REVISTA DE MEDICINĂ DE URGENȚĂ

REFERAT GENERAL

Revista de Medicină de Urgență Volumul 7, Numărul 1 - Martie 2018
www.revistademedicinadeurgenta.ro

Drug induced liver injury

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REZUMAT

Hepatita indusă medicamentos are o incidență scăzută în populația generală, dar gastroenterologii trebuie întotdeauna să ia în considerare acest diagnostic în momentul în care efectuează diagnosticul diferențial la un pacient cu hepatită acută sau cronică. O creștere a transaminazelor indică inflamație sau distrugere a hepatocitelor și trebuie efectuat un diagnostic diferențial pentru a determina cauza injuriei hepatice. Este important de asemenea să excludem alte cauze ce ar fi putut determina leziunile toxice hepatice. Diagnosticul diferențial pentru hepatita acută include hepatita autoimună, hepatita acută virală, ischemie hepatică acută, boala Wilson, sindromul Budd-Chiari. Mecanismele hepatotoxicității sunt împarțite în două grupe mari și anume reacții medicamentoase intrinseci sau previzibile și reacții medicamentoase idiosincrazice. Reactiile idiosincrazice metabolice afectează doar indivizii susceptibili, au o prezentare și o rată de răspuns variabilă și nu sunt dependente de doză decât într-o mică măsură. Cu toate acestea, trebuie luată în considerare când ne aflăm în fața unui pacient cu afectare hepatică. Istoricul expunerii medicamentoase și debutul alterării probelor hepatice, precum și evoluția acestora sunt cruciale pentru diagnostic. În cazuri atent selecționate se poate realiza biopsie hepatică pentru a diferenția dintre o hepatită de cauză autoimună și o hepatită de cauză medicamentoasă, deoarece ghidurile recente de diagnostic pentru hepatita autoimună includ histologie pozitivă. Primul pas ce trebuie realizat în ceea ce privește tratamentul hepatitei acute medicamentoase este întreruperea medicamentului incriminat.

În concluzie, prognosticul hepatitei acute medicamentoase depinde foarte mult de momentul prezentării pacientului la medic și de stadiul afectării hepatice.

Cuvinte cheie: Hepatita indusă medicamentos, reacție idiosincrazică, expunere medicamentoasă

ABSTRACT

Drug induced liver injury (DILI) has a low incidence in the general population, but gastroenterologists must always consider it as a possible diagnosis in patients with acute or chronic liver injury. Elevated liver enzymes may indicate inflammation or damage to hepatocytes and the physician must make a differential diagnosis to find out what is the cause of the acute or chronic liver injury. The differential diagnosis for acute hepatocellular injury includes autoimmune hepatitis, acute viral hepatitis, ischemic liver injury, Wilson`s disease, acute Budd-Chiari syndrome. There are two main categories of drugs that can produce liver damage: intrinsic drugs (predictable) and idiosyncratic drugs (unpredictable). Idiosyncratic DILI affects only susceptible individuals, is varied in presentation and has less consistent relationship to dose, but we must always think of it when we have a patient with acute or chronic liver injury. Also we must take into consideration the fact that idiosyncratic DILI is more difficult to diagnose and treat comparing with acetaminophen toxicity who has well established diagnostic and therapeutic guidelines. The history of medication exposure and the onset and course of liver biochemistry abnormalities is crucial for the diagnosis. Liver biopsy may be considered in selected cases. There are instances where biopsy is strongly recommended to help distinguish between autoimmune hepatitis and DILI. The first thing a physician must do is withdrawal of the offending drug.

In conclusion, the prognosis of DILI is highly variable depending on the patient`s presentation and stage of liver damage.

Keywords: Drug induced liver injury, idiosyncratic reaction, medication exposure

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Introduction

Drug induced liver injury (DILI) has a low incidence in the general population, but gastroenterologists must always consider it as a possible diagnosis in patients with acute or chronic liver injury. The physician must always be careful when prescribing certain medications like azathioprine and sulphonamides for example, but also, we must remember that a lot of herbal and dietary supplements can induce injury to the liver [1] [2].

