracetamol. Non-steroidal anti-inflammatory drugs (NSAIDs), along with antimicrobial agents and antiepiletics, are the most frequent causes of liver injury with conventional doses (Andrade et al., 2005; Andrade et al., 2007; Lucena et al. 2008). These drugs are consumed massively worldwide, and for NSAIDs a estimated incidence of 0,3-9/100 000 have been suggested (Bessone, 2010). Amoxicillin-clavulanate was the single agent responsible for the highest number of incidences in a report from a Spanish registry (Andrade et al., 2005).

1.2 Main types of drug-induced liver injury

Drugs can cause liver injury in several ways, but three main types are usually referred: dose-dependent (or intrinsic) toxicity, dose-independent (or idiosyncratic metabolic) toxicity and drug allergy (or idiosyncratic immunological). Overdose of most drugs can represent a threat to the liver, and psychotropic drugs are often involved. Increased use of antiepileptics, like lamotrigine, against depressive periods in bipolar disorder, are reflected by an increasing number of reports of deliberate overdose. Intrinsic toxicity is predictable and often caused by high concentrations of parent drug and/or a metabolite when the

liver`s defence systems against toxic damage are overwhelmed. Most people ingesting large amounts of a drug are affected, and liver injury is apparent within a few days. Injury is usually reversible within days to weeks if liver failure does not develop. A randomized, placebo-controlled trial where transaminases were monitored in healthy adults receiving therapeutic doses (4 g daily) of paracetamol, showed that more than 50% of the subjects who received drug showed an increase of alanine aminotransferase (ALT) more than 5 times baseline. Furthermore, this was in particular associated with subjects with Latin American background who showed two-fold increased risk of increase of ALT more than 3 times that of upper limit of the normal range (ULN) (Watkins et al., 2006). Thus, overdose is not always necessary to induce liver injury when using drugs with intrinsic toxicity in susceptible subjects.

With chronic high dose of a drug with intrinsic toxicity, like methotrexate, liver injury can manifest itself first after months or years. In the case of idiosyncratic metabolic toxicity, host factors that may enhance susceptibility to drugs, are of particular importance. Inherited defects in drug metabolism can give abnormal reactions to drugs, but liver injury can take weeks to years to develop. After drug withdrawal, reversibility is gradual over weeks and new injury develops slowly with rechallenge. It has been questioned if these reactions are dose–independent after all. A study showed that when drugs that caused idiosyncratic hepatotoxicity were given at a daily dose of 100 mg or higher, they were more likely to induce liver injury than when administered at a dose below 10 mg per day (Walgren et al., 2005). Therefore, the difference between intrinsic and idiosyncratic toxicity are not sharp, and liver injury in an individual depends on a complex relationship between susceptibility and drug factors. Besides dose-dependent and idiosyncratic toxicity, drug allergy may also cause liver disease, though it is supposed to be more uncommon. In these cases the liver is injured by inflammation caused by the immune system, and extrahepatic signs of hypersensitivity reactions like fever, rash and periphere eosinophilia can be present. Clinical characteristics like a relatively short period of therapy (1-4 weeks) before onset, rapid onset on rechallenge, and risk of cross-reactions to related drugs are associated with this type. After drug withdrawal, the injury is reversible within weeks. Thus, time-course of onset and reversibility of idiosyncratic immunological or metabolic liver injury is closely associated with adaptive reactions in the immune system and accumulation/elimination of toxic metabolites, respectively. However, the difference between these two types of idiosyncratic injury is not distinct. There are cases of idiosyncratic immunological reactions without fever, rash and eosinophilia, and there is growing evidence that immune cells or immune mechanisms are more important for both predictive and idiosyncratic liver injury than previously thought (Adams et al., 2010).

1.3 Main mechanisms of drug-induced liver injury

The liver has a central role as a detoxifying organ towards xenobiotics and chemicals. However, biotransformation to less toxic substances can actually involve production of molecules that can induce liver injury through various pathways. Important mechanisms involved in non-allergic drug-induced hepatic injury can be divided into (Han et al, 2010): (1) drug metabolism and reactive metabolite formation, (2) covalent binding, (3) reactive oxygen species generation, (4) activation of signal transduction pathways that modulate cell death or survival and (5) mitochondrial damage. Furthermore, immunological mechanisms can be triggered by these reactions. Most of the current knowledge of mechanisms for drug-

induced liver injury is associated with basic studies, and the clinical relevance of the present models of damage needs to be defined. In the following, only the main principles of injury are summarized. Because of the liver's capacity to regenerate, full recovery is possible even if drug-induced liver injury has caused extensive hepatocyte death.

1.3.1 Drug metabolism and reactive metabolite formation

Biotransformation of lipophilic xenobiotics to more hydrophilic substances before excretion in urine or bile is an important function in the liver. Phase I enzyme reactions involve among other cytochrom-P450 (CYP-450) reactions which converts xenobiotics to reactive metabolites. The metabolites can via Phase II enzymes be conjugated to hydrophilic molecules (glucuronide conjugation-most important reaction among several) before excretion. The reactive metabolite N-acetyl-p-benzo-quinone imine (NAPQI) is produced via CYP1A2 and CYP2E1 (CYP-450) enzymes. However, the majority of paracetamol is metabolized by glucuronidation (Phase II reaction), and the small amount (approximately 10% of a paracetamol dose) of NAPQI that is produced is immediately inactivated by conjugation with glutathione (GSH). With an overdose of paracetamol, glucuronidation is saturated and detoxifying pathways described above are overwhelmed. The reason why reactive metabolites can induce damage through idiosyncratic liver injury is based on a complex interplay between several factors. Age, sex, liver function and disease, environmental (enzyme induction and inhibition) and genetic (polymorphism) can influence the level or function of CYP-450, and thereby production of reactive metabolites. Inherent toxicity of these, their distribution and accumulation within the organ, cells and subcellular organelles together with the status of defence systems are likely to be of additional importance (Grattagliano et al., 2009).

1.3.2 Covalent binding

Bioactivation of drugs through Phase I reactions can produce electrophilic metabolites with intrinsic chemical reactivity toward several cellular macromolecules. Covalent binding of short-lived reactive metabolites to cellular components includes proteins, peptides, lipids and nuclear acids, and this modification is thought of as essential in hepatotoxicity of drugs (Kemper, 2008). An important pathway for bioactivation of many acidic NSAIDs involves formation of reactive acylglucuronides (Bailey & Dickinson, 2003). Thus, Phase II reactions of bioactivation, usually thought of as a detoxifying process, can also produce reactive metabolites associated with hepatotoxicity. Furthermore, covalent modification of cellular components can initiate both toxic and/or immunological mechanisms of liver injury (Bailey & Dickinson, 2003).

