

**Review Article****A Conspectus: Hepatotoxicity Caused by Drug's**Prasoon Kumar Saxena^{1*}, Rosaline Mishra¹, Abhishek Bhardwaj² Moumita Barman¹, Rahul Chaudhary¹¹ ITS College of Pharmacy, Muradnagar Ghaziabad, U.P. India² Department of Pharmacy, Teerthanker Mahaveer University, U.P, India**ARTICLE INFO:****Article history:**

Received: 5 July 2018

Received in revised form:

18 August 2018

Accepted: 20 August 2018

Available online: 30 September 2018

Keywords:

Hepatotoxicity, Cytochrome P450, Electrophiles, Cytolytic, Liver Biopsy, Liver Cirrhosis, Endotoxin.

Abstract

Liver is the principle organ for metabolism of various drugs, endotoxins. Hepatotoxicity is one of the reversible conditions. Drugs are an vital cause of liver injury. Drug-induced injury to the liver can mimic any form of acute or chronic liver disease. The action of cytochrome P450 can induce acute injury to liver, through which drug will break down into electrophiles or free radicals. These spontaneous metabolites can covalently bind to protein and unsaturated fatty acids or induce lipid peroxidation, respectively. The clinical presentation of liver damage may be either cytolytic or cholestatic. Systemic hypersensitivity reaction against the applied agent may be one of the major causes of liver damage. Drug- or toxin-induced liver damage includes vascular damage, induction of liver tumours and development of liver cirrhosis. The most important pre-emptive measure is judicious drug used by the prescribing physician. Early recognition of hepatotoxicity and termination of the offending agent is essential for treatment. The diagnosis may be confirmed by additional diagnostic measures (e. g. liver biopsy) or the clinical course after exposure to the causing agent has been stopped. Therefore, the main aim is to prevent chronic liver damage through early and correct diagnosis. Due to the extensive variety of possibly liver toxic drugs and chemical agents this aspect is a major challenge to physicians. Taking into account the significance of drug-induced hepatotoxicity as a key cause of liver damage, this review pitch light on various drugs which induce hepatotoxicity, with their mechanism of liver damage and clinical scenario.

Introduction

Acute liver failure (ALF) is a hazardous crisis, however possibly reversible condition, of changed etiology. The mortality is generally high except if belligerent and early treatment is founded, ordinarily in a intensive care setting. Treatment is coordinated at early acknowledgment of the reason, impediment, and general strong measures, however in spite of cutting edge escalated mind, mortality might be as high as 40 to 80%, which is for the most part identified with its inconveniences like cerebral edema and sepsis^[1]

Orthotropic liver transplantation (OLT) has now turned into a built up treatment choice in patients with ALF and is winding up progressively accessible in developing countries including India. Thus, there is a need to create more information about ALF as legitimate determination of cases generally advantage from OLT. Around the world, hepatitis A and E diseases potentially cause greater part of ALF, with mortality of up to

>50% detailed from the creating world [4]. A large portion of the reports on ALF have been prevalently from the West^[5,6] The biggest Indian arrangement of 423 patients with ALF detailed from Delhi in 1996 demonstrated that both the etiological and prognostic components differed from those revealed from the West^[7].

Drug-induced liver injury: Drug-induced liver injury (DILI) is very common disease and almost all classes of medications can cause hepatotoxicity. Mostly DILI are benign with treatment and develop after drug withdrawal. Most of the patient has similar clinical symptoms to hepatotoxicity. Treatment of drug and herbal-induced liver injury consists of rapid drug withdrawal and caring targeted to alleviate unwanted symptoms. It is very essential to recognize and get rid of the offending agent as quickly as possible to prevent the progression to hepatotoxicity^[8]

Medication initiated liver damage is a successive differential finding in patients with intense liver damage without clear etiology. Aside from rejection of contending etiologies, a critical component in the indicative procedure is the data about the known and potential hepatotoxicity of the operator. Nonetheless, information on hepatotoxicity isn't generally effortlessly open. A few medications have been convincingly archived to cause liver damage in various case reports and case arrangement. Numerous such medications have a known clinical mark (phenotype) of liver damage and causality has been additionally reported by cases of a positive re challenge.

