Hepatotoxicity: Mechanisms of Liver Injury

7

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Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (glutamic-pyruvic transaminase, SGPT)
AST	Aspartate aminotransferase (glutamic-oxaloacetic aminotransferases, SGOT)
CB	Conjugated (direct) bilirubin
GGT	γ-Glutamyltransferase (γ-glutamyltranspeptidase, GGTP)
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
TB	Total bilirubin (sum of conjugated and non-conjugated serum bilirubin)
ULN	Upper limit of the normal reference range (or N)

7.1 Introduction

Chemical injury to the liver presents diverse aspects including the nature of the toxic agents, the character of the injury, the mechanism for the toxic effects, the conditions of exposure, and the medical and social importance [1–5]. Some hepatotoxins are found in nature as products of plants or animals, fungal or bacterial metabolism [6–10]. Many hepatotoxicants are products of the chemical, food or pharmaceutical industry [11, 12]. Other hepatotoxins are industrial byproducts or waste materials that, by polluting the environment, access humans [13–15]. Several agents have been shown to be synthesized in humans [16].

Morbidity and mortality caused by medications or inappropriate administration created a concern to health policy makers, and even patients [17, 18]. Hepatotoxicity caused by exposure to an agent produces injury to the liver that may be associated with impaired liver function [19].

The exposure to a drug that leads to histological or functional damage to the liver and is associated with impaired liver role is defined as hepatocytotoxicity [20–23]. Drug-induced hepatic reactions may produce liver injury to engage liver cells' function such as detoxification and transport. Moreover, DILI is the source of impaired bilirubin transport. The hepatotoxicity of this severity is likely to result in liver failure, especially if the offending drug is not stopped [3]. Other drugs lead to cholestatic injury by mechanistically impairing bile flow, which may lead to jaundice. However, the parenchymal injury is small [24]. Some therapeutic agents may produce degeneration of liver cells or vascular lesions of the liver [25, 26].

Other agents direct to a mixed type with simultaneous features of cytotoxic and cholestatic injury. Therefore, there may be considerable variability in causation and frequency of injury because of differences in the intrinsic and extrinsic factors, and the availability and prescribing patterns of the health products. Genetic polymorphisms affecting metabolic and transport pathways may affect the local concentration of the product or reactive metabolite at the cellular level, which in some instances may either form a covalent complex or trigger damage directly [27, 28]. Susceptibility may also be increased by the presence of another condition that impairs function in one or more metabolic or regulatory pathways. Product-induced hepatotoxicity may occur as an expected dose-dependent hepatic toxicity or as an unexpected idiosyncratic reaction. Consequently, there is a connection between the stimulus, the individual response and risk of hepatotoxicity. Diagnosis of chemically-induced hepatotoxicity relies on the exclusion of multiple elements, such as the medical history (risk factors, exclusion of other diseases), and presentation (time to onset of symptoms, jaundice or laboratory findings, and clinical features [29].

Detection of drug-induced liver injury depends on valid causality assessment and a sufficient number of subjects.

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Absence of hepatotoxicity in clinical trials may only make available a limited predictive value on whether a product is hepatotoxic [3].

7.2 Hepatic Injury

Hepatic injury may result from direct damage to the hepatocytes, or from damage to bile canalicular cells, sinusoidal epithelial, stellate or Kupffer cells which alter function or indirectly damage the hepatocytes [21–26].

The liver has regenerative properties as an adaptive response to many agents. As a result, a range of clinical and pathological manifestations exist. Biochemical functions, metabolism and transport should be considered in assessing a drug's potential for causing hepatotoxicity [27–31].

Table 7.1 defines terminology utilised in this chapter while Table 7.2 describes the names of enzymes and proteins important for healthy liver function.

Table 7.1 Definitions

Definition	Explanation
Abnormal liver test	Any AST, ALT, Bilirubin test value greater than the population-defined upper limit of the normal reference range (ULN).
Adverse event	Any problematic medical occurrence in a patient administered a health product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.
Adverse reaction	A noxious and unintended response to a drug used for prophylactic, therapeutic or withdraw and includes an unwanted effect
Enzymes	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT)
Idiosyncratic	Host response where the individual is unable to tolerate usually prescribed doses of a product that may be safe in others. The reaction is not predicted by the pharmacokinetic or pharmacodynamic properties of the stimulus, it is not dose dependent, and is independent of the frequency of the drug administration.
Liver failure	Clinical manifestation of severe liver injury. The phenomenon encompasses both fulminant (within 8 weeks of symptoms) and sub-fulminant (late-onset) hepatic failure in a previously healthy liver.
Serious adverse reaction	A noxious and unintended response to a health product that occurs at any dose and that requires in-patient hospitalization or a prolongation of existing hospitalization; that results in significant disability or incapacity that is life-threatening, or that results in death.
Xenobiotic	A chemical that produces environmental contaminants.