1.3.3 Reactive oxygen species generation

Metabolic activation of drugs can involve production of reactive oxygen species. Through chemical modification of cellular macromolecules they can induce hepatocellular injury. Reactive oxygen species can initiate protein and lipid peroxidation, and deplete antioxidant defences like reduced glutathione (GSH), and modify sulphydryl (SH) groups on cellular components. These non-covalent reactions represent additional toxic mechanisms to covalent reactions. Depletion of GSH, and oxidation of SH groups on Ca^{2+}-ATPases are related to damage induced by NAPQI in the case of paracetamol overdose.

The subsequent increased cellular stress and uncontrolled increase in cytosolic Ca^{2+} concentration stimulate Ca^{2+}-activated degradative enzymes with further cellular injury. Disruption of membranes of cells, subcellular organelles including mitochondria, can affect energy production and further disrupt ionic homeostasis, and initiate cell death pathways.

1.3.4 Activation of signal transduction pathways

The stress in hepatocytes induced by reactive metabolites, including reactive oxygen species, can activate several signal transduction pathways. Several endogenous signal substances modify signal transduction including various cytokines. The pathways activate prodeath or survival proteins that determines the fate of the cell. Even in necrotic liver injury, associated with paracetamol, such pathways could be of relevance (Han et al., 2010). Important for liver injury is c-Jun N-terminal protein kinases (JNK). JNK can be activated with many stresses including reactive oxygen species, and represents a common mechanism of cellular injury associated with several diseases (Han et al., 2010).

1.3.5 Mitochondrial damage

Mitochondria have a central role in liver injury. Cytotoxic drugs and/or metabolites can attack the organelle directly or through pathways described above. Important pathological mechanisms are mitochondrial permeability transition (MTP) through opening of MPT pore in the membranes of the organelle, and activation of signals, death receptors and proapototic pathways. As a result acute necrosis, apoptosis and autophagic cell death can occur (Kass, 2006). Mitochondrial dysfunction is involved in most forms of drug-induced liver injury, and through dysfunction of the organelle more subacute or chronic injury can develop. Valproic acid can inhibit mitochondrial fatty oxidation, uncouple mitochondrial respiration and induce MTP (Pessayre et al., 2010).

1.3.6 Immunological mechanisms

Various types of immune cells, including lymphocytes, reside in the liver, and other leukocytes are distributed to this organ during inflammation (Adams et al., 2010). Furthermore, antidrug antibodies and autoantibodies can be detected during liver injury (Liu & Kaplowitz, 2002). A drug-modified protein formed due to reactions described previously (reactive metabolite formation and covalent binding) can initiate either classic immune responses against the drug or an autoimmune response against a modified protein. The classic immune response is characterized with short time period to onset of symptoms and a memory component, while the autoimmune response develops after a long time period with no memory. The different courses are based on interaction with different T helper cells, but involvement of B cells and other immune cells could be of importance (Adams et al., 2010). Drug-induced allergic hepatitis are usually thought of as mediated by type IV immunological reactions, and eosinophilia, atypical lymphocytosis and liver infiltrate are frequently observed together with the presence of sensitized T lymphocytes. Type II hypersensitivity reactions with circulating specific antibodies occur, but to a lesser extent. Halothane is associated with antibodies directed against CYP2E1 (Andrade et al., 2007). Due to a complex interplay with drug factors and individual susceptibility, an immunological reaction or tolerance to the drug can develop. Typical examples of drugs that can cause allergic hepatitis are sulphonamides.

1.3.7 Cell death, cell involvement and other targets of injury

In most cases, hepatocyte injury and death is the critical step leading to the clinical manifestations of drug-induced liver injury. However, in certain circumstances, cholangiocytes or endothelial cells may be the principle target cell (e.g., ductopenic cholestasis and sinusoidal obstruction syndrome) (Han et al., 2010). Non-parenchymal hepatic tissue like Kupffer and endothelial cells are also involved in causing injury, and can be activated by chemotactic factors. In immunological reactions different leukocytes are involved as mentioned earlier. Furthermore, besides mitochondria, microsomes and nuclear components can be targets for injury. Modification of cellular function by down- or up-regulation of genes can also mediate drug-induced hepatic damage. The modifying role of several cytokines and other signal substances in pathways of necrosis, apoptosis or survival are emerging, as is the relevance of various risk factors for the clinical course of the injury (acute liver failure, full recovery or development of chronic disease) (Russmann et al., 2009).

Figure 1 summarizes adverse effects of drugs and toxins on the liver.

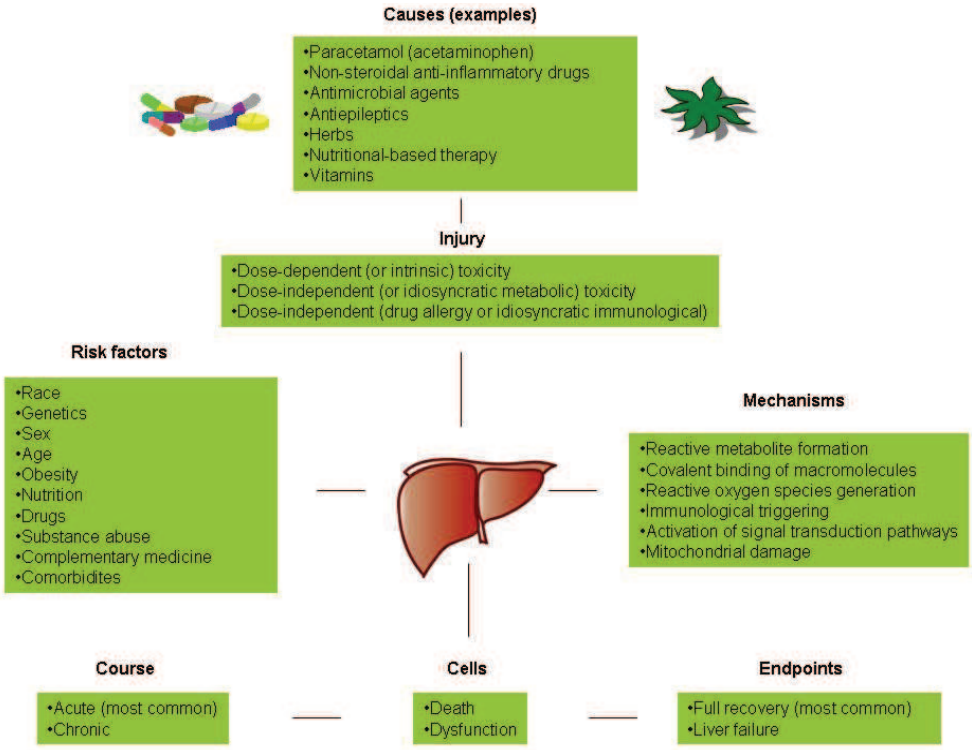

Fig. 1. Adverse effects of drugs and toxins on the liver. Notice that idiosyncratic forms of liver injury are associated with a complex interplay between individual risk factors (inborn, physiologic or environmental) and mechanisms of injury. In an individual this interplay determines if a threshold for disease is reached. Increased dose of the offending agent increases the likelihood of disease in most individuals in the case of drugs with intrinsic toxicity.