Elevated liver enzymes may indicate inflammation or damage to hepatocytes and the physician must make a differential diagnosis to find out what is the cause of the acute or chronic liver injury. Many diseases can contribute to elevated enzymes and there can be mild-moderate elevation and very high elevation of hepatic enzymes (*Table 1*).

Mild-moderate elevation	Steatohepatitis
	Chronic hepatitis B
	Chronic hepatitis C
	Chronic and acute alcohol use
	Obesity
	Hemocromatosis
	Autoimmune hepatitis
	Wilson`s disease
	Celiac disease
High elevation	Acute viral hepatitis A
	Acute viral hepatitis B
	Cytomegalovirus infection
	Epstein-Barr virus infection
	Cardiogenic shock
	Drug induced liver injury

Table 1. **Causes of elevated hepatic enzymes**

The hepatic injury appears in different ways at different rates. The majority of reactions are directed against the hepatocytes rather than biliary injury, but we can also encounter combined hepatocyte/biliary injury or damage to mitochondria [3]. In drug induced cholestasis, disruption of specific transport proteins or processes in hepatocytes may be the cause [4].

Inhibition of mitochondrial respiration may lead to micro vesicular steatosis [5]. This may lead to severe liver dysfunction because mitochondrial β – oxidation of fatty acids is affected and this leads to a decrease of cellular energy supply [6].

The pathogenesis of liver damage remains unclear for most drugs, but it's thought that high-energy unstable metabolites who result after the activation of P450 bind to cell protein DNA and disrupt cell function [7]. One idea that must be studied furthermore is that drug-induced injury may be modulated by inflammatory mediators that may trigger hepatocyte apoptosis [8].

Drug toxicity mechanisms

There are two main categories of drugs that can produce liver damage: intrinsic drugs (predictable) and idiosyncratic drugs (unpredictable).

Acetaminophen (paracetamol) is perhaps the best known and used drug to cause intrinsic DILI. Similar lesions can be found in humans and in animal models and the hepato-toxins of this group produce liver lesions in a dose-related fashion if high doses are ingested [9]. Taken in small doses of < 4g/day it is a safe drug, but its therapeutic index is low because a dose of only 10-12 g can cause extensive hepatic necrosis [10]. Although the prognosis is relatively good, the survival without liver transplantation is approximately 57% [11].

Other drugs in which a dose-response effect is observed are amiodarone, cocaine (it induces vascular collapse), oral contraceptives after prolonged usage, methotrexate, tetracycline, cyclophosphamide, cyclosporine, but except for acetaminophen-induced liver disease, intrinsic drug cases are rare.

Idiosyncratic DILI affects only susceptible individuals, is varied in presentation and has less consistent relationship to dose, but we must always think of it when we have a patient with acute or chronic liver injury. Also, we must take into consideration the fact that idiosyncratic DILI is more difficult to diagnose and treat comparing with acetaminophen toxicity who has well established diagnostic and therapeutic guidelines [12].

A lot of theories try to explain idiosyncratic DILI and they say that these reactions are not a result of the drug itself, but of something about the patient who ingest them and has a toxic reaction. Some drugs like antibiotics, nonsteroidal agents and anticonvulsants are highly associated with drug induced liver disease but there are also drugs who are rarely associated with DILI like hormones, antihypertensive drugs, digoxin, anti-arrhythmics.

Isoniazid per example, an antibiotic used for tuberculosis prophylaxis, is used even if it may develop increased transaminases, because his usefulness makes the risk acceptable. Less that 1% may develop severe hepatic necrosis [13]. It has been observed that many of the drugs that cause rare idiosyncratic DILI are associated with more frequent hepatic enzymes elevations that are limited and resolve even if the administration of the drug continues [14].

Aside from isoniazid, nonsteroidal drugs can cause idiosyncratic DILI and also the newer cyclooxygenase-2 inhibitors have been implicated [15] [16].

