RESEARCH ARTICLE OPEN ACCESS

Drug-Induced Hepatotoxicity—by Predictable or Spontaneous Causers

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Abstract:

Hepatic damage caused by various conventional drugs can result in symptoms that are predictable or spontaneous. The difference lies in the mechanism of action. The damages are said to be intrinsic when they are predictable due to the response dependent on the amount of the drug administered. While they are said to be idiosyncratic, when irrespective of the dose they show up i.e. they are impulsive or spontaneous. Several environmental inflammatory modulators along with genetic impactors impact the liver damage in intrinsic dose related manner. On the other hand, the un-planned idiosyncratic damage usually appears in smaller present of population. As it is spontaneous, its time of occurrence is not dependent of the dosage of medication neither is it shown up during various in-vivo assays in experimental setup. The cause of idiosyncratic damage may be accounted due to any cellular mitochondrial functioning impairment. It may also be due to elevation of inflammatory free radicals like reactive oxygen species causing tissue or cell death. Considering the fundamental dose response curves will surely assist in comprehension of the two types of liver damage. It is hypothesised that hepatic lethality of any drug is exhibited when the administered dose is on right of standard curves. Shift to left in this dosage curve due to any occasional modulator of inflammation are thought to save liver letting the predictions to be performed in experimental setup on lab animals even for idiosyncratic causers. This review aims to classify both idiosyncratic and intrinsic factors of liver damage dealing with the effect of inflammatory stress in each case. It also aims to compile various possible lab setups so as to help physicians in early detection of either of the hepatic injury causer.

Keywords **—drug induced liver injury, hepatic injury, classification of DILI, intrinsic cause, idiosyncratic cause.**

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I. INTRODUCTION

The damage of liver is common by two universally recognised toxicities. Both being unacceptable, one is predictable called intrinsic cause. Being anticipatable, this inducer of toxicity can be controlled by close monitoring of the drug dose. It has been reported to follow the protocols in toxicology studies. Being regulated by the drug dose, usually its overall effect remains similar among the study group and also beyond it i.e. from animals to humans [1].On the other hand, toxicity due to idiosyncratic factors is more harmful and big part is that it remains hidden under the fogginess of therapeutic dose of given drug. It remains unpredictable attributed to its ability to disobey dose response curve, which indicates established law for safe therapeutic action [2,3]. Various characteristics of these two damages are listed in table 1 under.

Table 1 Characteristics of predictable and unpredictable hepatotoxicity toxicity factors

Predictable/ Intrinsic	Spontaneous/ Idiosyncratic
Effects almost all animals & humans	Those at higher risk are more prone
Effects are dependent on dose-response	There is no such co-relation
Often there is period of latency, after the exposure	The onset is very unpredictable, with/ without latency
Adverse effects have very similar hepatic-pathology, in all the victims	The pathology is highly flexible varying individual to individual
These can easily pre studied in experimental setup, to modulate the therapeutic dose	Being highly random, these are difficult to created and studied in lab conditions

II. Hepatic Damage due to Predictable/ Intrinsic causers

It is well established that the foreign synthetic compounds i.e. xenobiotic which also include many pharmaceutical agents negatively impact certain organs denoted as 'target organs' by toxicologists [4,5]. Liver is one such organ in the list, as the dose at which the hepatic damage is exhibited is usually lower than that recorded as lethal. Also, as discussed earlier, the severity of the toxic responses gets aggravated proportionally with the increase in the exposure of the target tissue with the higher doses administered. Liver damage due to various drugs are now being reported as prime cause of mortality in many nations causing removal of these drugs from sell even after successful clinical trials [6,7]. Drugs like aspirin, acetaminophen, cocaine etc. [1] are known drugs to cause liver damage even on slight overdose, when taken for considerable longer time. Among these acetaminophen (APAP) is the drug that has been widely explored by many research groups for its dose dependent liver damage which is quite well predictable.

Once ingested, APAP undergoes a series of activation through various metabolic pathways in liver cells. Around 85 to 90% of administered APAP in liver tissue is acted upon by sulfotransferase (SULT),UDP-glucuronosyltransferase (UGT), important enzymes of second phase of conjugation. These break APAP into harmless products which are conjugates of sulphates and glucuronides. These along with very small fraction (<5%) of unchanged drug is removed from the body via kidney by urination. 5–9% of the left dose is further broken down in liver tissue by enzymes i.e. cytochrome P450 (CYPs) into intermediates that are highly toxic and reactive. These are N-acetyl-p-benzoquinone imine (NAPQI). Usually during normal dosing, these toxic intermediates are neutralised by formation of cysteine and mercaptouric conjugates with glutathione (GSH). At this stage, however there lies a limitation. When due to accumulation of APAP, enzymes involved in glutathione conjugations gets saturated, excess of the reactive NAPQI pile up in liver cells. As a consequence, a secondary mechanism gets involved. In this the sensitive agents start forming covalent bonds with the sulfhydryl groups of hepatic mitochondrial proteins. This bonding creates a kind of oxidative stress in cellular mitochondria. Their functioning gets disrupted causing necrosis and death of the hepatic cells. Also, it involves a number of progressive cascade of activities like stimulation of Kupffer cells, various T cells, activation of various inflammatory pathways leading to accumulation of inflammatory mediators like cytokines, free nitrogen, oxygen radicals etc. shown in Fig. 1 [8–10].