1.4 Diagnosis and clinical presentation of drug-induced liver injury

Suspected drug-induced hepatic injury is often based on an exclusion of alternative diagnosis. These include among others infectious, inflammatory and neoplastic diseases in the liver as well as complications in the organ due to systemic diseases, either aquired or inherited. Several diagnostic tools are available, but it is difficult to prove causality related to a specific drug. Notice, that as a general rule, drug-induced liver injury is usually benign with full recovery after withdrawal of the offending agent. However, in some cases acute liver failure due to massive necrosis or end-stage disease with cirrhosis due to chronic injury can be the result.

1.4.1 Liver enzymes, other laboratory data and imaging techniques

Measurement of liver enzymes remains the most practical tool to diagnose liver damage, and includes mainly alanine aminotransferase (ALT), an enzyme present in hepatocytes, and alkaline phosphatase (ALP), an enzyme in the cells lining the biliary ducts of the liver. Based on elevation of, and ratio between elevation of, these enzymes, hepatocellular, cholestatic or mixed liver injury is diagnosed (Benichou, 1990; Danan, 1993). Acute hepatocellular liver injury is defined by ALT > 2 ULN or an ALT/ALP ratio ≥ 5. Acute cholestatic injury is defined as an increase in serum ALP > 2 ULN or by an ALT/ALP ratio ≤ 2. Mixed hepatic injury features an intermediate between hepatocellular and cholestatic patterns, and features of either type may predominate. By definition, the ALT/ALP ratio is between 2 and 5, while ALT > 2 ULN and ALP increased. With already elevated ALT or ALP, increase from baseline rather than ULN is often used. Liver enzymes like aspartate aminotransferase (AST), lactate dehydrogenase (LDH), gamma glutamyl transpeptidase (GGT) and bilirubin are of less importance, but can give additional information about the type and extent of liver damage.

The most frequent type of drug-induced liver injury is acute hepatocellular. To exclude alternative causes, viral and bacterial serology and screening for autoimmune hepatitis are often performed. The lymphocyte transformation test, which measures the proliferation of T cells of a suspected sensitized patient when exposed to the causative drug in vitro, could be a consistent test for identifying a drug suspected of causing allergic hepatitis, but it is not fully reliable and associated with methodological problems (Andrade et al., 2007). Furthermore, in more specific cases complications in the liver due to systemic diseases, either inborn or acquired, could involve additional laboratory and other examinations. Abdominal ultrasound, computer tomography and other imaging techniques cannot discriminate drug-or toxin-induced hepatic injury from other causes. However, they can exclude benign or malign mechanical obstruction in the case of cholestatic or mixed hepatic injury, and visualize biliary tracts and main blood vessels (Andrade et al., 2007).

1.4.2 Liver biopsy and histological findings in drug-induced liver injury

There are no histological findings specific for drug-induced liver injury. Some drugs usually cause one clinical or pathological (signature) injury like estrogens with cholestasis, but other drugs can cause a variety of pictures. An illustrating example is a recent published case series of suspected liver injury to duloxetine where several patterns of hepatic injury occurred, including hepatocellular and cholestatic features with highly variable liver histology (Vuppalanchi et al., 2010). Liver biopsy is seldom performed do to these

arguments, and is not regarded as essential in all cases of suspected drug-induced liver injury. There is also risk of error in sampling of tissue, or time of sampling due to different courses of clinical disease. However, in spite of low specificity of liver biopsy it represents the most important tool for defining the pattern of hepatotoxicity. Furthermore, liver biopsy could be of prognostic value in the case of chronic liver disease, when progression is poorly reflected by other laboratory and clinical assessments (Andrade et al., 2007). Moreover, a biopsy can also be used to stage the severity of hepatotoxicity if a patient is dependent on a drug that may have to be continued (Kleiner, 2009).

Hepatitis, with or without cholestasis, is the most common histological pattern of drug-induced liver injury. The most serious is acute liver failure which shows necrosis with or without signs of inflammation, or microvascular steatosis with little or no inflammation. Chronic hepatitis can show signs of autoimmunity or not. Cholestasis, granulomatous hepatitis and different patterns of steatosis are other examples together with vascular abnormalities (Ramachandran et al., 2009). There are three types drug-induced acute cholestatic drug injury. Bland cholestasis is the result of abnormal biliary secretion without significant hepatocellular damage. In cholestatic hepatitis (mixed type) there is parenchymal damage; and the third form of acute cholestasis is defined by the presence of bile duct injury or cholangiolitis. Drugs may cause chronic cholestasis through two additional mechanisms: through the obliteration of bile ducts, also known as the vanishing bile duct syndrome, or by extrahepatic biliary obstruction, known as secondary sclerosing cholangitis (David & Hamilton, 2010). Cirrhosis, as a sign of advanced scarring of the liver, is a late finding. Importantly, a mixed liver injury is far more characteristic of drug-induced hepatotoxicity than of viral hepatitis. Almost all drugs that produce cholestatic injury are also capable of inducing a mixed pattern. Although drug-induced cholestatic and mixed lesions progress to acute liver failure less frequently than hepatocellular types, their resolution is generally slower. For example, a long-term follow-up of a large cohort in a registry demonstrated a significantly higher trend towards becoming chronic in cholestatic/mixed cases compared to hepatocelullar-type disease (Andrade et al., 2006).

1.4.3 Clinical suspicion and drug history

Onset and course of the reaction, response to drug withdrawal or reintroduction are examples of clinical factors to assess causality of drug-induced liver injury. Furthermore, the level of documentation for the type, frequency and other characteristics of liver injury associated with the suspected drug are important. The temporal profile between drug and reaction is crucial to establish the diagnosis of drug-induced liver injury, as the onset of liver disease follows drug ingestion (Lucena et al. 2008). However, the manifestation of liver toxicity may occur weeks or months after drug ingestion and even after the drug has been stopped. A toxic metabolite with a much longer half-life than the parent compound could accumulate during a treatment period, and liver injury could be unmasked some time after drug withdrawal. Notice that enzyme elevations can persist for months after the drug has been discontinued. In some instances, measurement of serum levels of the drug or its metabolite can be helpful; an example is diagnosis and treatment of toxicity due to paracetamol. Since the list of drugs capable of causing liver injury is long, a systematic literature search for each drug that the patient has been taking is necessary. Keeping in mind that patients frequently use several prescription drugs, over the counter drugs, and herbal and nutritional products means that finding the offending agent can be a difficult task. The

case for drug-induced liver injury is strengthened if the reported pattern of injury in the literature is similar to the observed clinical and histological picture (Lucena et al. 2008). Rechallenge with the drug can help to establish a drug etiology, but it is often not done due to the inherent risk involved (Fontana et al., 2010). Since diverse histological patterns of drug-induced liver injury can mimic virtually any primary liver disease, appropriate imaging and laboratory tests are necessary to exclude other etiologies before the diagnosis of drug-induced liver injury can be accepted. Figure 2 summarizes diagnosis of drug- and toxin-induced liver injury.

