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A REVIEW ON DRUG-INDUCED LIVER INJURY

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Abstract

Liver plays a remarkable role in maintenance and modification of homeostasis of the body. Hepatotoxins are the chemicals that may lead to liver injury. Drug-induced liver injury is a chief health problem which is threatening not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Drugs that induce liver diseases are likely to have a typical signature, with certain clinical and pathological pattern with a defined latency period. Drugs that induce liver diseases are likely to have a typical signature, with certain clinical and pathological pattern with a defined latency period. Mechanism of hepatotoxic drugs will be dependent on its metabolism from parent compound to active drug compound, or a mixture of both. This review discuss the epidemiology, pathphysiology, Risk factors, treatment and preventive measures of Drug-induced liver injury.

Key Wards: Hepatotoxins, Epidemiology, Pathphysiology.

Introduction

Liver plays a remarkable role in maintenance and modification of homeostasis of the body. Almost all the biochemical pathways for growth, immune resist to disease, nutrient supply, energy production and reproduction are maintained by liver[1]. Carbohydrate, protein and fat metabolism, detoxification, discharge of bile and storage of vitamin are the significant functions of liver. Thus, for the general health and wellbeing, it is indispensable to maintain a healthy liver[2]. Hepatotoxicity implies the chemical-driven liver damage. Organ may be injured, when some of the medicinal agents are taken in overdoses and also rarely when introduced within therapeutic ranges. Chemical agents that are used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies may also induce hepatotoxicity. Hepatotoxins are the chemicals that may lead to liver injury. There are above 900 drugs that may cause liver injury and it's the most widespread reason for a drug being withdrawn from the market. Chemicals that cause subclinical injury to liver is tested only as abnormal liver enzyme tests. Drug- induced

liver injury is the reason for 5% hospital admissions and also 50% of all acute liver failures. More than 75% cases of characteristic drug reactions upshot in liver transplantation are death [3]. Drug-induced liver injury (DILI) is a chief health problem which is threatening not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. According to the United States Acute Liver Failure Study Group,[3] DILI account for more than 50% of acute liver failure, including hepatotoxicity caused by overdose of acetaminophen (APAP, 39%) and Idiosyncratic liver injury tempted by other drugs (13%). Several drugs including Bromfenac, Ebrotidine, and Troglitazone have been isolated from the market by the U.S. Food and Drug Asministration (FDA) due to the significant patient morbidity and mortality associated with DILI[4]. Other hepatotoxic drugs, such as Risperidone, Trovafloxacin, and Nefazodone, have been assigned with "Black box" warnings. DILI has the most habitual basis for the withdrawal of drugs from the pharmaceutical market[5].

Epidemiology

In general the rate of drug-related liver disease was not accurately documented because most of the data that comes from retrograde studies was exact cohorts or using databases of prescriptions[6-7]. There is only published outlook community-based study, which was performed in France over a three-year period and creates an annual prevalence of hepatic reactions to drugs for 14 cases per 100,000 inhabitants[8]. Numerous studies were used to assess the comparative frequency of DILI as coincide with other liver diseases. Drug hepatotoxicity analysis was significantly less common than that of other causes of liver disease. Approximately most of the jaundice patients were admitted in hospital, toxic liver injury static for 4-10 percent of instances[9-10], but most cases of DILI in modern study results in acetaminophen toxicity, with idiosyncratic hepatotoxicity taking place in only 0.7% of patients[10]. A study accepted out in England regarding patients hospitalized with serum aspartate amino-transferase (AST) levels greater than 400 IU/l, the prevalence of drug hepatotoxicity was 9% [11].