Drugs inducing Hepatotoxicity

Non-Steroidal Anti-inflammatory drugs

Acetaminophen, Nimesulide, Diclofenac, Ibuprofen are Non-steroidal calming drugs (NSAIDs) which are the focal point of pharmacotherapy for generally rheumatological disarranges, and are utilized as a part of vast numbers as analgesics and antipyretics, both as doctor prescribed medications and over the counter buys. It is the most vital reason for the medication prompted harmful damage to a few organ frameworks, including surely understood damage to gastrointestinal tract and kidneys. Novel drugs belonging to this category such as COX-2 inhibitors (e.g Nimesulide, Celecoxib and Rofecoxib) have also known to be toxic to the liver, though to a lesser extent

A plethora of drugs has been withdrawn from the market due to being hepatotoxic. Naming a few

Anthranilic acid derivatives: Cinchophenz and Glafanine,

Acetic acid derivatives: Amphenac, Fenclozic acid, Isoxepac and Bromofenac,

Propionic acid derivatives: Benoxaprofen, Ibufenac, Pirprofenac, Suprofenac

Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone
Oxicams: Isoxicam, Sudoxicam.

Quinazonlonederivative: Fluproquazone^[9]

Mechanism of Hepatotoxicity induced by NSAIDs

The sub-atomic systems level of mechanism for liver toxicity has not yet been completely illustrated. In any case, trials confirm and recommend that they incorporate expanded centralization of the medications in the hepatobiliary compartment, development of receptive metabolites that covalently change proteins and deliver oxidative pressure, and mitochondrial damage. Hereditary as well as procured understanding elements can either enlarge the pathways prompting hepatic danger or obstruct the defensive and detoxifying pathways. Nimesulide for instance is a selective cyclo-oxygenase-2 inhibitor suggested for manifestation in cases of analgesia and inflammation but lately it is known to have been causing associated with rare but grave and random antagonistic reactions in the liver namely it enhances in the serum aminotransferase activities, hepatocellular necrosis, and/or intrahepatic cholestasis. Similar to other drugs causing idiosyncratic hepatotoxicity, both the molecule and the patient contribute to the hazard. Nimesulide is a slightly acidic sulfanilide the Nitroarene group upon bioreductive metabolism

gets converted into toxic intermediates that have been known to cause oxidative stress, covalent binding, and mitochondrial injury^[10,11].

As of late, various in vitro creature models have been utilized to explore the conceivable instruments of NSAID's-connected hepatotoxicity. Studies utilizing rodent liver mitochondria and newly secluded rodent hepatocytes demonstrated that diphenylamine, which is regular in the structure of NSAID's, uncouples oxidative phosphorylation, diminishes hepatic ATP content and actuates hepatocyte damage. Brooding of mitochondria with diphenylamine, mefenamic corrosive or diclofenac caused mitochondrial swelling^[12,13]. Also, an unearthly move of the safranine-restricting spectra to mitochondria happened, showing the loss of mitochondrial membrane possibilities (one of the attributes of uncoupling of oxidative phosphorylation). Expansion of oligomycin, which prevents ATPase, ensured against cell damage. In diclofenac-initiated danger in hepatocytes, no critical oxidative pressure (diminish in glutathione and lipid peroxidation) or increment in intracellular calcium fixation was seen. Paracetamol organization causes rot of the centrilobular hepatocytes portrayed by atomic pyknosis and eosinophilic cytoplasm took after by expansive inordinate hepatic injury. The covalent authoritative of N-acetyl-Pbenzoquinoneimine, an oxidative result of paracetamol to sulphhydryl gatherings of protein, result in lipid peroxidative corruption of glutathione level and in this manner, produces cell putrefaction in the liver

Anti Retrovirals

A few anti HIV drugs have been accounted for to cause lethal intense hepatitis; they regularly cause asymptomatic rises of transaminases. Liver toxicity is more continuous among subjects with ceaseless hepatitis C or potentially B. The occurrence of medication prompted liver lethality isn't notable for most hostile to retrovirals (Nunez, 1999). Liver lethality, particularly extreme danger, is unmistakably more visit in HCV (Hepatitis C) and additionally HBV (Hepatitis B) coinfecting people treated with HAART (Highly dynamic antiretroviral treatments more often than not mix of a few medications). Few examples of anti retrovirals which could have hepatotoxic effect can be listed as follows, Protease inhibitors Examples: Ritonavir, Indinavir, Saquinavir, Nelfinavir, Nucleoside analogues reverse transcriptase inhibitors (NRTI) Examples: Lamivudine (3TC), Tenofovir, Zidovudine, Didanosine, Stavudine, Abacavir (ABC) and Tenofovir (TDF), Non-nucleoside analogues reverse transcriptase inhibitors Examples: Nevirapine, Emtricitabine, Efavirenz [14]