The mechanisms of hepatotoxicity may cause presentations ranging from asymptomatic elevations of enzymes to severe dysfunction. Adverse drug reaction (ADR) can be consider any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning and drug abuse. Adverse drug reactions are classified as Type A and Type B. Type A reactions represent an extension of the drug's therapeutic effect. Type A, ADR occur frequently and are dose-related [5]. By contrast, type B reactions are unpredictable, occurring only in susceptible individuals. Type B 'idiosyncratic' reactions are dose-independent. Pirmohamed and Park's review ADR and make a classification of enzymes, transporters and immune response genes with associations to genetic individual susceptibility [32]. Table 7.3 presents a link between gene susceptibility and sensitivity specific medication.

ADRs are considered serious adverse drug reactions (SADRs) if they require hospitalization, prolonged hospitalization, and/or result in permanent disability or are fatal [33]. SADRs can arise via Type A or B mechanisms. The overall incidence of SADRs in hospitalized patients in the United States has been estimated at 6.2–6.7% and the incidence of fatal ADRs is estimated to be 0.15–0.3% [32]. This results in over two million estimated SADRs among hospitalized patients annually, with more than 100,000 deaths, in USA. Studies in Europe and Australia have yielded similar estimates [34]. The resulting cost has an impact on both the healthcare and the pharmaceutical industry internationally [35].

Pharmacokinetics relates to the absorption, distribution, metabolism and excretion of a drug and its metabolites in the body. Pharmacodynamics involves mechanism of action of a drug, including receptor binding and signal transduction [36].

Regarding morphology, the hepatic injury is classed as hepatocellular, cholestatic, mixed (cholestatic and hepatocellular), immunologic and mitochondrial. The mechanisms of hepatic injury may include: disruption of intracellular calcium homeostasis (membrane); disruption of actin filaments (canaliculus); covalent binding of a substance to cellular proteins resulting in immune injury, inhibition of cell metabolic pathways, blockage of cellular transport pumps, induction of apoptosis, and interference with mitochondrial function [37, 38].

Liver injury may develop within days or after several weeks after exposure to the incriminated agent. The injury pattern may be consistent for a class of products, but not all products have a characteristic time to onset, pattern of biochemical values, clinical course, or degree of severity [3].

Hepatocellular injury leading to hepatic necrosis is detected by increases in activity of serum aminotransferases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Table 7.2 Liver enzymes and proteins as laboratory tools in DILI