III. Hepatotoxicants with Predictable Sensitivity – Inflammatory Stress

It has been studied and is well established in various experimental setups, that different oxidative stress can trigger number of inflammatory reactions that initiate malicious sequence of hepatic cellular injuries like cirrhosis leading to more sever hepatic carcinoma as well [11]. These stresses due to increased oxidation within cell is attributed to disturbance in balance of oxidants like reactive oxygen, nitrogen species wrt the oxidation combating ability of cellular antioxidants. They result in enhanced expression of pro-inflammatory genes encoding various cytokines involved in inflammation leading to chronic liver diseases of proliferative or metabolic type [12].

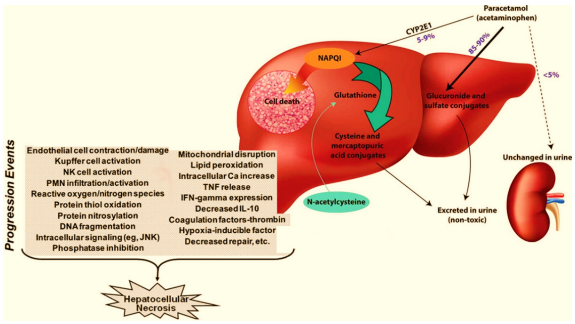

Fig. 1 APAP induced hepatic stress and injury

There are many factors exogenous environmental based as well endogenous generated within body that lead to liver inflammation (compiled in Fig 2). Some of the common factors are discussed under.

a) Various viruses and bacteria - bacterial and viral lipopolysaccharides, bind to different receptorsToll-like. This binding triggers synthesis of number of cellular inflammatory agents like cytokines, free oxygen and nitrogen reactive radicals, prostanoids etc. As a result, the homeostasis of hepatic tissue gets disturbed. Though this activity is helpful in getting rid of the invading virus or bacterial pathogen, still when aggravated it causes liver injury [12,13].

b) Drug like NSAIDs - as discussed previously APAP is well known to trigger a number of inflammagens increasing the risk of livery injury [14].

c) Alcohols – these mainly act by blocking glutathione. Also, it activates hepatic enzymes cytochrome P450, which increase conversion of APAP to NAPQI.As a result, reactive NAPQI gets accumulated. Further, the presence of alcohol hampers the healing ability of hepatic tissue delaying the process of recovery from damage [15].

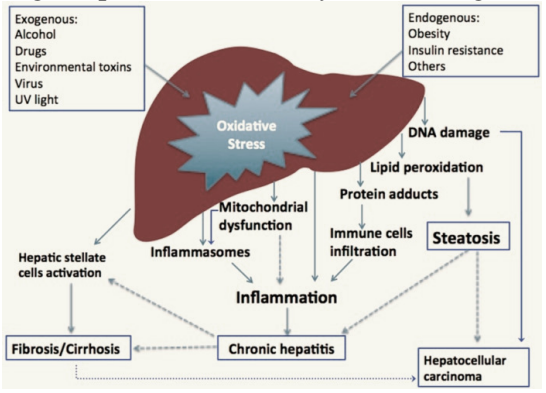

Fig. 2 Effect of various inflammatory stresses on liver injury

IV. Hepatotoxicants with Unpredictable Toxicity – Inflammatory Stress

The unpredictable or idiosyncratic outcomes of liver toxicity can be from mild to moderate to even severe injury of liver. These are very irregular in occurrence and their duration. As a result, often go undetected and remain ignored. It can be hypothesized that these irregularly occurring adverse reactions if monitored closely may help in controlling the severity of idiosyncratic liver damages. The incidences of these inflammation though not being regular, is often related with the commencement of therapeutic effect of given drug, which is based on time [16].

In present time, most of the drugs that have been reported to show any predicted adverse reactions are already removed from the market. As a result, most of the drugs presently being recommended are those that may induce idiosyncratic liver toxicity. As said earlier, these reactions are usually unpredictable and therefore remain independent of the pharmacological action of given drug. Drug that induce these category of liver injury by causing oxidative stress include for example hydroxychloroquine, ritonavir, azithromycin, lopinavir etc [17].