Clinical and Pathological Symptoms of Drug-Induced Liver Diseases

Drugs that induce liver diseases are likely to have a typical signature, with certain clinical and pathological pattern with a defined latency period (table1). It was earlier stated that common adverse reactions are similar to the symptoms of acute hepatitis, cholestasis or with mixed presentations. The established definitions for these reactions are given in (Fig 1). Not all drugs reveal specific reaction, where as augmentin, show more than one reaction. The latency period can be short (hours to days), midway (1–8 weeks), or long (1–12 months). This may occur up to 3–4 weeks after the conclusion of a course of antibiotic treatment. The mechanism is not understood, but the slow

spreading out of an immune response to the drug. Cholestatic reactions may exist for long-standing after the discontinuation of the causative drug; most probably, cholangiocytes repair and stimulate more slowly than hepatocytes. The gene-expression data is a current rising part of the signature reaction. A signature pattern of gene expressions of hepatotoxins were recognised by the use of toxicogenomics which helps in directing to a better understanding the impulsive reactions and its mechanism[12]. Identifying the potential of risk at every individual and determining its toxic potential to overcome the occurrence of liver damage small study population.

Table-1: Clinical and Pathological Features of Drug-Induced liver Diseases.

Signature disease	Drug(s) causing the feature
Acute hepatitis	Acetaminophen, Bromfenac, Isoniazid, Nevirapine, Ritonavir, Troglitazone
Chronic hepatitis	Dantrolene, Diclofenac, Methyldopa, Minocycline, Nitrofurantoin
Acute cholestasis	ACE inhibitors, Amoxicillin, Chlorpromazine, Erythromycins, Sulindac
Mixed pattern or Atypical hepatitis	Phenytoin, Sulphonamides
Nonalcoholicsteatohepatitis	Amiodarone, Tamoxifen
Fibrosis/cirrhosis	Methotrexate
Microvesicularsteatosis	NRIs, Valproic acid
Veno-occlusive disease	Busulfan, Cyclophosphamide

Figure 1Definition of drug-induced liver disease

- **Hepatitis (Cytotoxic) _ Parenchymal cell**
  _Necrosis/Apoptosis
  _↑ ALT (ALT/ULN÷alkptase/ULN≥5)
  _Jaundice and ↑INR: Prognostic
- **Cholestasis (canalicular or ductular)**
  _↑ Alkptase (ALT/ULN÷alkptase/ULN≤2)
  _Jaundice: prolonged
- **Mixed hepatitis/cholestasis**
  _ALT/alkptase>2 to <5

Risk Factors

Environmental factors has complex relationship between the chemical properties of the drug, age, sex, fundamental diseases (e.g., HIV or diabetes), and genetic factors,[13-14](Fig 2) are the main risk factors for developing hepatotoxicity. Affiliated drug use and diseases are the most broadly documented risk factor. Genetic factors contain

genes that deal with the handling of the drug (metabolism, detoxification, and transport), as well as those influence the cell injury and repair. In addition to the genetic polymorphisms, well-intended effects occur with many of the genes that encode drug-metabolizing enzymes and drug transporters[15]. However, genetic polymorphism of a drug-metabolizing enzyme has its own clinical application that depends upon its efficient role in the metabolism of a drug.