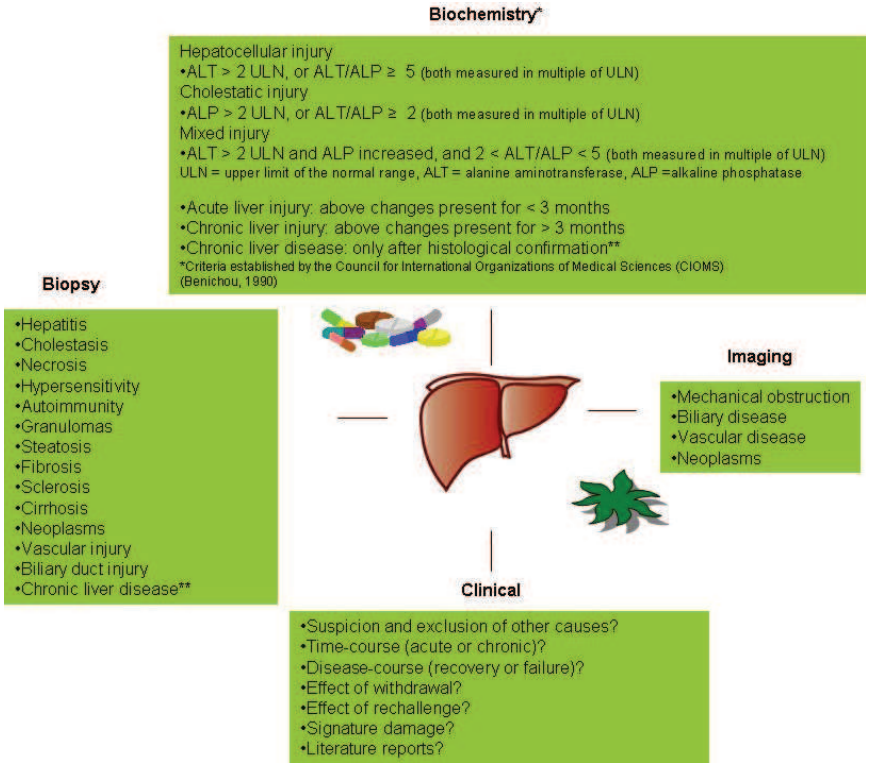

Fig. 2. Diagnosis of drug- and toxin-induced liver injury. Notice that due to the highly variable clinical presentation of this form of liver injury, that can be indistinguishable from other causes, causality is often based on circumstantial evidence.

1.4.4 Algorithms or scales, and clinical networks

More objective, systematic approaches with criteria for having an adverse effect (all types) or a more specific adverse effect (drug-induced liver injury) have been proposed. Three examples of these algorithms or scales are the Council for International Organizations of Medical Sciences (CIOMS) (Benichou, 1990; Danan, 1993), the Clinical Diagnostic Scale (CDS) or the Maria and Victorino (M&V) scale (Maria & Victorino, 1997) and the Digestive Disease Week-Japan (DDW-J) scale (Takikawa et al., 2003). The main principle of these scales is an evaluation of several criteria (numerical weighted), sum of scores or decision

trees to assess the probability that a liver disease is drug-induced. All of them use several diagnostic factors mentioned earlier in this chapter. A major problem is validation of the scales when there is no accepted gold standard, and lower reliability when the number of experts who evaluate the same cases increases (García-Cortés et al., 2011). Furthermore, sensitivity to various individual risk, drug and diagnostic factors can be limited when applying such categorical scales. To increase our knowledge of drug-induced liver injury in a more homogenous and standardized fashion, collaborating clinical networks in Europe (Andrade et al., 2005; Andrade et al., 2006) and the United States (Hoofnagle, 2004) have been established. The purpose of these networks is to study prospectively new cases to improve our understanding of etiology, pathogenesis and risk of drug-induced liver injury (Fontana et al., 2009). A promising task is development of more drug-specific assessment tools for causality (Fontana et al., 2010).

1.5 Liver disease and drugs

As a general rule liver injury has to be extensive before metabolism of drugs are reduced. Thus, patients with existing liver disease without cirrhosis often can use drugs in conventional therapeutic doses. However, there is no specific test to predict liver function with respect to the elimination of particular drugs. Liver function tests are often used to evaluate liver capacity with relevance to hepatic clearance of drugs. The level of albumin, and coagulation factors, through measurement of international normalized ratios (INR), are of importance for both pharmacokinetics (protein binding, metabolism and distribution), but also pharmacodynamics (increased risk of bleeding with anticoagulants). Furthermore, advanced liver disease can change both pharmacokinetics and -dynamics in the organ as well as systemic. Development of renal failure and hepatic encephalopathy in advanced liver disease are two examples. Increased volume of distribution of water-soluble drugs in ascites can require increased loading dose, while shunting of drugs due to cirrhosis can reduce presystemic elimination (first-pass effect) with high bioavailability as a result. Crucial to understanding of the pharmacokinetics of a drug is that the unbound fraction is available for either distribution or clearance, and this fraction is at the same time responsible for the pharmacodynamic effect. Liver disease can be associated with reduced protein binding and reduced metabolism, and an increased unbound fraction of a drug can be associated with toxic effects. With advanced liver disease, and extrahepatic effects as mentioned above, the net result can be difficult to predict (Verbeeck, 2005). Furthermore, drug concentration levels usually reflect the sum of bound and unbound drug, but not the ratio. Thus, dosing and monitoring of drugs in advanced liver disease must include these implications. Acute liver injury preferently gives parenchymal damage, but with little change in metabolic capacity similar to autoimmune hepatitis. Chronic liver diseases are associated risk of reduction in drug-metabolizing activities. However, it affects the two main phases of biotransformation differently. Phase II reactions is often considered to be affected to a lesser extent than Phase I, but can also be substantially impaired in patients with advanced cirrhosis. Some drug monographs give advice on dosage of drugs in liver disease in relation to the semi-quantitative Child-Pugh score (Verbeeck, 2005). The score employs five clinical measures of liver disease, and is frequently used to assess the severity of liver function impairment. However, it represents only a rough guidance for dosage adjustment because data on how the liver metabolizes individual drugs is missing.

1.6 Withdrawal of drug and treatment of drug-induced liver injury

Drug-induced liver injury can range from asymptomatic and reversible elevations of liver enzymes to a fulminant hepatic failure. Between these two manifestations, the clinician is faced with the question of withdrawal of a drug or continuation of therapy. A liver injury can develop into liver failure if the offending drug is not withdrawn despite symptoms and signs of hepatic disease. Risk factors like old age, preexisting cirrhosis, fasting, malnutrition, chronic alcohol abuse, may all increase the risk of liver injury, as the dose of a drug in case of dose-dependent toxicity. However, elevation of liver enzymes does not always predict the risk for acute liver failure of drugs (Larrey & Pageaux, 2005, Lewis, 2006), and this raises the controversial question of which drugs where regular monitoring of liver enzymes are of clinical value. The approval authorities are motivated by risk reduction, and the drug industry adds to this the economy of keeping drugs on the market while the clinician wants to reduce irrelevant alerts in practice. An illustrating example of the challenge this represent for physicians is the commonly prescribed statins, where mild elevation of liver enzymes is thought of as a pharmacodynamic effect of altered lipid homeostasis, and not a toxic damage of the drug (Onusko, 2008, Bader, 2010).