Enzyme/protein	Origin, importance and role in toxic reaction
Alanine aminotransferase (ALT)	ALT is present in hepatocytes, and in smaller amounts in skeletal muscle and intestinal epithelium. ALT is more sensitive and specific than AST for liver inflammation and hepatocyte necrosis. It rises rapidly in patients with acute damage to the hepatocytes. The absolute value of ALT increase is not directly proportional to the degree of liver damage, the value of 3×ULN can always be considered to be abnormal if the value persists. The value usually correlates well with the development of disease. If the hepatic injury is caused by biliary obstruction, then the increase in ALT is slower and is accompanied by increased ALP and GGT.
Aspartate aminotransferase (AST)	AST is found in many tissues (liver, skeletal muscle, heart, kidney, brain, erythrocytes, lung and pancreas) and may increase even if there is no hepatic injury. The increase in AST is usually less than the increase in ALT. AST higher than ALT may suggest, but not prove, alcohol-induced injury.
Alkaline Phosphatase (ALP)	ALP is a nonspecific screening test and may be increased by causes unrelated to liver (e.g. bone, kidney, breast, etc.). High ALP usually means that either the liver has bile duct damage or blockage or a condition causing increased bone cell activity is present. If other liver tests such as bilirubin, AST, or ALT are also high, usually the ALP is coming from the liver. If GGT or 5′-nucleotidase is also increased, then the high ALP is likely due to liver disease. If either of these two tests is normal, then the high ALP is likely due to a bone condition.
γ-Glutamyl-transferase (GGT)	Although present in many different organs, GGT is found in particularly high concentrations in the epithelial cells lining biliary ductules. It is a very sensitive indicator of hepatobiliary disease, but is not specific. Levels are elevated in other conditions including renal failure, myocardial infarction, pancreatic disease, alcohol use, and diabetes mellitus. Its major clinical use is to exclude a skeletal source of an elevated serum alkaline phosphatase level.
Bilirubin	Hepatocytotoxicity leads to increase of conjugated bilirubin (CB). Increased total or unconjugated bilirubin may be a result of hemolytic, sickle cell or pernicious anemias or a transfusion reaction. If conjugated bilirubin is elevated, there is an obstruction of the vascular path or bile ducts, hepatitis, trauma to the liver, cirrhosis, a drug reaction, or long-term alcohol abuse. Drug-induced hyperbilirubinemia may occur as a side effect due to inhibition of bilirubin UDP-glucuronyl-transferase 1A1 (UGT1A1) activity by certain drugs. Predominantly unconjugated bilirubin and is not associated with liver injury or indicators of hepatobiliary damage. If total bilirubin (TB) is elevated due to CB in order to differentiate cholestasis from hepatocellular injury. ALP should be determined for the same reason. An increase in INR may precede an increase in serum TB level. TB increase due to liver toxicity it is accompanied by a rapid increase in ALT. Increased bilirubin due to biliary obstruction, is accompanied by increased ALP and GGT,
Prothrombin time and International Normalized Ratio (INR)	Coagulation factor I (fibrinogen), II (prothrombin), V, VII, IX, and X. The prothrombin time is useful in assessing severity and prognosis of acute live disease. Deficiency of one or more of the liver-produced factors results in a prolonged prothrombin time. Prolongation of the prothrombin time in cholestatic liver disease may result from vitamin K deficiency. Other explanations for a prolonged prothrombin time apart from hepatocellular disease or vitamin K deficiency include consumptive coagulopathies, inherited deficiencies of a coagulation factor, medications that antagonize the prothrombin complex. Vitamin K deficiency diagnosis can be excluded if an administration of vitamin K 10 mg corrects or improves the prothrombin time within 24 h. This implies that hepatic synthetic function is intact. Prolongation of the prothrombin time that is unresponsive to vitamin K infusions suggests a fulminant liver disease.
Bile acids	Bile acids are synthesized from cholesterol in the liver, conjugated to glycine or taurine, and excreted in the bile. Bile acids facilitate fat digestion and absorption within the small intestine. They recycle through the enterohepatic circulation; secondary bile acids form by the action of intestinal bacteria. Elevated level of serum bile acids indicates biliary dysfunction. Normal bile acid levels in the presence of hyper-bilirubinemia suggests haemolysis or Gilbert's syndrome. High bile acid indicates chemical/drug/herbal-induced hepatotoxicity. This test provides diagnosis of hepatocellular dysfunction, but will not provide a definitive diagnosis of the nature of the hepatotoxicity. Additional test to establish or rule out liver failure are decreased albumin and clotting factors.

Cholestatic injury is due to disease or bile duct blockage or stricture among other reasons. The intrahepatic cholestasis causes include drugs, toxins, viral hepatitis, alcoholic liver disease, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis, steatohepatitis, and Wilson's disease. From the biochemical perspective, cholestatic injury shows increases in alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) activity, and bilirubin level. Cholestasis is due to specific agents like terbinafine is chronic. In order to diagnose a hepatic damage, it is necessary to look at all the enzymes (ALT, AST, ALP, GGT) and bilirubin [5].

The immunologic mechanism of hepatotoxicity involves formation of a covalent complex between the product or its reactive metabolite and cellular protein. Human leukocyte antigen (HLA) polymorphism leads to an inappropriate local T-cell response. In addition, mitochondrial injury develops due to oxidative phosphorylation, mitochondrial adenosine triphosphate (ATP) depletion, interference of lipid metabolism. This may be identified by the presence of lactic acidosis and microvesicular steatosis; and enzymatic activities of respiratory chain complexes II–IV, manganese superoxide dismutase