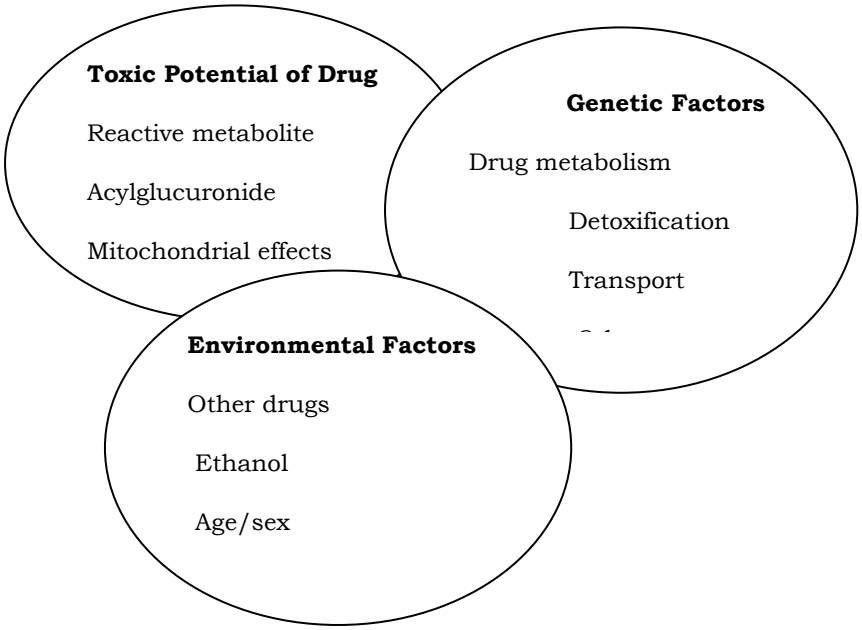

Figure 2.Risk factors for susceptibility to drug-induced hepatotoxicity

Treatment

Lifestyle and Diet

- Diet does not control the outcome of most forms of DILD, whereas malnutrition has a negative impact on liver transplantation outcomes.
- Fasting can increase the weakness to acetaminophen induced hepatotoxicity. Obese patients are at risk of halothane and methotrexate hepatotoxicity[16].
- Concurrent use of alcohol influences the seriousness of drug-induced liver injury[16].

Pharmacologic Treatment

- The aim of the treatment was to prevent the sequence of acute liver failure. Early intervention (antidote in the case of acetaminophenpoisoning, stopping incriminated agents with idiosyncratichepatotoxins such as isoniazid) is critical.
- Symptomatic measures, such as refill of fat-soluble vitamins and controls of pruritus (with drug-induced cholestasis) recover quality of life.
- The pharmacotherapy of end-stage liver disease (diuretics, beta-blockers, octreotide, somatostatin) is the same as for other forms of liver disease.

N-Acetylcysteine

Standard dosage:

- Intravenous: N-acetylcysteine (Parvolex, David Bull Laboratories, Victoria, Australia) 150mL/kg in 200mL 5% dextrose solution over 15 minutes, followed by 50mL/kg in 500mL 5% dextrose over 4 hours, and 100mL/kg in 1L 5% dextrose over 16hours[17].
- Alternate regimen: 140mg/kg in 5% dextrose over1 hour, followed by 12 maintenance doses (70 mg/kg) given over 1hour in 5% dextrose, given for 4hours apart[18-19].

Contraindications:

- Known sensitivity to acetylcysteine.

Main side effects:

Vomiting (oral route), Flushing, Urticaria, Wheezing, Respiratory distress, Hypotension, Hypertension. Usually occur early in the treatment. Minor reactions can be managed with antihistamines without intrusion of the infusion. Whenever severe reactions develop, the infusion should be blocked and antihistamines are administered. The infusion can be usually resumed after a hour[20].

Special points:

The unpleasant odour and flavour of the oral preparation can be covered by dissolving it in fruit juice and by dilution of NAC (made up to a 5% solution)[21].

Methionine

Standard dosage:

- Methionine (Methionine; Medical Research Pty Ltd, New South Wales, Australia), 2.5 g (36mg/kg) every4 hours in four divided doses [17].

Contraindications:

- Metabolic acidosis (may be exacerbated), chronic liver disease (can precipitate hepatic encephalopathy)[22.]

Main drug interactions:

- May decrease the therapeutic effects of levodopa.

Main side effect:

- Vomiting; May worsen hepatic encephalopathy if used beyond 12 hours following acetaminophen overdose.

Prednisolone

Standard dosage:

- Dose and duration were not clearly defined. The usual dose ranges from 30 to 60m.

Contraindications:

- Uncontrolled sepsis, Active tuberculosis.

Main side effects:

- Weight gain, acne, mood swings, psychosis, and development of candidiasis. It may worsen diabetic control.
- Long-term use was associated with osteoporosis, cushingoid features, cataract formation. Abrupt withdrawal may precipitate acute adrenal insufficiency.

Special points:

- Risk-to-benefit ratio has to be considered. Only limited evidence of efficacy was found for these pre-existing reactions and for emerging reactions such as rash, vasculitis, auto-antibodies for prolonged duration of these drugs.