Risk factors for drug induced injury

1. **Age**: drug reactions appear to affect the elderly more often because of the decreased clearance, reduced hepatic blood flow, drug-to-drug interactions. Adults are more susceptible than children when it comes to acetaminophen, isoniazid and less susceptible to aspirin for example [17]
2. **Gender**: hepatic drug reactions are more common in females, but the reasons are unknown
3. **Pregnancy**: the effects of drugs in pregnancy have been poorly studied
4. Certain **foods** like grapefruit for example, who contains an unknown substance that interferes with metabolism [18] [19].
5. **Alcoholic ingestion** because alcohol causes depletion of glutathione stores that make the person more susceptible. A depletion of glutathione is also seen in persons with AIDS, person who are malnourished and person who are fasting.
6. **Concomitant drugs** because of drug-to-drug interactions. For example, valproate and chlorpromazine together lead to cholestasis.
7. **Pre-existing liver disease** has not been thought to make patients more susceptible to drug induced injury, even if cytochrome P-450 is reduced in chronic liver disease. A patient with a chronic liver disease has a diminished liver reserve and the ability to recover is also diminished [20] [21].
8. **Renal disease**: if the clearance is low, the compound that result after metabolism are slowly eliminated [22]. For example, tetracycline and allopurinol toxicity are higher in renal disease.
9. **Genetic factors**: a unique gene encodes each P-450 protein and genetic differences in these enzymes can result in abnormal reactions to drugs, including idiosyncratic DILI.

Diagnosis in drug induced liver injury

DILI remains a diagnosis of exclusion and it`s based primarily on a detailed history and blood tests, hepatobiliary imaging and if the results are not enough to help us make a sure diagnosis, then we can perform a liver biopsy [23].

The history of medication exposure and the onset and course of liver biochemistry abnormalities is crucial for the diagnosis. The history must include dose, route of administration, duration, concomitant drugs including herbs. Usually DILI appears in the first 6 months after starting a new medication, but there are exceptions. The physician must exclude other causes of liver injury. When a single drug is involved, the diagnosis is relatively simpler, but when there are multiple agents involved the physician must consider the most common and the most rarely implicated DILI agents. When the patients take multiple drugs, the physician can stop the suspected drug to see if the level of serum transaminase decreases up to 50% within 8 days of stopping the drug.

The diagnostic approach to DILI can be made according to the pattern of liver injury at presentation and for that we must calculate the R-value (*Table 2*). The R-value is defined as serum alanine aminotransferase/upper limit of normal(ULN) divided by serum alkaline phosphatase/ULN.

R≥5	**Hepatocellular DILI**
R<2	Cholestatic DILI
2<R<5	Mixed DILI

Table 2. **DILI classification based on the R-value**

The differential diagnosis for acute hepatocellular injury includes autoimmune hepatitis, acute viral hepatitis, ischemic liver injury, Wilson`s disease, acute Budd-Chiari syndrome. Autoimmune hepatitis must be considered in the differential diagnosis of all cases of DILI because some drugs like nitrofurantoin for example, have high propensity to cause autoimmune-like DILI. It's recommended to routinely search for serum autoantibodies (like

antinuclear antibody and anti-smooth muscle antibody) and immunoglobulin Ig G levels. Low levels are of little help in differential diagnosis because 30% of adults may have such positive antibodies, especially women [24].

Although rare, the physician should screen for Wilson`s disease, especially in patients younger than 40 years, with a serum ceruloplasmin level. Ceruloplasmin is an acute-phase reactant and it`s levels can be falsely normal or higher in acute hepatitis, in which case if the suspicion remains one can perform other tests such as slit-lamp eye examination for Kaiser-Fleischer rings, 24-h urine collection for copper [25].

In patients with suspected cholestatic DILI, the etiologies are pacreatico-biliary in nature and can be extrahepatic or intrahepatic. Extrahepatic etiologies are choledocholithiasis or malignancies and they can be diagnosed using abdominal imaging tests such as ultrasonography, computerized tomography or magnetic resonance imaging. Intrahepatic etiologies must be taken into consideration and excluded using history and physical examination (sepsis, heart failure), serological testing for primary biliary cirrhosis or imaging for sclerosing cholangitis.

Liver biopsy may be considered in selected cases. There are instances where biopsy is strongly recommended to help distinguish between autoimmune hepatitis and DILI because current diagnostic algorithms for autoimmune hepatitis include histology [26]. However, the frequency with which a liver biopsy makes a definitive DILI diagnosis is low.