Table 7.3 Gene susceptibility to drug-induced liver injury

Drug	Gene	Drug class	Toxicity
Ximelagatran	*DRB1*07*	Thrombin	Elevation in transaminase
	*DQA1*02*	Inhibitor	
Tolcapone	*UGT1A16*	Catechol-O-methyl-transferase inhibitor	Transaminases
			Elevation
Amoxicillin/clavulanic acid	*DRB1*1501DRB5**	Antibiotic/amino-penicillin β-lactamase inhibitor	Jaundice
	*0101DQA1*0102D*		Serum bilirubin
	*QB1*0602*		
Diclofenac	*UGT2B7*	NSAID	High transaminase to acute liver failure
	CYP2C8		
Tranilast	*UGT1A1*	TGF-β-antagonist	Unconjugated hyper-bilirubinaemia
Rifampin	*DRB1*03*	Antibiotic	*High transaminase*
			Bilirubin > 3.0 mg/dL
Isoniazid	*CYP2E1*	Anti-tuberculosis antibiotic	*High transaminase*
	NAT2		Bilirubin > 3.0 mg/dL

(SOD2) and glutathione peroxidase (GPX1), which are involved in mitochondrial oxidative stress management [39–45].

7.3 Hepatic Function

The hepatic functions can be determined by measurement of total bilirubin (TB), conjugated (direct) bilirubin (CB), serum albumin and prolonged blood prothrombin time [5]. Clinically, acute liver failure is divided into: fulminant hepatic failure, with hepatic encephalopathy developing within 8 weeks of the onset of illness and subfulminant hepatic failure, with hepatic encephalopathy developing 8 weeks to 6 months after the onset of illness. Subfulminant hepatic failure is more often caused by product-induced hepatotoxicity or unknown factors [5].

In chronic liver failure, there is progression of the hepatic injury leading to end-stage signs and symptoms like cirrhosis, ascites, malnutrition, encephalopathy, coagulopathy, malaise and fatigue, with bilirubin, decreased albumin, and increased International normalized ratio (INR).

7.4 Hy's Law

Hy's Law or rule can be used to estimate severity and the likelihood that a therapeutic will cause an incidence of severe hepatotoxicity. Hy's Law is based on the combined evidence of hepatic injury, decreased hepatic function, and the absence of disease-induced damage [5, 46].

Criteria are: 1-injury: elevation of >3 × ULN ALT or AST activity; 2-function: >2 × ULN TB (another clinical marker for function, such as >1.5 × ULN INR may be acceptable if the change is clinically significant in the absence of obstruction) without >2 × ULN ALP; and 3-clinical verification to ensure that the liver injury is or is not induced by other diseases or another cause.

However, there are limitations since ALT is sensitive but not specific for liver injury, and TB is specific but insensitive for determining liver function [17]. A combination of both predicts the development of severe hepatotoxicity. The degree of ALT elevation determines serious liver injury. ALP >2 × ULN can be associated with subsequent liver failure. Sometimes a combination of the ratio: ALT [× ULN]/ALP [× ULN]) ≥5 with total bilirubin ≥2 × ULN at time of peak ALT may be considered a better and more predictive definition of Hy's Law [47]. However, a single case of drug-induced hepatotoxicity meeting Hy's Law should be considered as a signal of hepatotoxicity for the product.

7.5 Detecting and Assessing Hepatotoxicity

Clinical signs, clinical chemistry and microscopic changes should be made at multiple time intervals to determine the effect of exposure. When clinical chemistry or histologic evaluations indicate hepatic changes, studies on the mechanism of action should be conducted with serial specimens of blood, urine or tissues, including samples from matched asymptomatic treated individuals.

The identification of mechanisms and characterization of sub-population differences that result in hepatotoxicity, in vitro studies may help to identify the mechanism and the specific drugs, chemicals or natural product that induced liver injury. Factors such as timing, concomitant and/or pre-existing liver disease, concomitant medications, the exclusion of alternative causes of liver damage, the response to dechallenge, and where appropriate, rechallenge of the treatment should be considered [47–49]. The risk profile may

also be equally broad, and vary with factors including age, gender, ethnicity and concomitant diseases [50].

Assessment of hepatotoxicity requires a thorough clinical review of the patient and a systematic exclusion of other potential causes for the hepatic abnormalities as outlined in the chapter on DILI. Methods have been proposed for the assessment of hepatotoxicity in individual subjects, including but not limited to: Clinical Diagnostic Scale, Council for International Organizations of Medical Sciences (CIOMS)/RUCAM scale, Maria and Victorino Scales, the Naranjo Adverse Drug Reactions Probability Scale, and World Health Organization (WHO) causality algorithm [50–56]. European Medicines Agency and FDA present additional guidance for pharmaceutical industry [57–60].