Ursodeoxycholic acid

Standard dosage:

- Ursodeoxycholic acid Ursofalk; Orphan Australia (Pty Ltd, Victoria, Australia), 10 to 20mg/kg/day in two divided doses [17].

Contraindications:

- Acutecholecystitis or biliary-tract obstruction, pregnancy (first trimester)[17].

Main drug interactions:

- Ciprofloxacin, Cyclosporine, Cholestyramine, Charcoal, Colestipol, some antacids[21].

Main side effects:

- Diarrhoea, pruritus, sensitivity phenomena, increased cholestasis, nausea, vomiting and sleep disturbance[21].

Special points:

- Evidence regarding the efficacy was limited for many confine use to prolonged and severe cases.

Surgery

• To prevent death from difficulties of acute liver failure or during decompensated chronic liver disease.

• To develop the quality of life in patients with intractable problems (Pruritus, ascites, recurrent variceal bleeding, encephalopathy) of chronic liver disease.

Liver transplantation

Standard procedure:

- Total hepatectomy and shoot of donor graft.

Contraindications:

- Multiorgan failure, advanced age, severe psychosocial or psychiatric factors (especially in drug overdose patients), extrahepatic malignancy, systemic sepsis.

Complications:

- Adverse effects of immunosuppressive therapy, surgical complications including vascular and biliary problems, neurologic problems, metabolic troubles that include obesity, diabetes mellitus and hyperlipidemia, and osteoporosis.

Special points:

- Referral for transplantation should not be delayed as the clinical circumstances may change rapidly and may render the patient to inoperatable[23]. Early liaison with the transplant center is imperative. Indications may include deepening on jaundice, impaired coagulation, early changes in consciousness, repeated vomiting and failure to improve 2 to 3weeks after stopping incriminated agent.

Pathogenesis

Mechanism of hepatotoxic drugs will be dependent on its metabolism from parent compound to active drug compound, or a mixture of both (Fig 3). Mostly metabolism takes place in the liver, due to its impaired functioning leads to drug-induced injury[24]. The metabolites may be electrophilic chemicals or free radicals that reduce glutathione (GSH), and covalently binds to the proteins, lipids or nucleic acids by induced lipid peroxidation. Mainly the consequences include hepatocellular necrosis, apoptosis, or sensitization to cytokines or inflammatory mediators created by nonparenchymal cells. Simultaneously, the reactive metabolites may covalently bind or adjust liver proteins such as cytochrome P450s (CYPs) was important for sensitization and immune-mediated injury. Parent molecule has drug-dependent toxicity properties (or metabolite) and to collect the organelles [weak bases such as amiodarone accumulate in mitochondria[25], undergo nonspecific redox cycling (quinones cycle electrons from

NADPH to O_2 generating (O_2K)), or particularly inhibits the enzymes or transporters (nucleoside reverse transcriptase inhibitors block mitochondrial DNA polymerase[26] or cyclosporine inhibits canalicular transporters[27].

Haptenization.