A fluoroquinolone derived antibiotic, trovafloxacin was studied and reported to cause severe liver damage of idiosyncratic type in susceptible victims. Another antibiotic of same class, i.e. levofloxacin, on the other hand, fully was found to be devoid of this adverse tendency. Unlike this category of therapeutic, the NSAIDs that lack specificity for 1 and 2 subtypes of enzyme cyclooxygenase like sulindac, diclofenac etc., are all reported to produce unpredictable or spontaneous liver toxicity in susceptible individuals. Idiosyncratic liver damages have also been reported to be common among the drugs being metabolised in liver, as studied by Teschke et. al. [18]. In their study they reported that more than 61% of the drugs being degraded in liver are responsible for various idiosyncratic responses. Among these most were found to broken down by the isoforms of CYP450 i.e. CYP3A (4 &5) and CYP2C (8&9). It was also found that presence of carboxylic acid group in drug molecules helped in controlling the spontaneous severity in liver toxicity.

In spite of these many studies, still there is no proper preclinical method to predict the chances of idiosyncratic behaviour of any drug candidate. This may be due to lack in in-depth comprehension of the molecular basis of these sudden responses though number of hypothesis have been and are still being proposed. Often when compared to unaffected individual, it's found that patients exhibiting such sudden unpredicted liver disorders, must have experienced certain degree of oxidative stress a prior, during the start of the treatment or due to some other reasons like any other existing infection/ inflammation, or by alcohol ingestion etc. In terms of the dose response curve, it has been stated that left ward shift in the curve, resulting from any acute stress, increases the chances of liver damage, making liver as the target organ for toxicity. If the cause of stress is not known, and based on an individual's physiology, if it has the tendency to occur and get subsided with chances of re-occurrence, correlation between the dose related liver injury may remain unnoticed or sporadic. As is the case when due to various stress, breakdown of drug by CYP is hampered resulting in its pile up in plasma and thereby the probability of hepatic toxicity [19].

Some of the individual based risk factors that make them susceptible for hepatic injury are listed in table 2 under. As can be seen, among various factors, inflammation is also one. The individual based inflammatory causes may include issues like any existing inflammatory diseases eg: arthritis,bacterial infections,asthma etc. Additionally, if individual is an alcohol consumer, this may further enhance viral or bacterial inflammatory lipopolysaccharides to pass into circulation from intestine to worsen the liver condition. All these factors when interact with drug, may result in number of unexpected spontaneous idiosyncratic responses that may aggravate the liver damage.

Table 2 Individual based risk factors to hepatic toxicity

Age
Gender
Metabolism rate
Immunologic profile
Capacity to fight inflammation
Profile Absorption and drug distribution
History of any co-existing disease
Any pre-existing inflammation
Exposures to any virus/ bacteria
Nutritional/ dietary profile

V. Animal Models of IADRs

Unlike intrinsic reactions which are usually of shorter duration and easily reproducible in lab animals [20], the idiosyncratic reactions though rare, if occurs are harsher and being spontaneous these are difficult to reproduce in experimental animals [2,3]. Being uncommon and often unnoticed, these reactions remain hidden unless there happens significant damage to liver tissues, only after which these become evident. Due to lack in complete and clear understanding of the mechanism at the cellular level, responsible for these sudden harsh reactions and also as these agents often pass undetected in routine animal screening, animal models are scanty. Based on the concept that various different stress may induce sudden inflammatory reactions, certain animal models have been devised [21,22]. In these models the lab animals are treated simultaneously with the drug under question and an inflammagens like dose of LPS non-toxic to liver tissues.

Fluoroquinolone derived antibiotic trovafloxacin is often reported to cause various unpredictable sudden liver issues in patients under treatment. In study by Shaw et. al. using male mice, it was found that this drug when co-administered with lipopolysaccharide (LPS) from gram negative bacteria, even in non-liver toxicity dose, severely aggravated activity of plasma alanine aminotransferase enzyme [23]. This activation in turn elevated the expression and concentration of Tumor Necrosis Factor alpha in liver cells, causing sever hepatic necrosis and damage [24]. On the other hand, another drug of same category i.e. levofloxacin was reported to be non-reactive even when administered with LPS. In similar manner, ranitidine, chlorpromazine was found to react even with low doses of LPS, resulting in toxicity of human liver [16].

Likewise, among various NSAIDs, sulindac, diclofenac etc. are few that were found to interact with LPS resulting in various inflammatory reactions and ultimately damage of liver tissues [25]. These primarily act by inhibiting the COX enzymes, causing upsurge in passage of LPS (both viral and bacterial) from intestine into blood plasma.