Other factors and diseases may mimic or increase sensitivity towards drugs, or natural product-induced liver disease. These include: non-alcoholic steatotic hepatitis (NASH); Gilbert's syndrome; co-morbidity; paraneoplastic phenomena; metastases; viral hepatitis (A, B, C or E); alcohol and drugs of misuse; biliary abnormalities; autoimmune disease or immunosuppression; haemodynamic, genetic and metabolic disorders; concurrent and previous therapy, environmental and occupational exposures to xenobiotics including plant and animal toxins [5].

7.6 Morphologic Pathology

Nonspecific histologic lesions typically include: hepatitis, hepatocellular necrosis, granulomas, inflammatory cell infiltrates, zonal distribution of lesions, hepatocellular degenerative effects, apoptosis, cholestasis, steatosis, vascular lesions and neoplasia. Liver biopsy is required to assess structural changes. Additional assessments may include ultra-structural pathology, morphometrics, special histological stains, or antibody detection. The pattern of cellular injury, the presence of cellular infiltrates, and the presence of necrotic and/or apoptotic cells should all be assessed. The exclusion of other causes of liver injury requires a complete case report description, clinical laboratory radiology, and medical history to allow the evaluation of alternative causes [22, 23].

Hepatotoxins are found in nature as products of plants, fungal or bacterial metabolism, or as minerals [61–65]. Some toxins are products of the chemical or pharmaceutical industry [66, 67]. Still others are industrial byproducts or waste materials that, by polluting the environment, may gain access to humans [68, 69]. The injury also includes necrosis or apoptosis. Others lead only to interference with bile secretion and to jaundice with little injury to the hepatocytes [70].

A general scheme of toxin-induced liver injury is shown in Fig. 7.1.

Acetaminophen, may be safe in ordinarily therapeutic doses but hepatotoxic for a number of species in overdose or in individuals with increased susceptibility [71]. Acetaminophen mechanism of toxicity has been extensively studied [72]. A fraction of a dose is metabolized by a cytochrome P450 oxidase to a reactive intermediate. The metabolite is detoxified by conjugation with glutathione. If the dose given depletes glutathione reserves, metabolites may then covalently bind to cell macromolecules with resultant hepatotoxicity [73].

Schematically acetaminophen-induced toxicity is presented in Fig. 7.2.

Increased toxicity could result from cytochrome P450 enzyme induction or deficits in glutathione detoxification

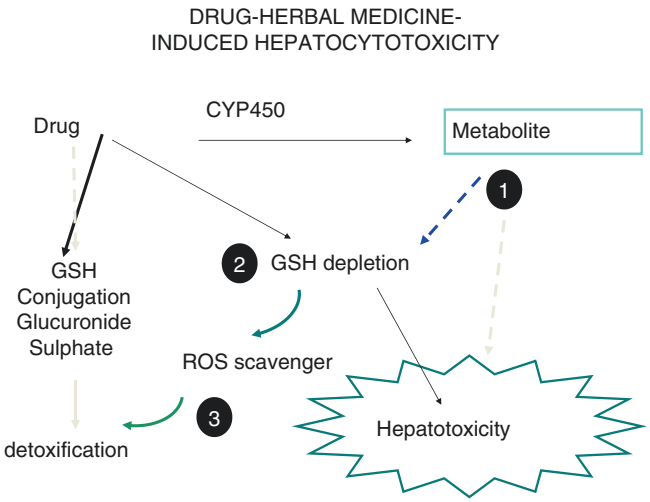


Fig. 7.1 Drug-herbal medicine induced hepatotoxicity. The drug at the therapeutical plasma concentration arriving to the liver is 1—glucuronate or sulphated to the non-toxic metabolite that is detoxify immediately or 2—undergo metabolization via Cyp 450 to the toxic metabolite. 3—Glutathione depletion does not permit detoxification leading to hepatotoxicity or a reactive oxygen scavenger can help to detoxification

