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DRUG INDUCED HEPATOTOXICITY: AN UPDATED OVERVIEW

Dr. Asif Rasheed[1], Aamir Khan Yusuf Khan[2], Arfia Afroze[3*], Qazi Syed Anas Arifi[4]
Department of Pharmacology, Deccan school of Pharmacy, Hyderabad-500001
Corresponding Author: Email: afrozearfia45@gmail.com

Abstract: *Drug-induced hepatotoxicity is common in clinical settings and is becoming a leading cause of death worldwide and its prevalence is increasing exponentially, there are several causes behind hepatotoxicity such as administration of acetaminophen that induced hepatotoxicity through the excessive formation of the toxic metabolite N-acetyl-para-benzo-quinone imine (NAPQI). It is an effective analgesic and antipyretic medication. In addition, the severity of liver damage varies from person to person depending on host variables, nutritional state, age, etc. Paracetamol toxicity has been described in accidental, iatrogenic, and purposeful intake. The primary organ for preserving the body's interior environment is the liver. In over 75% of cases, fatal medication responses or liver transplants are the outcome. Acute-dose dependent liver damage, acute fatty infiltration, cholestatic jaundice, liver granulomas, active chronic hepatitis, liver cirrhosis, liver tumours, etc. are a few examples of drug-induced liver problems. Drugs are the cause of 2-5% of jaundice hospitalisations and roughly 10% of all occurrences of acute hepatitis.*

Key Words: *Liver hepatotoxicity, Hepatotoxic Drugs, Liver damage.*

1. INTRODUCTION :

The metabolism and elimination of drugs from the human body are considerably facilitated by the liver, which is the largest solid organ and largest gland [1]. For the body to function properly, drugs and xenobiotics must be converted by enzymes in the liver to nontoxic substances. If these conditions change, the metabolism shifts toward the production of oxidants, which adhere to nuclear proteins or lipids and cause mutations, membrane damage, or changes in enzyme activity, respectively, which further causes organ dysfunction [2].Drug -induced liver injury (DILI) is an acute or chronic response to a natural or manufactured compound [3]. Hepatotoxicity can be caused by a number of different mechanisms, including mitochondrial inhibition, cytolytic T-cell activation, hepatocyte apoptosis, bile duct damage, and liver disassembly [4]. Phase I and Phase II enzymes are two groups of enzymes that are crucial for the metabolism and detoxification of a wide range of drugs and other toxins. The structural analogue of phenacetin, which was discontinued due to nephrotoxicity, is paracetamol [5]. The two hepatotoxic pathways are idiosyncratic, which is more unpredictable, and intrinsic, which is dose-dependent [6] [7].

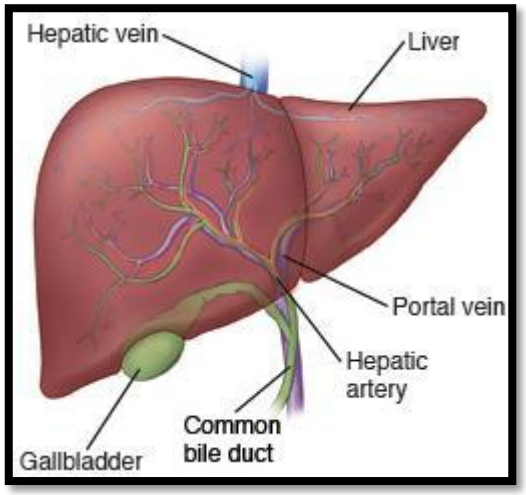

Fig no : 1. Liver

The majority of DILI cases are asymptomatic, but jaundice is the most typical symptom [8][9]. There is a special antidote for paracetamol-induced liver injury that can prevent acute liver failure, but it needs time to take effect, therefore when there is no clear history of intake, a high clinical suspicion should be held. Patients who have overdosed on paracetamol can be treated with N-acetyl cysteine (NAC), but it must be given as quickly as possible [10]. Alkaline phosphatase (ALP) is high in cholestatic injury while aminotransferases are elevated in hepatocellular injury. The first step in treatment is to get rid of the offending substance, and recovery prospects are typically good once the drug is stopped [11].The synthetic compounds that cause liver damage are called hepatotoxins of hepatotoxicants[12].

Examples of drugs commonly induce liver injury.

NSAIDs , Acetaminophen , Heparin , Phenytoin , Ketoconazole, Propylthiouracil.