Elevations of ALP > 2-3 or ALT > 3-5 ULN is suggested as a general thumb rule for evaluation of drug withdrawal, while long-time (months) elevation of liver enzymes irrespective of magnitude, can be a warning sign with therapy of drugs like valproic acid, methyldopa and methotrexate. However, for several drugs initial elevation of liver enzymes does not progress despite continuing the drug and the elevation can return to baseline. This phenomenon (often called tolerance in this context) is seen in up to 50% of patients taking tacrine, and is thought of as an adaptive process in the liver perhaps due to upgrading of protective pathways (Lewis, 2006). The choice of continued therapy despite significant elevation of liver enzymes is of course modified by how important the drug is for treatment of the patient. However, ALT > 8 ULN requires immediate drug withdrawal (Tajiri et al., 2008). Notice that withdrawal of the suspected drug is the most important therapeutic action in drug-induced liver injury, and there are currently no specific antidotes with the exception of N-acetylcysteine used to replenish GSH in paracetamol intoxication (David & Hamilton, 2010). Due to the fact that depletion of GSH could be associated with hepatotoxic effect of several other drugs than paracetamol, new animal and clinical studies emerge that describe treatment of drug-induced liver injury with this antidote (Baniasadi et al., 2010; Said & El-Agamy, 2010). Furthermore, modifying important signal pathways for liver injury could represent a therapeutic option in the future. Today, treatment of most cases of drug-induced liver injury is mainly symptomatic.

1.7 Further studies and prevention

Every aspect of drug-induced liver injury discussed so far is currently a subject of intense research. Both epidemiological studies and establishment of cooperative networks could give us valuable information and new understanding about relevant drugs, risk factors and diagnostic measures. To reveal the basic mechanisms of liver damage, further studies in genomics, proteomics, biochemistry and histopathology are essential. They can hopefully refine our current classification and reveal new predictive biomarkers to detect liver pathology or host factors associated with risk. Identifying genetic factors is difficult due to the low incidence of drug-induced liver injury, and the current thought that genetic associations with liver injury are generally drug specific (Daly, 2010). A recently identified

association between drug-induced liver injury due to flucloxacillin and the HLA-B*5701 allele, is the strongest reported association between any gene and drug-induced liver injury, with an observed odds ratio for disease development of approximately 80 (Daly et al., 2009; Daly, 2010). HLA genotype can also be associated with the type of liver injury. An illustrating example is the finding that particular types of liver injury (cholestatic/mixed liver injury) might be linked at least in part to an inherited HLA genotype (Andrade et al., 2004). The HLA class molecules are associated with immunological processes, and a relevant question discussed earlier in this chapter concerns the current classification in idiosyncratic toxic or immunological types of injury. The hapten hypothesis (Castella et al., 2006) postulates that drugs, or reactive moieties derived from the drugs (toxic compunds), can react with cell proteins forming covalent drug–protein adducts (immunological triggering), and as mentioned earlier there is growing evidence that immune cells or immune mechanism are more important for both predictive and idiosyncratic liver injury than previously thought (Adams et al., 2010).

Pharmaceutical companies have traditionally used cell lines or subcellular fractions (microsomes) for in vitro safety (toxicology) studies, but recent evidence suggest that co-cultures of primary hepatocytes and Kuppfer cells are a useful supplement (Sahi et al., 2010). Hepatocytes in culture retain hepatic key functions compared to cell lines, and represent a more relevant model to study metabolism, transport and toxicity for extrapolation to humans. Thus, initial studies in cultures can then be supplemented with subsequent studies in cell lines to evaluate particular toxic mechanisms (Gómez-Lechón et al., 2010). Pharmaceutical companies in collaboration with medical agencies in Europe and USA are eager to find what combination of "omics" technologies that best can predict hepatotoxity. Both of concern for preclinical drug development, but also by the fact that non-clinical data at the time of marketing of some drugs indicated potential risk of liver injury (Hughes, 2008). However, as will be discussed later, assessment of retrospective data from clinical reports can still be of value to formulate useful hypotheses of causative mechanisms, and risk factors of relevance, to be tested in basic studies.

2. Toxins from herbal medicine and nutritional-based therapies

Due to the increasing popularity of complementary and alternative medicine, several new substances have been suspected to induce liver injury. These include among others ingredients from herbal products, vitamins and minerals. Consumption of these forms of complementary medicine is not unusual. A study from the UK showed that 44% of patients on warfarin, a drug with a low therapeutic index and highly sensitive to interactions, used nutritional-based therapy on a weekly basis or more often (Leung et al., 2009). Furthermore, more than 90% of the patients did not discuss use of complementary medicine with their physician (Nutescu et al., 2006). The common belief that these substances and therapies are only beneficial to humans is challenged by an increasing number of reports of adverse effects including hepatic injury. Currently the mechanisms behind these effects are poorly described, but there is no reason to believe that they are different from the principles of drug-induced liver injury described above. Thus, toxins from these products represent xenobiotics that the liver is exposed to, and potentially damaged by, in much the same way as conventional drugs. However, problems with formulations, standardization, epidemiology and current research on the products makes causality of liver injury even more complicated in comparison to that of conventional drugs.

2.1 Problems with formulation and standardization of complementary products

Most herbal medicines are classified as dietary supplements, and together with nutritional-based therapies they are not subjected to the safety, quality assessment and standardization which we associate with conventional drugs supplied by the pharmaceutical industry (Stickel et al., 2005). Herbal medicines often contain several active ingredients, and composition of the product (quantity and purity) is often poorly described. Furthermore, the quality and strength of the individual ingredients depends on climate, growth, collection, preparation and extraction of plant material. Thus, geographical location, part of the season for which the material is collected, and routines for extraction and processing can show considerable variation for different products with the same ingredients (Chang et al., 2006). Moreover, this variation indicates that batch to batch or lot differences of the same product can be expected (Gurley et al., 2000). A serious safety problem is the fact some medicines contain synthetic drugs not declared by the package, or that the content does not reflect label claims. Examples of such adulteration are stimulating substances like caffeine and ephedrine, but also steroids have been found in complementary products after patients developed signs of Cushings syndrome (Byard, 2010). Importantly, the product or ingredients could be contaminated by lead, other toxic metals, pollutants, pesticides, bacterias and mold (Stickel et al, 2005; Byard, 2010). The product could also contain allergens that can mediate hypersensitivity reactions in susceptible persons. Similar to the case with conventional drugs where excipients cannot be ruled out as causative agents, solvents like ethanol and acetone could contribute to damaging effects. Some of these solvents were not present in traditional preparations of the plants. Thus, essential when using complementary medicine is that the product contains a clear definition of ingredients with extensive description of the production process together with statements of potential adverse effects and interactions. However, the complicated terminology of complementary medicine with use of several synonyms and botanic names confuse both health care professionals and patients.

