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Hepatotoxicity by Drugs

Alejandra Cano Paniagua and Pedro Amariles

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Abstract

Hepatotoxicity is the injury or liver damage caused by exposure to drugs; it is an adverse drug reaction that may be uncommon but serious. The hepatic injury can be classified into hepatocellular, cholestatic and mixed, caused by increase in alanine aminotransferase and alkaline phosphatase than upper limit of normal. The risk factors include idiosyncrasy, age, gender, alcohol consumption, concomitant use of other drugs, previous or underlying liver disease, genetic and environmental factors. Liver toxicity manifestations are generally accompanied by nonspecific symptoms such as abdominal pain, jaundice, fever, nausea, vomiting, diarrhea, pruritus and rash. Identification of hepatotoxicity is a complex process to perform; therefore, clinical scales have been developed, such as the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) and the Clinical Diagnostic Scale (M & V CDS). Additionally, there is no specific treatment for hepatotoxicity, which is based on suspending the suspected drug and treating symptoms. The most commonly associated pharmacological groups are antibiotics, nonsteroidal anti-inflammatory analgesics (NSAIDs), antidepressants and anticonvulsants. Drug-induced liver injury has been an adverse event, hard to identify, prevent and treat; thereby, the pharmacist intervention can contribute to the diminution of the deleterious effects in patient health.

Keywords: drugs, hepatotoxicity, drug-induced liver injury, anti-infective agents, antineoplastic agents, pharmacist intervention

1. Introduction

The objective of this chapter is to explain hepatotoxicity by drugs and provide relevance to a health problem that can lead to death if neglected; even though there is published information about it, it is still limited in some parts of the world. On the other hand, it is intended to disclose some activities developed by a pharmacist in a case of one patient with hepatotoxicity by drugs, which can contribute to the improvement of a patient's health status by helping to

identify and to prevent the cause of the problem. In addition, we present the key results obtained by a structured review made in PubMed/Medline using the terms such as "liver disease" and "drug-induced liver Injury", until December 2015, and articles available in English, Spanish and French that recognized any drug as a possible trigger of hepatotoxicity were selected. The information obtained in this structured review was analyzed and compiled to give a better understanding about hepatotoxicity.

Thereby, use of drugs had generated some noxious effects on patient's health; one of the organs that may be affected is the liver, because substances or its formed metabolites in the biotransformation process; drugs can induce liver injury. Hepatotoxicity is the injury or liver damage caused by exposure to drugs or other nonpharmacological agents [1]. It is an adverse drug reaction that may be uncommon but serious, and is the most common cause of drug withdrawal from the pharmaceutical market [2]. Hepatic toxicity incidence by drugs is variable, because several retrospective and prospective studies were reported [3].

There are two types of hepatotoxicity: intrinsic reaction which is dose-dependent and predictable (less common) and idiosyncratic reaction which is not dose-dependent and not predictable (more common). Besides, the hepatic injury can be classified into hepatocellular, cholestatic and mixed, caused by increase in alanine aminotransferase (ALT), that is, >2–3 times and/or increase in alkaline phosphatase (ALP), that is, >2 times the upper limit of normal [4, 5]. The risk factors include: idiosyncrasy, age, gender, alcohol consumption, smoking, concomitant use of other drugs, previous or underlying liver disease and genetic and environmental factors [6, 7]. Clinical and pathological manifestations of hepatotoxicity include acute and chronic hepatitis, fulminant hepatitis, cholestasis, ductopenia, granulomatous hepatitis and steatosis (steatohepatitis, macrovesicular or microvesicular steatosis) [6], generally accompanied by nonspecific symptoms such as abdominal pain, jaundice, fever, nausea, vomiting, diarrhea, pruritus and rash [8].