Diclofenac a commonly prescribed anti-inflammatory analgesic has been reported to cause sever idiosyncratic liver damage in elderlies [26]. It is suggested that diclofenac not only increase LPS in circulation but also elevate the reactivity of liver cells towards it aggravating other inflammatory conditions.

However, it is necessary to recognize that there are many unknown gaps in the interaction profile of idiosyncratic adverse drug reaction (IADR) producing drugs with inflammatory stress. Histopathological changes observed in the liver lesion in LPS/drug –treated animals include: in all the IADR associated drugs, animals display evidence of Midzonal Hepatocellular Necrosis accompanied by neutrophil infiltration. Regarding the triggers, which lead to the development of lesion, it is still not clear, though cytokines, neutrophils etc. homeostatic system seems to be involved in magnifying the lesion. This can mean that LPS acts in Accordance with hypersensitivity of the drugs to the liver because The characteristics of the lesion and progression severe factors are similar to that one that characterizes the injury from big LPS doses and toxically hepato-protective action. However, it is possible to observe certain quantitative differences in the model of interaction between the drug and LPS, when compared with LPS hepatotoxicity Therefore, despite certain qualitative differences are possible to determine, the overall picture of the situation remains not very clear. However, it is to some extent inflammatory that at least of the factor progression in the interaction between LPS and IADR producing drugs some of the factors apply to the setting of LPS and interaction with endogenous hepato-toxicant.

same as it has been said above about other IADR theories, the concrete data about the specific inflammatory interaction with drugs for IADRs in human is still very limited. Among the published case reports for chlorpromazine and ranitidine, in around 52 patients, fever, vomiting, diarrhoea, and other signs appeared, that indicate the presence of prodromal signs typical of a preceding inflammatory phase. The exact reason for this is not fully understood but it might not be mere coincidence that two classes of drugs mainly held responsible for idiosyncratic drug induced liver injury are antibiotics and NSAIDs both classes of drugs commonly used to treat conditions that involve inflammation. Some part of bacterial cell components like lipopolysaccharide (LPS) which was only shed when bacteria were lysed by antibiotics elicited inflammation. People who use NSAIDs normally suffer from inflammatory conditions like arthritis, and that polymorphic genes that result in deficiency of anti-inflammatory cytokines such as Interleukin 10 and Interleukin 4 may be present in patients with diclofenac induced hepatotoxicity. Such polymorphisms could increase the inflammatory mediators' sensitivity particularly when released in response to LPS that originates from the intestine that is irritated by the NSAID. This is positive evidence and is not rivalled by many of the drugs in the current pharmacopoeia as a treatment for addiction However, Further studies in human are going to be required to support these findings.

VI. SUMMARY AND PERSPECTIVE

Drug-induced hepatotoxicity (DILI) is a major reason for agent withdrawal and it is also a frequent type of liver injury observed in post-marketing surveillance. DILI is not an uncommon phenomenon and one of the most common types includes acute liver failure. Besides, DILI is a relevant source that contributes to drug recall and ALF. While distinctions mentioned above are made about the two types of DILI (intrinsic or idiosyncratic) there are still more cases of hepatotoxicity on the global scene. It is important to notice that if the relationship between the dosage administered and the response elicited is to be examined, the basic concepts of a dose response might also suggest that the two types of reactions are similar. When liver is not typically a target for toxicity for a given drug which is capable of initiating idiosyncratic hepatotoxicity, then for most of the users, the normal dose – response curve of hepatotoxicity is below the lethal dose line. However, it may coincide with an inflammatory episode in the organ, thus bringing hepatotoxic dose to within a therapeutic level and, consequently, development of a toxic response to the drug in the absence of any external exertion.

As mentioned earlier, increasing evidence showed that our current data for the direct adverse effects of xenobiotics on the liver were obtained using healthy organs, while a diseased organ was more vulnerable to the toxic insults. Consequently, it would be expected that such patients face a higher health risk owing to toxic compounds that contain drugs in patients with an impaired metabolism in their liver. If confirmed, these effects could have broad consequences for evaluating hepatotoxicity and DILI in drug development where safety has to be assessed in models of both healthy and disease state liver. In both such models, inflammation or other stresses have the potential of altering the dose-response curve to the left for hepatotoxicity. Thus, there remains much to learn about DILI, and unquestionably, future studies could be helpful to physicians who aim to treat this challenging diagnosis of exclusion. Presently, there is no well-defined DILI biomarkers that are helpful in determining the presence of DILI, and the evaluation is carried out based on the opinion of an expert.

ACKNOWLEDGMENT

This Review article has been compiled with equal contributions from all the authors and thereafter approved for the publication. All authors have reviewed and thereafter approved the final manuscript.

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