2.2 Problems with epidemiology of liver injury of complementary products

Complementary products lack the rigorous process of toxicology and safety assessment we associate with clinical testing of conventional drugs. Thus, preclinical data on potential for liver injury is not available in most cases (De Smet, 2002). Furthermore, the products usually contain a mixture of several ingredients, and to determine the safety of each would be a rigorous task. There are examples of clinical trials to study the effects of herbal medicines, but most of our knowledge of adverse effects comes from case reports and reviews (Smith & Dillon, 2009). Keeping in mind that use of complementary medicine often remain unknown to clinicians, the suspicion of ingredients in these medicines as causative agents for liver injury can be ignored. Thus, the true incidence of adverse effects due complementary products is not known (Smith & Dillon, 2009; Shaw, 2010). The available epidemiologic data of adverse reports is also influenced by the fact that selected populations with risk factors that increase the potential for liver injury are in particular exposed. Complementary products are proposed as effective against aging, obesity, liver disease, hypersensitivity, and psychiatric diseases as examples. Patients with such diseases already use several conventional drugs with their own risk of liver injury, and interactions with complementary medicine could be the final trigger to elicit acute hepatic damage. The retrospective and partial nature of our knowledge makes detection of liver

injury from complementary medicine even more challenging than for conventional drugs. Medical agencies and poison units in several countries as well as the serious part of the industry are well aware of this problem, and initiatives like establishment of databases and public information against under-reporting are emerging, besides strategies for licensing of herbal medicine (Stickel et al., 2005).

2.3 Examples of toxins

To mention all the examples of toxins from complementary medicine suspected of causing liver injury is beyond the purpose of this chapter. However, a few examples will illustrate how difficult it is to establish a causative relationship, in particular which ingredient in a product that actually represent the offending toxin. Furthermore, the problem with extrapolation from basic studies in cells and animals to the clinical situation is described.. Lack of relevant dose-effect or -toxicity data from preclinical assessment faces the basic scientist with the question if clinically relevant quantities are used in the model, while the clinical scientist wonders if the clinical situation of liver injury is due to a therapeutic dose or an overdose. There is often abundant data of in vitro cytotoxicity of substances, yet evidence is lacking of in vivo hepatotoxicity in animal models under conditions similar to human use. Finally, the quality of the individual test substance in such studies should ideally be identical to compare studies, but this is not always the case. The following examples are chosen based on herbs and toxins known to induce liver injury in the last two decades, and where studies have emerged that suggest the plausible mechanisms involved.

2.3.1 Kava

Kava (kava kava, awa, or kew), derived from the plant Piper methysticum, has been used in the South Pacific as a ceremonial aqueous beverage since ancient times. Kava has been marketed as an anxiolytic and mood enhancer (Singh & Singh, 2002). Products containing derivates from the plant has been implicated in a number of human liver failure cases, which led to its ban in Germany, France, Switzerland, Australia, and Canada (Lim et al., 2007). This was a surprise due to the long history of safe use of the Kava beverage as a part of the culture in the South Pacific. The principle pharmacological activities of Kava are due to kavalactones, where kavain is the most important. Kavalactones can form electrophilic, quinone metabolites, potentially leading to GSH depletion and oxidative stress (Zhou et al., 2010). Furthermore, kavalactones inhibit CYP-450 enzymes in vitro (Mathews et al., 2002). Studies in isolated rat livers suggest that kavain (a major kavalactone) is associated with ultrastructural damage (Fu et al., 2008). However, these in vitro and ex vivo data were not supported by the in vivo observation that rats fed with aqueous kava root extracts containing as much as 500 mg kavalactones/kg body weight for 4 wk exhibited no noticeable toxicity (Singh & Devkota, 2003). Recently it was reported that a piperidine alkaloid, pipermethystine (PM), induces apoptosis in human hepatoma HepG2 cells (Nerurkar et al., 2004), but fails to induce hepatic toxicity in vivo (Lim et al., 2007). Furthermore, pipermethystine is not present in significant quantities in roots and rhizomes from the plant used in herbal medicines (Zhou et al., 2010). A new report suggest that the principle damaging substituent is flavokawain B, a lipohophilic chalcone (Zhou et al. 2010). The authors suggest that flavokawain B can through induction

of oxidative stress and depletion of GSH modulate signalling pathways including JNK to induce cellular apoptosis. However, a critical review summarizing the current evidence for the possible offending agents in Kava, dismiss kavalactones, pipermethystine, and flavokawain B as a cause of liver injury. The authors instead suspect contamination of products by aflatoxins or other mould hepatotoxins (Teschke et al., 2011).

2.3.2 Chaparral

Chaparral (Larrea tridentate) is a desert shrub traditionally used by Native Americans for treatment of aging and obesity. The herbal preparation was used for its antioxidant properties (Gordon et al., 1995). A study of 18 reports of illnesses associated with the ingestion of chaparral, found evidence of hepatotoxicity in 13 cases. Clinical presentation, characterized as jaundice with a marked increase in serum liver enzymes, occurred 3 to 52 weeks after the ingestion of chaparral, and it resolved 1 to 17 weeks after most individuals stopped their intake of the product. The predominant pattern of liver injury was characterized as toxic- or drug-induced cholestatic hepatitis; in 4 individuals, there was progression to cirrhosis; and in 2 individuals, there was acute fulminant liver failure that required liver transplants (Sheikh et al., 1997). The mechanism of chaparral toxicity involves its active ingredient, nordihydroguaiaretic acid (NDGA). NDGA is described as an antioxidant which several proposed toxic effects including inhibition of lipo- and cyclooxygenase, reduction of cellular ATP, increase in intracellular Ca^{2+} and inhibition of CYP-450 (Arteaga et al., 2005; Stickel et al., 2005).

2.3.3 Ma Huang

A common herbal ingredient in weight loss products is Ma Huang (Ephedra sinica). Ma Huang contains ephedrine alkaloids, although not so potent CNS stimulant as the pharmaceutical ephedrine. Ephedrine is structurally related to amphetamine. In traditional Chinese medicine, this is seen as useful herb for treating asthma, cough and wheezing. However, content of ephedrine alkaloids is supposed to induce liver injury in susceptible persons. A retrospective study reviewed the records of 12 patients, who had hepatotoxicity thought to be related to the ingestion of herbal weight loss compounds from various ingredients, including Ma Huang (Neff et al., 2004). A problem with Ma Huang was suspicion of misuse, and the substance was banned by the Food and Drug Administration (FDA) in 2004 (Shaw, 2010). Several adverse reaction reports included serious psychiatric effects combined with a history of substance abuse (Maglione et al., 2005). A problem with products with ephedrine alkaloids is development of tolerance with risk of increasing doses. Although obese patients used Ma Huang, ephedrine alkaloids were also popular among young healthy people due to proposed effects like appetite suppression, increased sport performance and energy. Given the fact that Ma Huang is often mixed with other ingredients (potentially hepatoxic) in products, increased dose could represent additional risk of liver injury.