It is estimated that approximately 1100 drugs, excluding substances of abuse and natural products, are associated with hepatotoxicity reactions [9]. Although most lipophilic drugs may cause hepatic disorders, the most commonly associated pharmacological groups are antibiotics (amoxicillin-clavulanic acid and rifampicin), nonsteroidal anti-inflammatory analgesics (NSAIDs) (diclofenac and ibuprofen), antidepressants (paroxetine) and anticonvulsants (phenytoin, carbamazepine and valproic acid) [1, 10]. Identification of hepatotoxicity is a complex process to perform; therefore, in practice, this is based on considering the presence of such alteration, conducting a thorough investigation related to the use of any substance and ruling out other causes of liver disease [11]. In order to solve the difficulty of identification and to try to estimate the probability that a therapeutic agent is associated with a hepatic disease, clinical scales have been developed; there are scales such as the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) and the Clinical Diagnostic Scale (M & V CDS) that assess factors such as absence or presence of confounding factors, temporal relation of hepatotoxicity with drug consumption, coexistence of risk factors, previous description in the literature, exclusion of other causes and effects of readministration of the drug [12]. In general, there is no specific treatment for hepatic toxicity by drugs, which is based on suspending the suspected drug, treating symptoms, avoiding other possible hepatotoxic agents and monitoring laboratory tests [13, 14].

The liver injury generated by hepatotoxic medicines has been an adverse event, hard to identify and prevent, because of the sensibility of each patient. There is no specific treatment, except with a few drugs, hence, it is not possible to guarantee the recovery of symptoms in all cases. In such a way, it is necessary to search strategies that allow optimization of the health care process of patients with hepatic toxicity. Thereby, the pharmacist intervention can contribute to the diminution of the deleterious effects in patient health, promoting the proper use of the drugs.

2. Drug-induced hepatotoxicity: an overview

Hepatotoxicity is defined as injury or liver damage caused by exposure to drugs or other nonpharmacological agents [1]. It is an adverse drug reaction that may be uncommon but serious, and therefore, have a considerable impact on health [2]. Hepatotoxicity generates between 1/600 and 1/3500 of all hospital admissions, 2–3% of hospitalizations for jaundice, 10% of acute jaundice hepatitis (being more than 40% in people over 50 years of age) and between 15 and 30% of cases of fulminant hepatic failure [15, 16]. In the United States, a multicenter prospective study showed that drugs, including acetaminophen, are the most common cause of acute liver failure, explaining 39% of cases and overcoming viral hepatitis A and B, which represent 12% [17]. On the other hand, in France, an incidence of 13.9 ($\pm$2.4) cases per 100,000 inhabitants is estimated, corresponding to an annual global frequency of 8.1 ($\pm$1.5) cases [18]. In Switzerland, the estimated incidence is 2.2 per 100,000 inhabitants over 15 years of age; while in Spain, the annual incidence of severe liver disease is estimated as 7.4 per 1,000,000 population (95% confidence interval between 6.0 and 8.8) [10]. There are some countries in which evidence about incidence of liver injury by drugs is limited [19], generally, published information is based on clinical case reports.

Although hepatotoxicity is less frequent than other adverse drug effects, due to its severity and is the most common cause of drug withdrawal in the pharmaceutical market, it is assessed as a major adverse event [20], so, it is a frequent impediment to the development of drugs by pharmaceutical companies. In the past 20 years, in Europe and the United States medications such as troglitazone, bromfenac, trovafloxacin, ebrotidine, nimesulide, nefazodone, ximelagatran, lumiracoxib, pemoline and tolcapone have been withdrawn from the market [10, 21–23]; currently, some of them are retired worldwide.

The identification of hepatotoxicity is a complex process to perform; therefore, in clinical practice, it is based on considering the presence of such alteration, investigate about the use of any substance and ruling out other causes of liver disease [19]. It is necessary to identify all drugs used (prescription and over-the-counter), natural products, food, exposure to industrial toxics or substance abuse; moreover, try to identify the offending agent and to search for a description in literature may help. Besides, the chronological relationship between exposure to the suspected agent and the hepatotoxic reaction is a key to define causality; the drugs used in the last 3 months should be considered as suspects. The presence of hypersensitivity manifestations (rash, fever and eosinophilia) improves identification process as well as histological analysis through liver biopsy [24]. When a re-exposure to the suspected agent appears, it becomes a very conclusive indicator of causality.