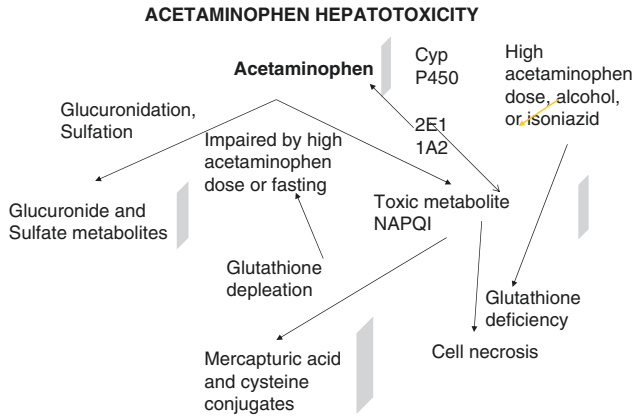


Fig. 7.2 Acetaminophen-induced liver injury. A small fraction of a dose is metabolized by a cytochrome P450 oxidase to a reactive intermediate. The metabolite is detoxified by conjugation with glutathione. If the dose given depletes glutathione reserves, metabolites may then covalently bind to cell macromolecules with resultant hepatotoxicity. High doses of acetaminophen or a combination of acetaminophen with alcohol deplete further the glutathione leading to hepatotoxicity

from dietary deficiency or inborn errors of metabolism such as glutathione synthetase deficiency or regular alcohol consumption [74–76].

There is a wide range of hepatotoxic potency among intrinsic toxins. Moreover, within the group of "true" toxins and the group that depends on idiosyncrasy, several different mechanisms may be responsible for the production of hepatic injury [5].

Some phytotoxins, like the amanitin from *Amanita phalloides* and the pyrrolizidine alkaloids from *Caleolepis laureola*, are environmental hazards [77]. The phytotoxins are taken as "natural" medicines [78–81].

Important contributors to liver damage are environmental and occupational hazards. Ingestion of toxic agents (e.g. CCl4) [82–86], were reported. Bromobenzene, phosphorus, ethionine and dimethyl-nitrosamine may play a role in the production of hepatic injury [87–90].

Microbiome attention focused on the demonstration the nitrosamines may be formed by intestinal bacteria in animals that ingest food preserved with nitrites. These observations have led to the concern that ingestion of nitrites and secondary amines by humans might provide exposure to the powerful hepatotoxic and hepatocarcinogenic effects of dimethylnitrosamine. Some strains of *Escherichia coli* can produce ethionine. This implies a microbiome-induced hepatotoxic effect. The production of lithocholate by microbiome should also be included [91].

The role of drug-induced hepatic injury becomes ever more important among elderly patients because of frequency of drug use and perhaps susceptibility.

The advances in the understanding of hepatotoxicity are due to revealing the enzyme mechanisms. The critical role of the cytochrome P-450 and its isoforms in drug metabolism as well as the development of molecular biology and the identification of cytokines have shed important light on the mechanisms of toxic hepatic injury.

7.7 Direct Hepatotoxins

Hepatotoxins that damage the liver by a directly destructive effect on the membranes of the hepatocyte are *direct* hepatotoxins. An example is carbon tetrachloride [82–86]. The halogenated aliphatic compounds are used in industry and the home and are found in the environment. Chloroform (CHCl3) and carbon tetrachloride (CCl4) are hepatotoxins. CC14 is a potent hepatotoxin leading to hepatic zonal necrosis [5].

Alcohol and drugs of use and misuse induced hepatotoxicity.

The pathological consequences of acute and chronic alcohol abuse are multi-factorial and multi-systemic. The dynamic interaction between chronic and acute alcohol abuse appears to play differential roles in the patterns of tissue injury and fibrogenesis between young individuals and elderly individuals [92–95].

Table 7.4 Elements to determine chemical or drug induce-toxicity

Pathology	Histopathology	Critical for identification of certain hepatic changes
	Gross pathology	Critical for determination of pathogenesis/mechanism of change
	Biochemistry	
Clinical	Clinical observations	In itself does not identify selected hepatic change, but does provide complementary data and clinical consequence to hepatic changes, includes accumulation of parent substrate and metabolite(s)
	Body weight, Diet Alcohol consumption,	
	Other drugs of use and misuse or complementary and alternative medicine	
Expression	Metabolism and transport: inhibition/induction	Provides complementary data for morphologic pathology findings
		Critical for determining certain potential interactions

CYP2E1 induction leads to increased metabolism of acetaminophen, valproic acid and methotrexate. Their toxic intermediates result in hepatocytes injury [96].