2.3.4 Particular liver toxins and mechanisms

The three examples described above illustrate several aspects of complementary products and liver injury. The difficult extrapolation from toxicity observed in vitro to animal studies when the products and ingredients in question lack standardization. Furthermore, the intriguing problem of how to explain idiosyncratic, rare, reports of toxicity with traditional

products used apparently safe for hundred of years. Moreover, ingredients that are similar to substances of misuse add a risk of dose-dependent toxicity of such products. Notably, individual herbal liver toxins with some documentation are the unsaturated pyrrolizidine alkaloids. They occur in several plants, including Senecio and Symphytum species, and chronic use results in a very specific liver injury, veno-occlusive disease, with occlusion of the central and sublobular hepatic veins which can progress to cirrhosis (Shaw, 2010). Pyrrolizidine alkaloids are absorbed in the intestine and transported to the liver where they are metabolized to pyrroles. Pyrroles are very reactive chemically and cross link with double stranded DNA. They bind both proteins and nucleic acids within hepatocytes, but also damage sinusoidal endothelial cells by depletion of GSH and increased oxidative stress (Chen & Huo, 2010). Toxins from the herb Germander (Teuchrium chamaedrys) are an example of liver damage caused by the formation of reactive compounds by metabolism (Shaw, 2010). Reactive metabolites are generated by metabolism of its constituent neoclerodane diterpenoids. Neoclerodane diterpenoids is metabolised by CYP3A4, and electrophilic metabolites are believed to deplete GSH and damage cells through reduced defence system. However, depletion of cellular SH groups, binding to cytoskeleton of hepatocytes with altered cell membranes, and apoptosis are part of hepatoxic damage as studied in rat hepatocytes (Chitturi & Farrell, 2008). Interestingly, immune-mediated pathways in initiating liver injury were also associated with ingestion of Germander. When rechallenged with the herb, a rapid rise of serum transaminases was observed in some of the patients. Furthermore, autoantibodies (antinuclear, smooth muscle and antimitochondrial) were present in sera from patients who drank germander teas (Polymeros et al., 2002). In particular, a specific autoantibody (antimicrosomal epoxide hydrolase) was identified from sera of long-term drinkers of germander tea (De Berardinis et al., 2000). The target for this autoantibody is an epoxide hydrolase on the hepatocyte surface. These examples demonstrates the use of clinical experience (veno-occlusive disease, effect of rechallenge) to generate, examine and test mechanistic hypotheses in basic studies.

2.3.5 Vitamins

Daily use of vitamins and dietary supplements is common. In 2007, vitamin C, vitamin E, and multivitamins were among the five best-selling supplements, and most people consider vitamins and supplements safe (Rosenbloom, 2010). However, liver injury related to excessive doses of vitamins has been described for decades. The clinical picture of liver injury ranges from mild elevations of serum liver enzymes to cirrhosis. In the case of vitamin A, toxicity does not usually occur with standard doses below 50 000 international units (IU) per day as contained in common multivitamin preparations, but individual tolerability may vary (Stickel et al., 2011). Comorbidity, liver disease and chronic alcohol consumption can be associated liver injury with doses as low as 20 000 IU/day. A study in cultured HepG2 cells and freshly isolated rat hepatocytes, polar retinol metabolites caused marked cytotoxicity in a concentration- and time-dependent manner in both cell types with injury mainly caused by apoptosis (Dan et al., 2005). Alcohol-induced CYP2E1 is supposed to transform retinoids into highly reactive and toxic polar metabolites, and points to caution with supplements of vitamin A combined with chronic ingestion of ethanol. The above example is just one of several ingredients in nutritional-based therapies that can cause liver injury, and often use of excessive doses of the products can be the reason. However, the interaction with alcohol is of particular relevance due to the high prevalence of ethanol

ingestion in the public. Nutritional-based therapies advertised against a multitude of diseases on the Internet are often a mixture of vitamins, proteins, herbs, salts and other ingredients. However, their composition can be far from the evidenced based nutritional therapies in hospitals, and they are in principle associated with all the problems mentioned earlier (aldulteration, contamination, etc). Based on the experience that fasting and malnutrition can increase the risk of serious paracetamol toxicity, there is a risk of liver injury due to irrational use of such supplements rather than the accepted diet in a community.

2.4 Further studies and use of retrospective data

The previous sections have clearly demonstrated that toxins from herbal medicine and nutritional-based therapies potentially can damage the liver in much the same way as conventional drugs. However, due to the aforementioned problem with formulation, standardization and epidemiology in complementary medicine, this type of liver injury is even more challenging to sort out than that of conventional drugs. Preventive measures in the form of information to health care professionals and the public about risk, regulative measures by medicinal agencies, and involvement by the industry itself are of paramount importance. Secondly, retrospective data from human cases should ideally include a thorough description of the product, chemical analysis of the quality and amount of the ingredients, history of the clinical course (effect of rechallenge? particular risk factors?), histopathological samples (signature injury?) from liver biopsy with other laboratory and clinical information. To test different hypotheses of basic mechanisms, a standard test substance should be formulated and then subsequently tested in established in vitro, ex vivo, and animal models. To effectively share knowledge between research groups this requires cooperation between the scientific communities in collaborating clinical networks as described previously for drug-induced liver injury (Andrade et al., 2005; Andrade et al., 2006; Hoofnagle, 2004).

Collection of tissue specimen during liver injury should not be discarded as a valuable biobank and ideas for subsequent studies of mechanisms and causality. A clinical pharmacologist would like to have relevant drug concentrations of suspected drug or toxins with metabolites if analytical assays were available. This would provide information on compliance (is the drug or toxin actually present in the blood?), and furthermore on exposure (is the substance found in a high concentration-higher than expected)? Although methodologically difficult, comparison of such data with drug or toxin concentrations in the offending organ would be an ideal tool to study tissue accumulation of substance. This could give clues to inherited (genetically defect cell transporters?) or environmental (other drug or toxin block a cell transporter?) risk factors of relevance. Liver biopsy during drug- and toxin-induced liver injury is of course not commonly used for this purpose. However, development of liquid chromatography-mass spectrometric (LC-MS/MS) assays for tissue specimens of tacrolimus from liver biopsy have been shown to be better correlated to histopathologic rejection scores than conventional immunoassays of ordinary blood concentrations (Capron et al., 2007). With further development of highly sensitive LC-MS/MS assays, specific determination of substances with metabolites can hopefully be useful in the context of drug- and toxin-induced liver injury. Development of imaging techniques (like nuclear magnetic resonance, NMR) and contrast agents for non invasive evaluation of substances and/or injury in the organ represent additional tools. Based on the experience that current methods for early detection and prediction of drug-induced liver

injury in patients are not optimal, applications of analytical technologies such as NMR and LC-MS/MS to profile individual metabolite formation in biofluids (plasma and urine) after conventional dosing are suggested (O'Connell & Watkins, 2010). The hope is that alterations in the profiles of endogenous metabolites ("the metabolome") may precede development of clinically overt drug-induced liver injury.