There is no specific treatment for hepatic toxicity by drugs, which is based on suspending the suspected drug, treating symptoms (use of corticosteroids for hypersensitivity reactions), avoiding other possible hepatotoxic agents and continuous monitoring of laboratory tests [13, 14]. There are some exceptions of antidotes for treating liver toxicity by certain drugs such as the use of N-acetyl cysteine as an antidote for acetaminophen toxicity, or N-acetyl cysteine itself for the treatment of hepatotoxicity by phenytoin and carbamazepine, or carnitine for valproic acid toxicity [25]. With the suspension of the offending drug, in most cases, the health of the patients tends to improve; however, in other cases, the damage continues to progress and hospitalization is necessary, when irreversible liver failure occurs, liver transplantation is required and if the liver tissue damage is severe, patients can die in a few hours.

3. Hepatotoxicity associated to drugs

3.1. Expression of hepatotoxicity

Hepatotoxicity induced by drugs or toxins can be grouped into two types: intrinsic reactions (less common) and idiosyncratic reactions (more common) [6, 7, 26]. Intrinsic reactions are predictable, dose-dependent and reproducible in animal models; injury is produced trough toxic metabolites of drugs such as free radicals (generating lipid peroxidation), electrophilic molecules (formation of covalent bonds with hepatic proteins) or active oxygen molecules (generating peroxidation as well). Idiosyncratic reactions are not predictable, not dose-dependent and not reproducible in animals; there are many drugs capable of causing this type of reaction [11, 27]. The underlying mechanism of the idiosyncratic reaction may be a genetic polymorphism of the cytochrome P450 (CYP450) system, responsible for the drugs hepatic biotransformation. There are two types of idiosyncratic reactions: immune (characterized by hypersensitivity-type reaction) and metabolic [7, 13] (related to metabolism of substances).

3.2. Mechanisms of hepatotoxicity

The hepatocytes, cholangiocytes, Kupffer cells, ductal and endothelial cells are involved in the mechanisms by which drugs cause hepatotoxicity [28]; having direct effects on cellular organelles such as mitochondria, endoplasmic reticulum, cytoskeleton, microtubules or nucleus.

The drug metabolites generated in the liver through biotransformation can cause hepatic damage because formation of toxic or reactive substances such as electrophilic chemicals or free radicals [29], and thus an unchain a variety of chemical reactions may happen. These mechanisms can either generate necrosis or apoptosis or both. The following are some of the main mechanisms of liver injury [30]:

- Mitochondrial dysfunction: may be generated by the disruption of β-oxidation of lipids and oxidative energy production within the hepatocytes. Mitochondrial membrane permeabilization can lead to apoptosis, a rupture in mitochondrial membrane can lead to ATP depletion and subsequent necrosis, and an abnormal function can also lead to fat accumulation, so steatosis can be present [31].

- Immune response: is attributed to the formation of new antigens, this give origin to the idiosyncratic hepatotoxicity. Moreover, it can be accompanied by presence of inflammatory cells such as neutrophils and lymphocytes.

- Oxidative stress: is produced by ATP depletion accompanied by increase in intracellular calcium concentration, it can generate necrosis [28].

- Lipid peroxidation: is generated by the interaction between free radicals and fatty acids in membrane, the subsequent reaction may produce electrophilic metabolites generating DNA damage [32].

3.3. Type of injury

Liver histology is the ideal tool to define the pattern of hepatic toxicity; however, in clinical practice, most hepatotoxic lesions are classified according to biochemical tests [16]. In this way, according to Council for International Organizations of Medical Sciences (CIOMS), liver injury is considered, if at least one of the main hepatic enzymes, such as alanine aminotransferase, aspartate aminotransferase (AST), alkaline phosphatase and total bilirubin (TB), increases by two times, the upper limit of normal (ULN) [33]. Besides, liver injury is classified into the following three types of lesions:

- Hepatocellular lesion is characterized by damage in hepatocytes, which is manifested by elevation in ALT is more than two times the ULN or a ratio (R) of ALT/ALP greater than or equal to five.

- Cholestatic lesion is presented in cholangiocytes when ALP increases more than two times the ULN or R greater than two.

- Mixed lesion is showed when ALT and ALP increases more than two times the ULN or R is between two and five [4, 34].

On the other hand, Hy's rule defines liver damage when ALT level increases more than or equal to three times the ULN accompanied by bilirubin elevation [5, 35] and with or without rise of APL levels.

3.4. 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 [36]:

- Age: the elderly population is mostly affected by toxicity of drugs because of physiological changes and polymedication [10]; however, with valproic acid, young population is the most affected.