The interaction between alcohol and the anti-TB drug, isoniazid, also presents clinical importance since the metabolism of this drug involves acetylation. Since acyl transferase, the enzyme responsible for this step, is polymorphic, individuals who possess an acyl transferase with low activity may accumulate an intermediate which is then activated by CYP2E1 [97].

The interplay between alcohol and cytokine-mediated cellular effects is also important in the mechanism of liver injury. Chronic alcohol consumption may damage the liver by inhibiting the hepatoprotective actions of some cytokines, while adding to the pro-inflammatory effect of other cytokines. The co-morbidity of ALD and hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection or human immunodeficiency virus (HIV) infection leads to enhanced liver damage. Moreover, medications used to treat viral infections or other co-morbidities can interact with alcohol [98, 99].

Table 7.4 presents some elements that may help to determine chemical or drug induce-toxicity.

Phenotypic both chemical-drug and herbal induce injury present as immuno-hepatitis autoimmune hepatitis, hepatic necrosis/apoptosis, Acute liver failure, Cholestatic hepatitis, Steatosis/Steatohepatitis Sinusoidal obstruction syndrome, Vanishing bile duct syndrome.

The micrographs (Figs. 7.3, 7.4, 7.5, and 7.6) present the biopsies of individuals diagnosed with hepatotoxicity due to interactions between alcohol consumption and drugs of use or misuse.

Acknowledgements All the micrographs presented are cases that consulted Dr. Neuman and belong to In Vitro Drug Safety and Biotechnology.

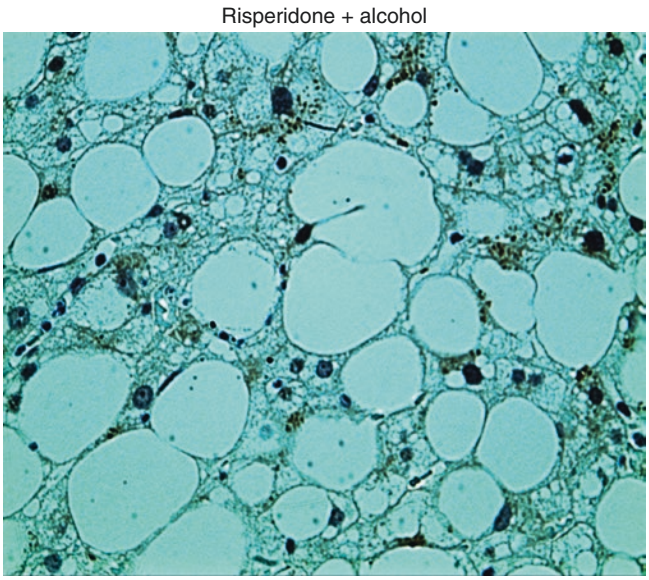


Fig. 7.3 Micrograph of a liver biopsy from a patient that consume alcohol and took risperidone. The diagnostic is non-alcoholic steatohepatitis. Large lipid droplets cover almost the entire hepatocyte and necrotic cells can be seen (magnification ×60)