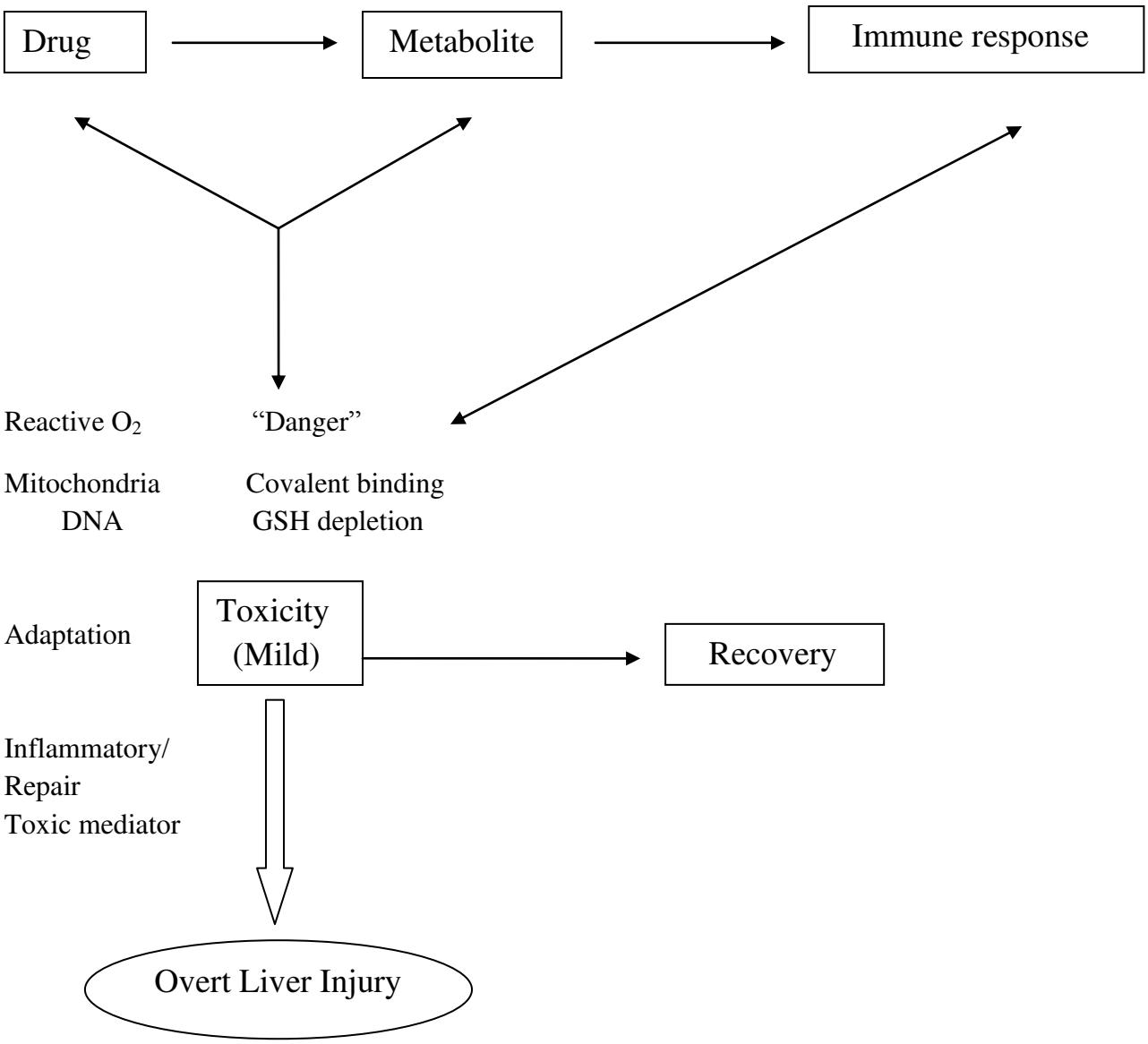

Figure 3 Pathogenesis of drug-induced liver diseases.

Classification of Drug-Induced Hepatotoxicity

Drug induced hepatotoxicity can be categorised into two types: intrinsic or idiosyncratic. The adverse hepatic event is highly expected and dose dependent in intrinsic hepatotoxicity. When a toxic amount of drug is administered liver gets injured. Hepatic injuries present after a short period of drug administration, and this kind of hepatotoxicity typically identified during drug development contained by the situation of the preclinical animal studies. Acetaminophen, Isoniazid and Tetracycline are example of drugs with dose-dependent hepatotoxic reaction when higher than suggested dosages can cause chronic liver injuries (table 2).

Table-2: Drugs with dose-dependent hepatotoxicity.

Drugs	Hepatotoxicity
Acetaminophen	Hepatocellular necrosis
Amiodarone	Chronic steatosis
Cyclosporine	Cholestasis
Methotrexate	Fibrosis
Niacin	Vascular injury
Oral contraceptives	Hepatic tumor
Tetracycline	Steatosis

Acetaminophen is most commonly used drug, which can cause intrinsic hepatotoxicity and may leads to hepatic necrosis with as little as 10 to 15g[28]. Most drug-induced hepatic injuries are impulsive or idiosyncratic, in which the amount is infrequent and may or may not be dose-dependent (table 3).