- Gender: female patients are the most susceptible for toxicity of drugs because of biological differences and pharmacokinetics; moreover, sex-specific factors such as menopause, pregnancy and menstruation may have influence.

- Alcohol consumption: may increase the toxic potential of pharmacological agents [37].

- Concomitant administration of drugs or herbal remedies: becomes a risk factor because it increases the probability of drug interactions.

- Previous or underlying hepatic diseases: may increase the risk of hepatotoxic agents [38].

- Genetic factors: related with genetic polymorphism in cytochrome P450 can unchain a hepatic lesion.

3.5. Clinical manifestations

The mechanisms of drug-induced liver injury are related with the clinical manifestations. The main clinical-pathological manifestations of hepatotoxicity and its histological findings include [6, 24, 26, 39]

- Acute hepatitis: caused by a wide variety of drugs and characterized by parenchymal inflammation, necrosis and Kupffer cells in sinusoids, which include symptoms like malaise, asthenia, anorexia, jaundice can be present but not always [15].

- Chronic hepatitis: characterized by persistent biochemical abnormalities beyond 6 months; fibrosis or cirrhosis may be present.

- Fulminant hepatitis: also called acute liver failure may cause death and its manifestations are necrosis and microvesicular steatosis.

- Cholestatic hepatitis: manifested by mixed hepatocellular and cholestatic injury accompanied by inflammation.

- Cholestasis: caused by bile plugs; include symptoms like jaundice and pruritus is characterized by minimal inflammation.

- Vanishing bile duct syndrome: presented by a paucity of bile ducts; inflammation and cholestasis may appear.

- Granulomatous hepatitis: presence of granulomas in portal tracts or parenchymal, accompanied with inflammation.

- Steatohepatitis: is the presence of fat in hepatocytes accompanied by inflammation and fibrosis.

- Macrovesicular steatosis: characterized by the presence of medium- or large-sized fat droplets in the cytoplasm of hepatocytes.

- Microvesicular steatosis: characterized by the presence of small-sized fat droplets in the cytoplasm of hepatocytes.

Many drugs have a specific pattern of injury in the liver but in some cases, the same drug can generate different patterns in the patients, the patterns and the drugs that cause them are presented in **Table 1**.

Many of these manifestations are accompanied by unspecific symptoms like discomfort, fever, nausea, vomiting, abdominal pain, jaundice, dark urine, pale stools, pruritus, loss of weight or

Clinical pattern	Drugs
Acute hepatitis	Acetaminophen, allopurinol, carbamazepine, diclofenac, phenytoin, ibuprofen, isoniazid, naproxen, metoprolol, piroxicam, pyrazinamide, valproic acid [2, 39, 40]
Chronic hepatitis	Methyldopa, isoniazid, phenytoin [40], amoxicillin-clavulanic acid, bentazepam and atorvastatin [26]
Fulminant hepatitis	Lamotrigine, nimesulide, isoniazid, clarithromycin [40]
Cholestatic hepatitis	Phenytoin, amoxicillin-clavulanate [39], carbamazepine, chlorpromazine [6, 15]
Cholestasis	Anabolic steroids [6, 39], estrogens, contraceptive steroids [2, 26]
Vanishing bile duct syndrome	Sulfonamides, beta-lactams [39], carbamazepine [2]
Granulomatous hepatitis	Allopurinol, aspirin, carbamazepine, chlorpromazine, diltiazem, hydralazine, nitrofurantoin, penicillin, phenylbutazone, phenytoin, pyrazinamide, quinidine, sulfasalazine [6, 26, 40]
Macrovesicular steatosis	glucocorticoids and methotrexate [26], steroids, nitrofurantoin, gold, methotrexate, ibuprofen, indomethacin, sulindac, metoprolol [6]
Microvesicular steatosis	tetracycline, valproic acid, zidovudine, minocycline [6, 9, 26]
Steatohepatitis	Amiodarone, tamoxifen [6, 9, 36]

Table 1. Clinical patterns caused by drugs.

appetite, besides, signs like hepatic encephalopathy or increase in hepatic enzyme levels, making the identification of liver toxicity difficult.