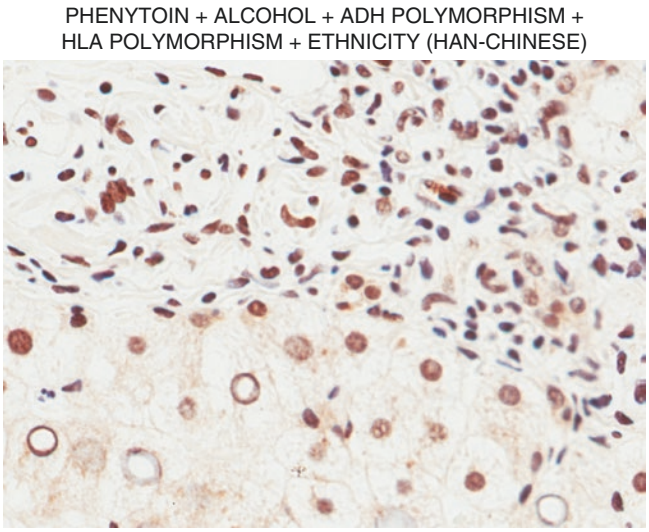
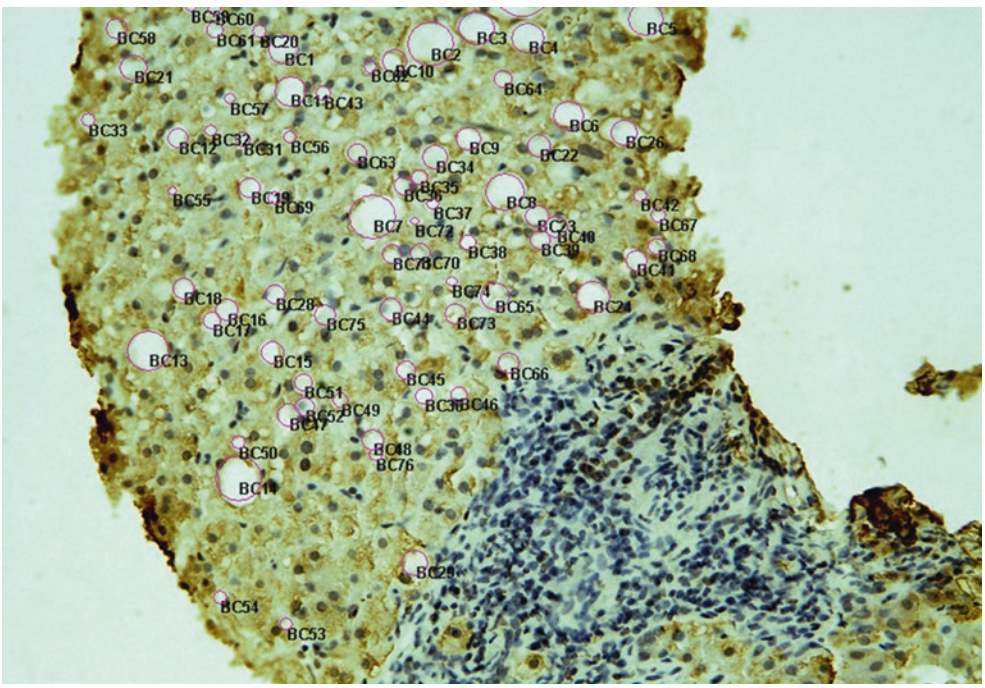


Fig. 7.4 Micrograph of a liver biopsy from a patient that consume alcohol and took phenytoin. The patient is ethnic Han-Chinese. He has a alcohol dehydrogenase polymorphism and a human leucocyte antigen polymorphism. Diagnosis is liver failure

Fig. 7.5 Micrograph of a liver biopsy of a patient that combine consumption of alcohol and *Cannabis* sp. Diagnosis is massive necrosis (Magnification ×20)



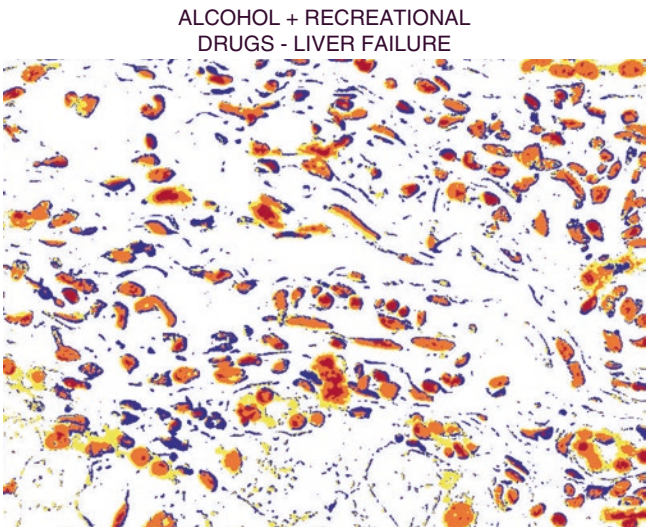


Fig. 7.6 Micrograph of a liver biopsy from a patient that consume alcohol and recreational drugs. Diagnosis is liver failure

Self Study

Questions and Answers

Which statement is true

1. Acetaminophen at therapeutic concentration taken concomitantly with alcohol in normal doses is
   (a) not harmful
   (b) a deadly combination
   Response correct (b)
2. In drug-induced hepatitis, which of the following is correct?
   (a) ALT is higher than AST
   (b) AST is higher than ALT
   Response correct (a)
3. Herbal and complementary medicine may produce:
   (a) Liver damage
   (b) Enhancement of liver function
   (c) Liver failure
   (d) All of the above
   Response correct (a)

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