Table-3: Drugs with idiosyncratic liver injuries.

Drugs	Forms of Liver Injuries
Isoniazid, trazodone, diclofenac, venlafaxine, lovastatin, telithromycin	Hepatocellular necrosis
Chlorpromazine, estrogen, erythromycin and other macrolides	Cholestasis
Phenytoin, sulfamethoxazole	Hypersensitivity reaction
Diltiazem, sulphonamides, quinidine	Granulomatous hepatitis
Didanosine, tetracycline, valproic acid	Acute steatosis
Nitrofurantoin,methyldopa, lovastatin, minocycline	Autoimmune hepatitis
Methotrexate	Fibrosis
Amoxicillin, carbamazepine, cyclosporine, methimazole	Mixed hepatocellular/ cholestatic Injury

In these cases, there is a latency period, and cases are often fatal if the drug was repeatedly administered if once the injury has occurred[29]. Idiosyncratic hepatotoxicity can be classified as allergic or nonallergic, and only a small proportion of individuals were exposed to the causitive drug results in liver damage. Idiosyncratic allergic

hepatotoxicity may be qualified to hypersensitivity when the presenting symptoms are accompanied with fever, rash, and eosinophilia. The injury usually started after a sensitization period of 1 to 5weeks, whereas the injuries seen with nonallergic hepatotoxicity appear after a widely variable latency period.

Prevention

Several strategies were used potentially to prevent severe liver injury from drugs.

Patient education

Patients taking drugs related with liver injury should be warned about the indications that are commonly associated with liver injury, and should be instructed to stop the medications on these developing symptoms and to consult physician and to use right medications. This action will be severing for those drugs such as INH that are linked with a moderate to higher frequency in severe liver injury. Patients should be educated regarding drug interaction, food interactions such as alcohol, diet, smoking and other substances with sever toxicity. After providing detailed information, patients who go through significant DILI should be warned to avoid re-exposure to the concerned drugs.

Liver test screening

Episodic screening of liver biochemistries, mainly serum ALT is suggested for many drugs that have been connected with liver injury. However, serum ALT monitoring throughout drug treatment in effective to prevent severe DILI remains controversial.

For example, some patients have acute liver failure due to troglitazone (antidiabetic) which is residentially a life-threatening problem undergoing and so, monthly monitoring was suggested[30]. The implication of high serum ALT is not always clear, as some patients appear to adjust; liver injury improves in the face of ongoing use of the medication[31]. In fact, anxiety is caused by the exposure abnormally, but asymptomatic high aminotransferases may eventually result in improper drug withdrawal in some patients.

Legislation

It's a way to reduce the problem of DILI threw legislation that was aimed at eliminating highly toxic drugs from the flea market. For example, acetaminophen, opiate drugs. Almost half of acute liver failure cases in the United States are due to acetaminophen toxicity. Many of these cases are from preconcerted acetaminophen overdose in suicidal patients[32], many of these patients are prescribed acetaminophen-opiate combinations such Vicodin, as combination of the opiate hydrocodone and acetaminophen that is most commonly prescribed drugs in the United States. Ultimately, many patients treated with acetaminophen-opiate drug for chronic pain which was seen tolerant to analgesics-opiate

combination drug that leads to attain adequate pain relief. The concept of combination is greatly addictive drug (an opiate) and a dose-dependent liver toxin (acetaminophen) into a single tablet with defies reason and is mostly analogous as mixing candy and poison[33].These drugs are combined together in a single pill, they can be taken concurrently as separate tablets, an opiate (Eg, hydrocodone) and acetaminophen, with similar analgesic affect. But the patients should not be prescribed with acetaminophen-opiate combination for chronic pain, and patients taking these drugs should be warned about the high risk of severe liver injury. Although patient and physician education is important, the most efficient solution is perhaps the legislative action is a part of FDA to separate the acetaminophen and other drugs, counting opiates as well as cold remedies. Such important legislation would help to reduce the death rate each year in the United States from unintentional acetaminophen overdoses. The FDA announced strategy to limit the acetaminophen use to 325 mg per tablet over the next few years.