3.6. Hepatotoxic drugs

It is estimated that approximately 1100 drugs, excluding substances of abuse and natural products, are associated with hepatotoxicity reactions [9]. Although most lipophilic drugs may cause hepatic impairment, the most commonly associated pharmacological groups are antibiotics (amoxicillin-clavulanic acid and rifampicin), nonsteroidal anti-inflammatory analgesics (NSAIDs) (diclofenac and ibuprofen), antidepressants (paroxetine) and anticonvulsants (phenytoin, carbamazepine and valproic acid) [8, 10, 18, 19]. In addition, a recent study shows that among intravenous drugs, antibiotics and antineoplastic are the pharmacological groups most associated with hepatic toxicity [41].

A structured review in PubMed/Medline was made using the terms: "liver disease" and/or "drug-induced liver injury", until December 2015, and articles available in English, Spanish and French that recognized any drug as a possible trigger of hepatotoxicity were selected; this review excluded articles reporting hepatotoxicity related with other agents different to drugs, any liver disease, reports of clinical trials about predictive patterns of injury or studies of stem cells. Then, some information was extracted regarding: expression of hepatotoxicity, type of injury, mechanisms of hepatotoxicity, risk factors and clinical manifestations. To assess the probability of occurrence of hepatotoxicity and the type of injury, three categories were established: definite, probable and possible probability, according to evidence [42]. To report

the results, a list was made with 181 drugs and 17 combined pharmaceutical forms or therapeutic regimen; these were selected as substances likely to develop hepatotoxicity. Eight drugs had definite probability: methotrexate, minocycline, vancomycin, everolimus, isoniazid, rifampicin, pyrazinamide and tamoxifen (**Table 2**). The drugs assessed as probable were 61 (**Table 3**) and as possible were 119 (**Table 4**) [43].

Drugs assessed as definite					
Drug [code ATC]	**Hepatic toxcity expression**	**Lesion type (probability of occurrence)**	**Hepatic toxcity mechanism**	**Risk factors**	**Clinical and pathological manifestations**
Vancomycin [J01XA01]	Idiosyncratic (immunoallergic)	Hepatocellular (definite)	Direct toxicity or immune adverse reactions	Adult population	Increase of aminotransferases. Rash, fever, eosinophilia
Minocycline [J01AA08]	Idiosyncratic	Hepatocellular (definite)	Lipid peroxidation (necrosis)	Women from 16 to 57 years	Autoimmune hepatitis. Steatosis. Periportal inflammation, swelling and collapse hepatocytes, antinuclear antibody, eosinophilia. Increase of aminotransferases. Jaundice, fever, abdominal pain, rash, anorexia, nausea, arthralgia, fatigue, pruritus
Isoniazid, rifampicin, pyrazinamide [J04 AM05]	Idiosyncratic	Hepatocellular (probable)	Lipid peroxidation (necrosis). Formation of hepatotoxic metabolites	Genetic polymorphisms. Female, old age, VIH co-infection	Hepatic encephalopathy. Steatosis. Granulomatous inflammation, central necrosis. Increase of liver enzymes. Jaundice, abdominal pain, anorexia, nausea, dark urine, vomiting, asthenia
Tamoxifen [L02BA01]	Idiosyncratic	Hepatocellular (definite)	Disrupt of β-oxidation of lipids. Steatohepatitis	Women from 50 to 70 years. Overweight, hyperlipidemia, hypertension, diabetes, osteoporosis, alcohol consumption <20 g/ day	Steatohepatitis. Fibrosis. Micronodular cirrhosis. Necrosis. Inflammatory infiltrate. Hepatomegaly, peliosis hepatis, increase in aminotransferases. Nausea, vomiting, malaise, right upper quadrant pain
Everolimus [L01XE10]	No information	No information	Possible direct toxicity or hepatotoxic metabolites	Neoplasms, liver transplantation	Increase of aminotransferases, fatigue
Methotrexate [L04AX03]	No information	Hepatocellular (possible)	Direct toxicity. Lipid peroxidation (necrosis). Dysfunction mitochondrial	Previous hepatic disease. Alcoholism, obesity, diabetes. Cumulative dose. Use of steroids. Previous exposure to hepatotoxins	Steatohepatitis. Fibrosis, cirrhosis. Inflammatory infiltrate. Necrosis. Increase of liver enzymes

Table 2. Drugs assessed as definite.