Etiology

Female sex, older age, and elevated body mass index (BMI) are all patient risk factors related to the occurrence of DILI[13][14]. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) maintains a searchable database called LiverTox[15] that lists more than 1000 drugs that are known to induce hepatotoxicity. Acetaminophen is the drug that causes intrinsic DILI the most frequently; aspirin, tetracycline, and vitamin A are less frequently associated with it. Cases of idiosyncratic DILI are brought on by: [16]

- Antibiotics (45.4%): amoxicillin-clavulanate (most common), sulfamethoxazole-trimethoprim, ciprofloxacin, isoniazid.
- NSAIDs
- Cardiovascular drugs (10%): statins, amiodarone
- Central nervous system agents: valproate, phenytoin
- Antineoplastic drugs: tyrosine kinase inhibitors, tumor necrosis factor inhibitors, alpha inhibitors, methotrexate

Signs & Symptoms

Hepatotoxicity is a term used to describe liver damage caused by specific toxins. Recreational and prescription medications are common causes of this illness. Understanding the symptoms and signs of hepatotoxicity is essential because if left untreated, it can cause liver failure. [17].

Risk factors

The influence of sensibility or idiosyncrasy of each person is recognized as an important risk factor. In addition, there are some factors that increase the probability of occurrence of hepatotoxicity [18]:

- Age: Drug toxicity primarily affects the elderly because of physiological changes and polymedicating [19], but with valproic acid, it primarily affects the younger population.
- Gender: Due to biological and pharmacokinetic variations, female patients are more likely to experience medication toxicity; in addition, sex-specific factors such menopause, pregnancy, and menstruation may also be at role.
- Alcohol intake has the potential to make pharmaceutical compounds more harmful [20].
- The simultaneous administration of medications: this factor raises the danger of drug interactions.
- Previous or underlying hepatic diseases: may increase the risk of hepatotoxic agents [21].
- Genetic factors: related with genetic polymorphism in cytochrome P450 can unchain a hepatic lesion.

Pathophysiology

There are two distinct pathways that contribute to DILI pathogenesis:

- intrinsic and
- idiosyncratic.

From drugs that are known to cause liver harm in a dose-dependent manner with a brief latency time, the intrinsic mechanism is predictable and reproducible [22]. For instance, in acetaminophen toxicity, the drug's metabolism results in the formation of reactive metabolites that accumulate and cause hepatocyte apoptosis and necrosis[23].The idiosyncratic mechanism of DILI is characterized by a more unpredictable course and is not reproducible. Despite the fact that the precise mechanism is unknown, it is assumed that a combination of host, medication, and environmental factors are cause. Patient age, gender, genetic variations, immunological function, and metabolism are considered the host factors. Drug factors include the dose, duration, weight, and degree of lipophilicity. Environmental factors consist of concomitant alcohol use, diet, tobacco, and toxins [22].

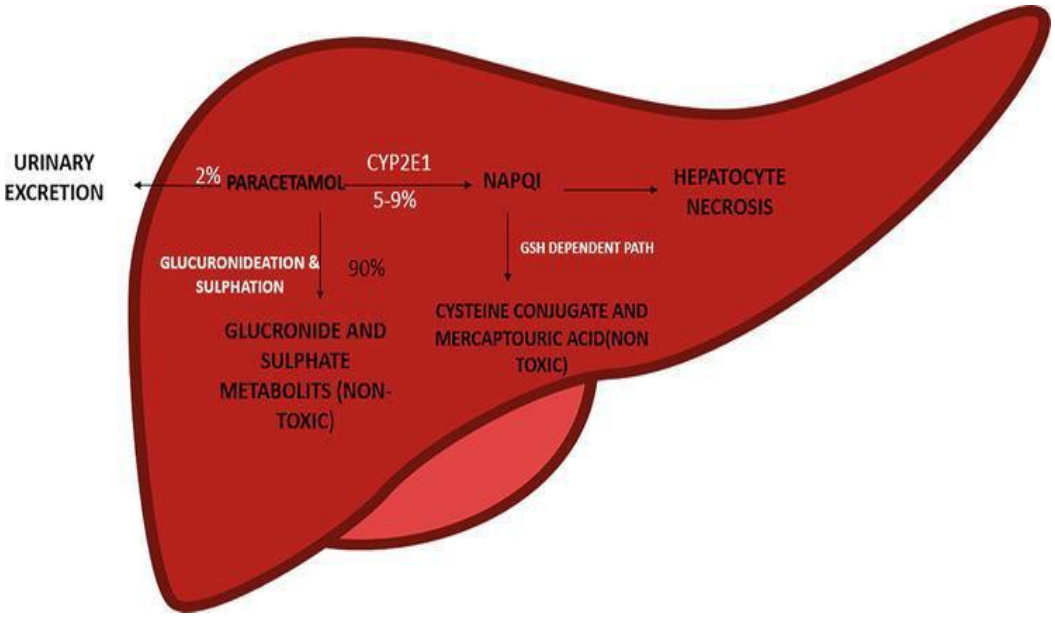

Fig no : 2 Metabolism of paracetamol

Idiosyncratic DILI mechanisms can be further divided into immune-mediated (allergic) liver injury from hypersensitivity or non-immune-mediated metabolic (non-allergic) mechanisms from mitochondrial injury[23].