Mechanism of Toxicity

The conceivable mode associated with the induction of hepatotoxicity related with the utilization of antiretroviral is abridged beneath. It is plausible that various pathogenic pathways at the same time agree in a few patients, being troublesome to recognize the correct components associated with the advancement of hepatotoxicity. Coordinate danger Hostile to retrovirals, as some other medication, can incite coordinate Toxic quality in the liver. Medications processed in

the liver through the cytochrome pathways may cause liver poisonous quality when there are polymorphisms in the proteins [15]. Since numerous of the counter retrovirals are utilized in the liver through the cytochrome pathways, peculiar polymorphisms of the enzymatic buildings may prompt critical heterogeneity in tranquilize digestion, inclining to the advancement of hepatotoxicity in specific people. A few medications may potentiate the initiation of death receptors as well as intracellular pressure pathways.

Mitochondrial toxicity

It is rare yet an unmistakable sort of hepatotoxicity that may develop to intense liver injury. The primary component of the hepatic injury is the collection of miniaturized scale vesicular steatosis in liver cells and mitochondrial exhaustion. This early injury may develop to large scale vesicular steatosis with central rot, fibrosis, cholestasis, expansion of biliary conduits, and Mallory bodies, a clinical picture looking like liquor actuated liver harmfulness, pregnancy steatosis or Reye's disorder. Of intrigue, the basic liver malady does not incline to this kind of injury [15]. It is trusted that the aggregate introduction to NRTI is a critical factor for the improvement of lactic acidosis, since it normally shows up after delayed treatment, normally years, and corresponds with the quantity of attending NRTI. In vitro information bolster an added substance or synergistic long haul mitochondrial danger with some NRTI blends.

Anti lipidemic Drugs

The example of liver damage from anti hyperlipidemics is normally hepatocellular or blended in nature with uncommon occasions of unadulterated cholestatic picture [16]. The proposed components of hepatotoxicity are fluctuated relying upon the medication or tranquilize class, and incorporate consequences for the cytochrome P450 framework, debilitation of bile corrosive transport proteins, resistant intervened provocative reaction to the medicine or its metabolites, invulnerable intervened apoptosis by tumor corruption factor, and oxidative worry because of intracellular harm. The antihyperlipidemic medicate with the most elevated potential for hepatic damage is the supported discharge plan of niacin. HMG CoA reductase inhibitors, also called statins, infrequently cause clinically noteworthy liver damage, albeit asymptomatic height in amino transferases is normal (17).

Category of anti lipidemic drug include statins like Lovastatins, Atorvastatins etc., they usually act as HMG Co A reductase it is an enzyme essential for cholesterol biosynthesis; they also act in several ways to decrease the level of low density lipoprotein (LDL) and increase the stability of atherosclerotic plaques (18).

Anti psychotic Drugs:

The liver is the organ by which the larger part of substances are assimilated, including psychotropic medications. There are a few pharmacokinetic changes in end-organize liver infection that can meddle with the utilization of psychotropic medications. This reality is especially valid in drugs with broad first-pass digestion, profoundly protein bound medications and medications relying upon stage I hepatic

metabolic responses. Psychopharmacological drugs are additionally connected with a danger of hepatotoxicity

List of common antipsychotics are tabulated below fig 1

Fig 1 : Common anti psychotics

S.No	Class of Drug	Examples
1	Selective serotonin re uptake inhibitor	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
2	Atypical antidepressant	Ibuproprion, Trazodone, Mirtazapine
3	Tri Cyclic anti Depressants	Clomipramine, DEsipraminE, Doxepin, Imipramine, Nortriptyline
4	Mono Amino oxidase inhibitor	Isocarboxazid, Phenelzine, Selegiline

The main enzyme responsible for metabolism of most of the antipsychotics is Cytochrome P450 (in the liver) is responsible for the metabolization of most antipsychotics. Liver injury is mainly initiated in three forms Hepatocellular, cholestatic, steatosis^(19,20).