Diagnosis

DILI is a vital cause of abnormal liver biochemistries observed in clinical practice. Many patients has mild DILI, few were completely asymptomatic and are only diagnosed due to other hospital visits. When symptoms of DILI are present, in cases of severe hepatocellular DILI, these are often similar to viral hepatitis and include malaise, anorexia, nausea and vomiting, right upper quadrant abdominal pain, jaundice, alcoholic stools, and dark (tea-colored) urine. Fever and rash are the hallmarks of hypersensitivity that may be current with DILI from some drugs (eg, anticonvulsants such as phenytoin, sulfa drugs such as sulfamethoxazole and trimethoprim). A hallmark of acute liver failure is characterized with severe form of clinical manifestations such as severe memory loss, confusion, and even coma, the prognosis is grim without a liver transplant[34].

Diagnosis of DILI is usually made during a process called causality assessment, which is broadly related to a criminal investigation, mainly one in which there are no actual witnesses to the crime. During the process of causality assessment, many characters of the drug reaction are considered, which includes:

- Was the drug in the "right place at the right time?" Occasionally if the drug was started after the signs and symptoms of liver injury, the drug basically has an excuse and it must be exculpated.
- Does the drug have a "prior record?" That has to previously report to cause liver injury in similar patients?
- Are the characteristics of the DILI event (the "crime") is constant with the known signature, or modus operandi of the implicated drug? The drug used to treat tuberculosis, usually cause hepatocellular injury with elevated serum aminotransferases and in severe cases, jaundice. Anticonvulsants, such as phenytoin

(Dilantin), can cause liver injury as part of a hypersensitivity reaction so, that rash and fever was often well-known features. An irregular signature of amoxicillin-clavulanic acid (Augmentin), which can be caused by liver injury in a cholestatic or mixed pattern with jaundice. Another antibiotic, nitrofurantoin (Macrobid), normally causes a chronic hepatitis after many weeks, months, or even years of therapy, and is often coupled with serum antinuclear antibodies (ANA). So the patient does not exclude a particular drug from causing liver injury.

- Are there any other explanations for the liver injury? Critical for diagnosing of DILI, it's the exclusion of other possible causes of severe liver diseases. In essence, DILI is a diagnosis of exclusion.
- Is the clinical course of the reaction consistent with DILI? Most cases of DILI, particularly when not very severe, decide relatively when the drug is discontinued. If the drug is reintroduced the liver injury often returns, sometimes more fast and vigorously than the initial exposure. However, rechallenge of the patient with the suspected drug is not usually advised as a diagnostic test because the liver injury that follows sometimes be quite severe, even life-threatening.

Diagnosis can never be truly definitive because, very few exceptions, specific diagnostic testing's are missing, and it's almost impossible to prohibit every possible competing cause of liver injury. Serologic testing is to rule out the viral hepatitis A, B, C, and sometimes even E (albeit very rare in the United States) in most of the patient's serologic markers of autoimmunity is seen (eg, an ANA, smooth muscle antibody, and γ-globulins). In some cases, a history is needed to exclude severe hypotension former the onset of liver injury, which would suggest "shock liver" as possible to diagnosis if the liver tests suggest this possibility. Alcohol abuse must also be expelled by careful interrogation of the patient. Fatty liver is a common cause of low-level abnormal liver tests that can be further evaluated by liver imaging. Finally, most of the patients will require some type of liver imaging, by ultrasonography, computed tomography, magnetic resonance imaging or in cases of suspected biliary obstruction, possibly endoscopic retrograde cholangiopancreatography. Liver biopsy is also sometimes useful to diagnosis drug-induced liver injury, but it is rarely diagnostic, because pathologically DILI can imitate virtually the entire spectrum of other causes of liver injury, including viral and autoimmune hepatitis, biliary tract disease and in some cases even alcohol abuse. Liver biopsy also carries a small but major risk of bleeding and other complications.