Also, to decide whether a certain drug is responsible for the liver disease encountered in a certain patient we can use the RUCAM score (Roussel Ulaf causality assessment method) [27]. Causality assessment methods include temporal relationship, risk factors, concomitant drugs, course after cessation of drug, search for another cause like viral hepatitis, previous information concerning the drug and response to rechallenge, which is usually not available. The RUCAM score could be classified as highly probable (RUCAM score>8), probable (score 6-8), possible (score 3-5), unlikely (score 1-2) and excluded (score ≤ 0) [28].

Treatment

The first thing a physician must do is withdrawal of the offending drug. Most clinicians use antihistamines like diphenhydramine and hydroxyzine for symptomatic pruritus. Also ursodeoxycholic acid was given to a group of patients in a prospective study but the efficacy of this agent in acute and chronic DILI is not established [29].

Corticosteroid therapy has been proposed as treatment for DILI, but unlike alcoholic hepatitis there are no controlled trials of steroid therapy made for DILI. N-Acetylcysteine, the proven antidote for intrinsic DILI caused by acetaminophen (APAP), was subjected to a randomized placebo-controlled trial for DILI caused by other drugs than acetaminophen and there were seen significant improves with early coma grade patients (I-II) [30] [31]. FDA has not approved N-Acetylcysteine for the indication of non-APAP acute liver failure.

No specific antidote is available for the vast majority of hepatotoxic agents. Considering early liver transplantation is important. Kings College criteria for liver transplantation in non-acetaminophen DILI are:

- ✓ PT (prothrombin time) greater than 100 seconds (irrespective of grade of encephalopathy)
- ✓ Any 3 of the following criteria:
  - ➢ Age younger that 10 years or older than 40 years
  - ➢ PT greater than 50 seconds
  - ➢ Duration of jaundice of more than 7 days before onset of encephalopathy
  - ➢ Serum bilirubin level greater than 17 mg/dl
  - ➢ Etiology of non-A, non-B hepatitis, halothane hepatitis or idiosyncratic drug reactions

Kings College criteria for liver transplantation in acetaminophen DILI are:

- ✓ PT greater than 100 seconds or INR > 7.7
- ✓ pH <7.3 (irrespective of grade of encephalopathy)
- ✓ serum creatinine level greater than 3.4 mg/dl in patients with grade III or IV of encephalopathy

Prognosis

The majority of patients with symptomatic DILI are expected to completely recover after discontinuation of the suspected drug. Patients with clinically significant liver injury also have a good prognosis [32]. In contrast, the prognosis of patients with DILI who progress to acute liver disease with concomitant coagulopathy and encephalopathy is usually poor [33] [34].

The most frequently identified etiology of DILI is acetaminophen overdose and fortunately the prognosis is better in patients treated with N-Acetylcysteine than in acute liver failure with idiosyncratic DILI [35]. In patients who develop idiosyncratic reactions to prescription drugs, the liver injury varies in severity and occur at varying time intervals after exposure, from a few days to 1 year [36].

Overall, it is recommended in patients with severe DILI to recommend them to a transplant center in case of poor outcomes [37]. Liver transplantation provides a rescue for patients when signs of spontaneous recovery are not evident. The MELD (Model for End Stage Liver Disease) score and coma grade upon admission are considered to be the strongest predictors of liver transplantation [38].

Conclusions

In conclusion, the prognosis of DILI is highly variable depending on the patient`s presentation and stage of liver damage. The physician must exclude other causes of liver injury like acute viral hepatitis and autoimmune hepatitis using standard serology. Also, Wilson`s disease should be considered when clinically appropriate.

In case of cholestasis DILI it's recommended to perform an abdominal imaging to exclude infiltrative processes and biliary tract pathology and serological testing for primary biliary cirrhosis.

If autoimmune hepatitis remains a competing etiology a liver biopsy should be considered.

When a drug is suspected of causing liver injury, it must be stopped immediately and re-exposure to that drug is strongly discouraged, especially if the liver injury was associated with elevated transaminases like 5 times the normal value, or jaundice. Patients should be advised to report any new symptoms like yellowing of their eyes, nausea, itching, dark urine and monitor serum liver biochemistries at 4-6 weekly intervals, especially in the first 6 months of treatment.

The use of potentially hepatotoxic drugs should be based upon the risk vs benefit of the proposed therapy on a case-by-case basis.

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