The mechanisms by which these drugs might cause liver injury are briefed in the below table 2

Table. 2: Mechanism by which anti psychotics cause liver injury [21,22,23]

S.No	Types of anti psychotics	Types of lesions	Mechanism of action
1	Cloropromazine	Cholestatic	Immuno-allergic
2	Haloperidol	Cholestatic	Immuno-allergic
3	Clozapine	Hepatocellular Cholestatic Chronic esteatosis	Immuno-allergic Chronic estatosis
4	Olanzapine	Hepatocellular Cholestatic Chronic esteatosis	Immuno-allergic, Chronic estatosis
5	Risperidone	Hepatocellular Cholestatic Chronic esteatosis	Immuno-allergic Chronic estatosis

Routinely performed liver function test

Following liver function test are based on disorder.

Abnormalities of bile pigment and bile salts excretion

1. Serum total, direct and indirect bilirubin.
2. Urine bile salt, bile pigment and urobilinogen.

Changes in certain enzymes Test

1. SGPT(ALT)
2. SGOT (AST)
3. Alkaline phosphate (ALP) and if necessary than Gamma-GT

Changes in Plasma Protein

1. Thymol turbidity test
2. Determination of total protein, albumin globulin and A/G ratio.

Other Liver Function Test

1. Determination of serum bile acid
2. Determination of serum-prealbumin, Ceruloplasmin, alpha-1-antitrypsin, haptoglobin.
3. Determination of serum cholinesterase.
4. Determination of serum Beta-2-microglobulin
5. Determination of plasma coagulation proteins
6. Determination of prothrombin time (PT).
7. Determination of serum triglycerides and esterified cholesterol
8. Determination of lipoprotein X (LP-X) and total serum cholesterol and phospholipids.
9. Determination of serum Urea
10. Determination of plasma ammonia.
11. Determination of total serum cholesterol.

Additional liver function tests

1. Bromsulphthalein Test
2. Determination of fibrinogen

Screening Method for Liver Fibrosis

In experimental model acute and chronic injury can be induce the necrosis, steatosis, hepatic injuries, cirrhosis and cholestasis. Aim of hepatoprotective model is tested for the isolated compounds, extracts and fractions to avoid the damage caused by hepatotoxins.

Several approaches to induce fibrosis in animal are described and this model can be divided according to their stimulus from inciting injury. This tested model may be in vitro or in vivo.

In vivo models

One of the widely used method for hepatoprotective activity. In this model easily determine the protective mechanism of the isolated compounds, fraction and extract. The damage in experimental model can be produced by different hepatotoxin at fix dosage. Protective effect of compounds can be measure by histopathological examination as well as different biochemical and metabolic markers.

1. **Toxic damage hepatocytes:** CCl₄, dimethylnitrosamine (DMN), galactosamine etc.
2. **Toxic damage bile duct epithelial cells:** Thioacetamide (TAA) etc.
3. **Immunological induced damage:** heterologous serum and experimental schistosomiasis.
4. **Biliary damage:** Common bile duct ligation (BDL) or occlusion.
5. **Alcohol induced damage:** baboon ethanol diet or tsukamoto/ French model in rats.
6. **Fatty liver disease.**

Disadvantages of in vivo methods: In vivo method studies on the animals so for the correct statics we require the large number of animals. Studies include the long period of time. Motility rate is more and in the last financial and ethical aspects will be increased.

In vitro methods: An *in vitro* study is one of the best method for screening the different fractions or isolated compounds, to

check out the potential at cellular and molecular level. In these model fresh hepatocytes, primary hepatocytes culture and immortalized cell lines are used. Primary hepatocytes have the property to maintain the normal metabolic liver properties for short time. Cell lines are able to maintain his properties for long time. Protective effect can be measured by evaluating the parameters like cell multiplication, morphology, transaminase liberation, macromolecular synthesis, oxygen consumption etc.

Merits and demerits of in vitro model: Test can be performed within two to three days. Small amount of sample is required. More samples can be analyzed in the same time. Lack of complexity present in the organ of biological system, result should be interpreted with caution. Sample does not go any biotransformation process [24, 25.]

Conclusion

The available data on drug-induced hepatic toxicity are mostly from known cases few from clinical trials but most of them are for the newly developed. It is hence difficult to know the actual about the prevalence and sternness drug induced hepatotoxicity, therefore people should be made more cautious regarding the severity of the disease and should be motivated to go for regular check-up of the liver especially the ones which are on long term therapy of a drug .