3. Case reports and drug information centres

Drug information centres (DICs) have been established in Europe and other parts of the world in order to give health professionals, i.e. physicians, dentists, nurses, midwives and pharmacists, non-commercial information about drug treatment, drug problems and pharmaceuticals (Hedegaard & Damkier, 2009; Schjøtt et al. 2002). The RELIS network is today made up by the four regional drug information centres (DICs) in Norway. The centres are organised in close collaboration with the departments of clinical pharmacology at four university hospitals. Pharmacists and clinical pharmacologists answer problem-oriented drug-related queries from health care professionals. The queries are published along with the answers and reference sources in a web-based, full-text query-answer database (the RELIS database), which is accessed through the RELIS homepage. Question-answer pairs are indexed, and can be retrieved form the database through a search function. Furthermore, each RELIS function as a regional pharmacovilance unit processing spontaneous adverse drug reaction reports in cooperation with the Norwegian Medical Agency. Reports are retrievable from the Norwegian Adverse Drug Reaction database, and relevant information about drug and toxin associated liver injury are published on the RELIS homepage, in newsletters to physicians and in national and international journals. Of importance is the close collaboration between RELIS and clinical pharmacologists. Thus, analytical pharmacological competence and skills in laboratory diagnostics are supplemented with knowledge of practical pharmacokinetic tools in the diagnosis of adverse effects. As a problem-oriented DIC, RELIS believe that presentation of clinically relevant examples instead of more general warnings and alerts are a useful medium to inform health care professionals about risk of drug- and toxin-induced liver injury. In the last section of this chapter, we present two illustrating examples of information about such liver injury from RELIS.

3.1 Green tea and the quality of a case report

In 2009, RELIS published as an adverse drug reaction report about Lotus-f3 (Bergman & Schjøtt, 2009). Lotus-f3 contains an extract of green tea, which has been associated with hepatotoxicity. The presentation of the case followed the guidelines for submitting adverse event reports for publication (Kelly et al., 2007). The guidelines were developed because deficiencies in vital information in published cases can often limit the value of such reports by failing to provide enough details for either (i) a differential diagnosis or provisional assessment of cause-effect association, or (ii) a reasonable pharmacological or biological explanation. Importantly, the authors (Kelly et al., 2007) claim that properly described, a published report of one or more adverse events can provide a useful signal of possible risks associated with the use of a drug or medical product which might warrant further exploration. Through communication with the reporting physician and the local hospital, RELIS was able to obtain relevant clinical information including successful withdrawal of

Lotus-f3, liver biopsy, laboratory data and subsequent successful rechallenge with a concomitant drug. Importantly, RELIS had previously received several questions concerning the possible association between natural products and hepatitis or jaundice since 1995. Moreover, in five of these questions, the suspected natural products contained green tea, among other constituents. Thus, availability of relevant documentation based on previous suspicion was retrievable from the RELIS database which was valuable during the processing of this case description.

3.2 Fortodol and fatal addulteration

Fortodol was marketed in Norway as nutritional-based product, containing curcumin from Turmeric (Curcuma longa) as the active ingredient. Curcumin is proposed as an analgetic and anti-inflammatory agent. From 2007, RELIS received several queries and adverse reaction reports associated with Fortodol. In several of these, increase in liver enzymes and suspicion of liver injury was related to ingestion of the product. Five cases of liver failure, including three women (47-65 year) and two men (67-69 year), where reported. The case of the oldest man was fatal and this prompted RELIS in 2009 to retrieve capsules of the product from the relatives of the diseased. The capsules were subsequently analysed, and contained a mean of 42 mg of nimesulid per capsule. Nimesulid is a NSAID, not registrated or marketed as a legal drug in Norway. The drug has been withdrawn from the market of several European countries due to suspicion of liver injury. The European Medical Agency (EMEA) recommends that nimesulid should be used for up to 15 days at a daily maximum dose of 100 mg x 2. Fortodol was sold in packages containing 100 capsules, with recommended daily dose of 1-2 as needed. RELIS together with the Norwegian Medical Agency warned health care professionals and the public through interviews and articles in the media. The Norwegian Food Safety Authority subsequently contacted the importer of the product, and Fortodol was withdrawn from the market. In Sweden, four cases of serious liver injury was known with one fatal (Kechagias et al., 2010). The Swedish Medical Agency analysed Fortodol, and found nimesulid in two out of nine packages. This example demonstrates consequences of adulteration and the important role of DICs in the process of detection of and information about a health problem.

4. Conclusion

The present chapter summarizes damaging effects of drugs and toxins on the liver, in particular adverse effects of herbal medicine and nutritional-based therapies. It has been emphazised that toxins from complementary medicine can damage the liver in much the same way as conventional drugs. Liver injury due to drugs or toxins represents a diagnostic challenge for the clinician and a complex research issue for the scientist. Both pre-marketing and post-marketing data associated with a drug are of importance to describe potential for liver injury and risk factors of relevance. The search for relevant predictors of liver injury during pre-clinical and clinical phases of drug testing (chemical properties that increase the potential for drug-induced liver injury?) as well as risk factors (inherited, environmental or acquired characteristics that increase the likelihood of clinical liver disease?) in individuals prescribed legal drugs continues. Future studies are associated with “omics” technologies (genomics, proteomics, metabolomics) and "the metabolome" (variation in the profiles of endogenous metabolites) to describe new predictive biomarkers. However, cooperation in clinical networks represents a significant contribution to our understanding of etiology,

pathogenesis and risk of drug-induced liver injury. Furthermore their aim at developing more drug-specific assessment tools for evaluation of causality is promising. In the case of toxin-induced liver injury, preventive measures in the form of information to health care professionals and the public about risk, regulative measures by medicinal agencies, and involvement by the industry itself are of importance. Due to the idiosyncratic nature of drug-or toxin-induced liver injury, case reports provided by DICs represent a source of signal generation of risk and formulation of hypotheses of relevance to explain clinical events.

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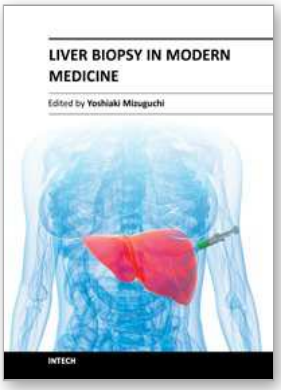

Liver Biopsy in Modern Medicine

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Liver biopsy, first performed by Paul Ehrlich in 1883, remains an important diagnostic procedure for the management of hepatobiliary disorders and the candidate/donated organ for transplantation. The book "Liver biopsy in Modern Medicine" comprises 21 chapters covering the various aspects of the biopsy procedure in detail and provides an up-to-date insightful coverage to the recent advances in the management of the various disorders with liver biospy. This book will keep up with cutting edge understanding of liver biopsy to many clinicians, physicians, scientists, pharmaceutics, engineers and other experts in a wide variety of different disciplines.

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