Causality analysis in many cases of liver injury proves challenging. Cases of potential DILI in patients with underlying liver disease or who are taking multiple drugs are particularly vexing.

Various causality instruments are present. The most popular was the Roussel-Uclaf Causality Assessment Method (RUCAM), also referred to as the CIOMS because the Council for International Organizations of Medical Sciences sponsored development of the instrument, uses of mathematical weighing plays a key features in 7 domains: Temporal relationship, risk factors, concomitant drug use, elimination of other aetiology, prior information about liver injury and the drug, and the response to rechallenge[37]. The total score is divided into ranges that represents high probability (>8), probable (6–8), possible (3–5), unlikely (1–2), and excluded (≤0). The instrument that are incorporated into online calculator. Although the RUCAM instrument have some attributes, including a check-list for the consultant faced with assessing causality in cases of possible DILI, it has been recently shown to be less reliable than expert opinion[35-36].

Hepatitis E Virus Masquerading as DILI

Hepatitis A, B, and C are part of the standard assessment of possible DILI, testing for hepatitis E virus (HEV) was performed rarely residential countries, including the United States. A recent report recommended that in some areas of the United States, up to 20% of blood donors are immunoglobulin G (IgG)–seropositive for HEV, suggesting earlier exposure and immunity to the virus, with the maximum prevalence in states that are large producers of swine[37]. It's probable that some cases of apparent DILI may actually characterize occult HEV infection. Supporting this hypothesis, a latest publication from Great Britain explained 6 cases of previously unrecognized HEV that had apparently been misdiagnosed as DILI[38]. In the absence of specific testing, it is not shocking that hepatitis E and DILI might be confused clinically. The clinical features of hepatitis E are similar to hepatitis A. Earlier it's more commonly coupled with jaundice and overall more severe disease[39]. It's hoped that growing attention in HEV infection both in developing and developed countries will stimulate the progress accurately and reliable diagnostics in this area.

Acetaminophen Adducts

Acetaminophen is an abnormal drug that shows a dose-dependent liver toxin, but remains popular as an effective analgesic for mild to moderate pain which is relatively safe as long as it is used in low doses. Although there is a definite idiosyncratic feature of acetaminophen toxicity it was poorly reflected. Defined genetic polymorphisms and environmental exposures, was reported when taken in adequate quantities leads to liver injury basically in everyone. Acetaminophen-related ALF go unrecognized because of several features. Firstly, the history of additional acetaminophen ingestion, whether acute or more chronically it's often variable or unavailable (e.g., due to hepatic

encephalopathy). As a result, a low acetaminophen level should never be used as grounds for not administering the antidote, N-acetylcysteine (NAC)[40]. In tests of daily serial samples measurement of serum acetaminophen-protein adducts reliably known acetaminophen toxicity, and may be useful for diagnostic test for cases that are lacking with historical data or other clinical information. Thus the development was rapid, inexpensive, whereas the assay regarding point-of-care is eagerly awaited.

Summary and Future Perspectives

The impact of DILI on public health and drug development is important to recognize the mechanism leading to injury and to predict and prevent the problems. Current literatures suggests that these reactions are initiated by hepatocyte damage and followed by a series of secondary events, as well as activation of innate immune cells, release of inflammatory cytokines and chemokines, and elicitation of drug-specific T- and B-cell responses. An effective path toward better understanding of the molecular and cellular basis of these events in development of animal models of DILI, in which one or more pathways described above account for the mechanism.

An important part of preventing DILI is identifying the patients at risk. The low incidence of DILI suggests that polymorphisms within a single gene cannot account for a patient's susceptibility, therefore multiple genetic and environmental factors must converge to influence the incidence of DILI. Widening up with the search of risk factors using global genomic and proteomic approaches are proven to be successful in the identification of population at risk.

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