References

1. Gill R, Sterling R. Acute liver failure. J Clin Gastroenterol. 2001 Sep;33(3):191-198.
2. Williams R. The need for artificial liver support. In: Williams R, Murray-Lyon M (eds), Artificial Liver Support. Pitman Medical, London. 1975;3-10.
3. Sherlock S. Chronic hepatitis. Gut 1974;15:581-97. Tisdale WA. Subacute hepatitis. N Engl J Med 1963;268:85-9.
4. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013 Dec;369(26):2525-2534.
5. O'Grady J, Schalm S, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993 Jul;342(8866):273-275.
6. O'Grady JG, Alexander G, Hayllar K, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology. 1989 Aug;97(2):439-445.
7. Acharya S, Dasarathy S, Kumar T, Sushma S, Prasanna K, Tandon A, Sreenivas V, Nijhawan S, Panda S, Nanda S. Fulminant hepatitis in a tropical population: clinical course, cause, and early predictors of outcome. Hepatology. 1996 Jun;23(6):1448-1455.
8. Stefan D, James P Drug-induced Liver Injury, US GastroenterolHepatol Rev. 2010 Jan 1; 6:73-80.
9. Lewis J. Nonsteroidal anti-inflammatory drugs and leukotriene receptor antagonists: pathology and clinical presentation of hepatotoxicity. (2007); In N. Kaplowitz, L.D. DeLeve (Eds.) Drug-induced liver disease. (pp. 377-390). New York: Informa Healthcare USA.
10. Mitchell J, Jollow D, Potter W, Davis D, Gillette J.R., Brodie B.B. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. J Pharmacol Exp Ther 1973; 187:185-194.
11. Boelsterli A, Hyman J, Anke K Idiosyncratic Liver Toxicity of Nonsteroidal Antiinflammatory Drugs: Molecular Mechanisms and Pathology Journal Critical Reviews in Toxicology 1995, Volume 25, - Issue 3

12. Lui S, Steve T., Lam M., Cheung Eric F.. Case Report: Possible olanzapine-induced hepatotoxicity in a young Chinese patient. *Hong Kong Med J.* 2009; 15:5
13. Mitchell J, Jollow D, Potter W, Davis D, Gillette J.R., Brodie B.B. Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism. *J Pharmacol Exp Ther.* 1973; 187:185–194.
14. Breen DP, Marinaki A, Arenas M, Hayes P. Pharmacogenetic association with adverse drug reactions to azathioprine immunosuppressive therapy following liver transplantation. *Liver Transpl.* 2005; 11: 826–833.
15. Bricquir Y, Bissuel F, Bruneel F, Habersetzer F, Chassar D, Cotte L, Chevallier M, Bernuau M, Lucet JC. Trepoc. Fulminant hepatitis with severe lactate acidosis in HIV-infected patients on didanosine therapy. *J Intern Med.* 1994; 235:367–371.
16. Bertolami M. Mechanisms of hepatotoxicity. *Arq Bras de Cardiol.* 2005; 85(5): 25-27.
17. Cohen DE, Anania F, Chalasani N. National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists.. 2006; 97: 77–81.
18. Jacobson T. Statin safety: lessons from new drug applications for marketed statins. *Am J Cardiol.* 2006; 97: 44–51
19. Bressolle F, Bres J, Blanchin M, Gomeni R. Sulpiride pharmacokinetics in humans after intramuscular administration at three dose levels. *J Pharm Sci.* 1984;73:1128–1136
20. Urichuk L, Prior T, Dursun S, Baker G. Metabolism of atypical antipsychotics: involvement of cytochrome p450 enzymes and relevance for drug-drug interactions. *Curr Drug Metab.* 2008;9:410–418
21. Fontana R, Seeff L, Andrade R, Björnsson E, Day C, Serrano J, Hoofnagle J. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. *Hepatology.* 2010; 52:730–742.
22. Aronson J. *Meyler's Side Effects of Psychiatric Drugs.* Oxford: Elsevier; 2009.
23. Marwick K, Taylor M, Walker S. Antipsychotics and abnormal liver function tests: systematic review. *Clin Neuropharmacol.* 2012; 35:244–253.
24. Gupta S. *Drug Screening Methods (Preclinical Evaluation of New Drug).* Jaypee Brothers Medical Publishers (P) LTD ,New Delhi. 2nd edition 185-201.
25. Singh S *Practical Manual of Biochemistry.* CBS Publishers, New Delhi 5th edition 2004. 299-301.

Cite this article as: **Prasoon Kumar Saxena, Rosaline Mishra, Abhishek Bhardwaj, Moumita Barman, Rahul Chaudhary. A Conspectus: Hepatotoxicity Caused by Drug's. *Indian J. Pharm. Biol. Res.*2018; 6(3):55-59.**