Only a little portion of the drug is excreted by the kidneys after 95% of it has been metabolised in the liver and stomach through the processes of glucuronidation and sulfation. The typical elimination half-life of paracetamol taken at therapeutic doses is 2.7 hours [24]. In about 5% of the drug, oxidation produces the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), which further binds to cysteine, DNA, and lipids. Glutathione (GSH), an antioxidant, detoxifies NAPQI by creating a metabolite called mercapturic, which is excreted by the kidneys. When a larger dose of paracetamol is consumed, intracellular GSH is reduced and the metabolism of paracetamol shifts more toward oxidation, producing more NAPQI.

Although CYP_2E_1 plays the major role in the oxidation of paracetamol, additional CYP isoforms, such as CYP_3A_4 and CYP_1A_2, have also been discovered. On biopsy, centrilobular necrosis can be found as a result of the distribution of CYP_2E_1 in the hepatic lobule's centrilobular regions [25]. CYP_2 E_1 and CYP_3 A have the highest intrinsic activity for paracetamol of all the known CYPs.

Diagnosis

Serum AST, ALT, bilirubin, prothrombin time, blood urea nitrogen (BUN), creatinine, electrolytes, complete blood count, and urinalysis should all be performed as biochemical parameters. Ideally, the plasma paracetamol levels should be measured 4 hours after administration or as soon as 24 hours, but not before, as continuing paracetamol absorption can result in falsely low levels. Following the initial test, at 4, 16, and 32 hours following consumption, the test should be repeated. A paracetamol overdose revealed that centrilobular hepatocytes produce paracetamol adducts[41]. When a liver biopsy is performed, the liver tissue's histology reveals centrizonal necrosis and mild inflammation [42]. The main autopsy finding in those who died due to liver failure is centrizonal hemorrhagic necrosis with no or little inflammatory reaction and normal histologic appearance of portal tracts [43].

Toxic dose in adults and children

For a single oral consumption, the toxic dose for children is greater than 200 mg/kg body weight, whereas it is greater than 7.5 g for adults and adolescents. Toxicity develops in children under the age of six after ingesting more than 75 mg/kg body weight per day. However, toxic dose also differs in different ethical groups, such as in Japanese lower doses may produce intoxication [27]. Children are found to be less sensitive to acute intoxication than adults, and this may be due to larger glutathione stores and comparatively larger liver [28].

Treatment / Management

The principal treatment for drug-induced hepatotoxicity is the removal of the offending agent[7][11].

The antidote for paracetamol overdose is N-acetyl-cysteine (NAC), which stimulates glutathione regeneration by attaching to NAPQI and by increasing conjugation in hepatocytes to produce non-toxic products. [29] If administered within the first eight hours of ingestion or overdose, a good response is observed[3]. In cases of paracetamol hepatotoxicity, it has been discovered that beginning NAC therapy as late as 36 hours after the overdose greatly improves the outcome [30].On assessment of paracetamol overdose, a detailed history should be taken, which include ingested dose, co-intake of other pharmaceutical drugs or herbal medications, alcohol intake, presence of any liver disease or disorder, and any other co-morbidity.

Management for paracetamol overdose includes prevention of absorption from the gut, elimination of absorbed paracetamol from the blood, inhibition of formation of toxic metabolite NAPQI, and detoxification of NAPQI. Gastric lavage, administration of activated charcoal, and ipecacuanha (induces emesis) can prevent or decrease gut absorption within the first few hours after ingestion [31].

If ALF is suspected, early liver transplant consideration is essential because there is high mortality[7]. Reporting cases of DILI to regulatory organisations to assess whether the suspected drug needs to be withdrawn from the market is a crucial supplementary component of management [14].

Alternative Treatment

Homeopathy Treatment

Natrum Sulphuricum 200c (Nat Sulph-200) is a homoeopathic remedy that we previously reported to have ameliorating potentials against azo dye-induced toxicity in mice [32], but neither the efficacy of Natrum Sulphuricum 30c nor the efficacy of cholesterinum 200c (Chol-200, which is also advised for use against stubborn cases of liver ailment) had previously been studied alone or in combination with Nat Sulph in mice. With reportedly positive results, different potencies of Nat Sulph, lycopodium, and cholesterinum are frequently used to treat a variety of liver problems in humans.

Ayurvedic Treatment

One of the earliest and most extensively studied plants for the treatment of liver problems is silymarin, which may be produced from Silybum marianum (L.) Gaertn. (Asteraceae), more generally known as "milk thistle"[33]. Silymarin, with the empirical formula $C_{25}H_{22}O_{10}$ is a complex mixture of four flavonolignan isomers, including silybin, isosilybin, silydianin, and silychristin[34]. Silybin is credited with the majority of its hepatoprotective properties. The therapeutic implications of silymarin's stimulation of protein synthesis in the repair of injured hepatocytes and restoration of the liver's normal functioning are significant. [35]

Picroliv has been discovered to have strong hepatoprotective properties against a variety of hepatotoxins. Picroliv has been shown to have hepatoprotective properties against thioacetamide, CCl4, and alcohol[36]. Elevation of serum ALT and AST and reduction of liver GSH, G6PD, catalase and membrane-bound Na^+/K^+ ATPase which was reversed by administration of Picroliv[37].

Unani Treatment

The formation of NAPQI by CYP is a component of the paracetamol toxicity mechanism. Lipid peroxidation (LPO) levels rise as a result of NAPQI induces the production of ROS, which then target nearby tissue [38]. With the help of glutathione, NAPQI is converted into a nontoxic metabolite that is eliminated in the urine as mercapturic acid and related conjugates. As a result, high levels of liver function tests show that paracetamol increased LPO and CYP while

decreasing glutathione and its conjugating enzymes, both of which are related to liver damage. Through its antioxidative and hepatoprotective activity, Habb-e-Asgand both alone and in combination reduced the paracetamol-induced hepatotoxicity.

Chinese Treatment

Rhubarb is prepared from the dried roots and rhizomes of Rheum palmatum L., also known as the "General (Jiang Jun)" in Chinese medicine and mentioned in the 2015 Chinese Pharmacopeia[39]. It is known as Dahuang in Chinese and belongs to the genus Rheum L. in the family Polygonaceae. Rhubarb protects the liver from damage, and anthraquinone chemicals are primarily responsible for its hepatoprotective pharmacological effect. One of rhubarb's most important active ingredients is antraquinones. Nearly all varieties of rhubarb are rich in free anthraquinones, particularly rhein, emodin, physcion, aloe-emodin, and chrysophanol, which not only have beneficial anti-inflammatory, anti-tumor, and cardiovascular protective actions, but also play a significant role in hepatoprotection [40].

2. RECENT ADVANCEMENTS :

New Biological Markers

New indicators are urgently needed for several stages of idiosyncratic DILI, including the identification of true liver injury and its type, the severity of liver injury, and the causality of liver harm. New hepatotoxicity biomarkers have recently been created to aid in the early detection of DILI and to determine the severity of liver injury.

The newly discovered biomarkers for hepatocyte necrosis are glutamate dehydrogenase (GLDH) and sorbitol dehydrogenase (SDH) [41][42]. Because keratin levels are significantly greater in patients who have died or undergone liver transplantation as a result of paracetamol overdose than in people who have recovered on their own, keratin may be a predictive marker for liver damage [41].

High mobility group box 1 (HMGB1), a chromatin binding protein, has been identified as a marker for immunological activation. It is passively released by necrotic cells and contributes to the immune system's activation, as is the case with some idiosyncratic hepatitis [43]. Other suggested biomarkers included microRNA-192, M-30 (apoptosis), and M-65 (apoptosis/necrosis) (unspecified liver damage). These novel biomarkers have some limitations, despite the promise for greatness, as was recently recognized [41]. In fact, the ideal biomarker for DILI would not only be a marker for liver damage but would also be able to identify the offending medicine or at the very least a group of chemical substances.

3. CONCLUSION :

The morbidity and mortality associated with paracetamol overdose varies from patient to patient and is also depend on underlying comorbidities, nutritional state, a history of alcoholism, and concurrent drug use. The prognosis for an overdose can range from moderate liver damage to clinically significant hepatotoxicity or death, depending on when the antidote is administered. After the usage of N-Acetyl cysteine, deaths from paracetamol overdose in developed countries, which were formerly significantly greater (6-25%), reduced to 1-2%. Elevated liver enzymes, fever, and jaundice are frequent warning signs and symptoms. When the offending medication is identified and stopped, patients progress as expected.

On the other hand, it's crucial to keep in mind that some individuals are asymptomatic and that the only way to identify liver impairment is by an increase in liver enzymes; therefore, monitoring of liver tests is important to prevent serious effects. In the near future, new diagnostic and prognostic methods to aid in drug-related hepatotoxicity will be available.

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