Drugs assesses as probable

Acarbose	Propylthiouracil	Diclofenac	Flutamide
Troglitazone	Methylprednisolone	Lumiracoxib	Etopóside
Papaverine	Doxapram hydrochloride	Nimesulide	Imatinib
Vitamin A	Benzarone	Sodium aurothiomalate	Ipilimumab
Amiodarone	Fluconazole	Allopurinol	Oxaliplatin
Propafenone	Itraconazole	Dantrolene	Temozolomide
Metildopa	Ketoconazole	Cyproterone acetate	Tioguanine
Perhexiline	Rifampicin	Halothane	Glatiramer
Enalapril	Efavirenz	Isoflurane	Azathioprine
Atorvastatin	Nevirapine	Bentazepam	Infliximab
Ezetimibe	Paracetamol	Lamotrigine	Buprenorphine
Flupirtine	Telithromycin	Valproic acid	Clometiazol
Nitrofurantoin	Ciprofloxacin	Tolcapone	Carbamazepine
Ornidazole	Trovafloxacin	Dextropropoxyphene	
Flucloxacillin			

Table 3. Drugs assessed as probable.

Drugs assessed as possible

Ranitidine	Carmustine	Zolmitriptan	Amphotericin B
Glibenclamide	Cyclophosphamide	Enflurane	Clindamycin
Gliclazide	Cytarabine	Methoxyflurane	Dapsone
Glimepiride	Dacarbazine	Propofol	Fosfomycin
Metformin	Mitoxantrone	Sevoflurane	Sulfadimethoxine
Pioglitazone	Trabectedin	Thiopental	Amoxicillin
Rosiglitazone	Leflunomide	Imipramine	Nafcillin
Mesalamine	Sirolimus	Mirtazapine	Oxacillin
Mesalazine	Thalidomide	Nefazodone	Cefdinir
Sulfasalazine	Tocilizumab	Nomifensine	Erythromycin
Oxymetholone	Alfuzosin	Sertraline	Spiramycin
Esomeprazole	Tamsulosine	Felbamate	Doxycicline
Orlistat	Cyclofenil	Phenytoin	Levofloxacin
Thioctic acid nilutamide	Raloxifene	Phenobarbital	Daptomycin
Actinomycine D	Testosterone	Clozapine	Brivudin
Busulfan	Disulfiram	Quetiapine	Didanosine
Donepezil	Simvastatin	Risperidone	Zidovudine
Indicine N-oxide	Pravastatin	Methylphenidate	Atomoxetine
Loratadine	Naftidrofuryl	Amodiaquiea	Spironolactone
Octreotide	Piroxicam	Mefloquine	Fosinopril
Ibuprofen	Rofecoxib	Quinine	Lisinopril
Oxaprozin	Aurothioglucose	Etretinate	Bromfenac
Indomethacin	Glucosamine	Alendronate	Acetylsalicylic acid
Terbinafine	Nicotinic acid	Methimazole	Pazopanib
Ajmaline	Labetalol	Dabigatran	Nafamostat
Quinidine	Nicardipine	Clopidogrel	Dipirone
Hydralazine	Diltiazem	Dalteparin	Mebendazole
Candesartan	Tienilic acid	Phenprocoumon	Metronidazole
Irbesartan	Ferrous fumarate	Bosentan	
	Ticlopidine	Sitaxentan	

Table 4. Drugs assessed as possible.

4. Probability and causality assessment of drug-induced hepatotoxicity: scales and proposals

To solve the difficulty of identification of hepatotoxicity and to try to estimate the probability that a therapeutic agent is associated with a hepatic injury, clinical scales have been developed; these assess aspects such as absence or presence of confounding factors, temporal relation of hepatotoxicity with drug consumption, coexistence of risk factors, previous description in the literature, exclusion of other causes and effects of readministration of the drug. According to the score obtained, a range of causal probability is established.

In this sense, there are scales, such as the Roussel Uclaf Causality Assessment Method scale (RUCAM) and the Clinical Diagnostic Scale (M&V CDS), considering that the RUCAM scale is more appropriate than M&V CDS [12], besides, facilitates to distinguish when patient is using concomitants drugs. However, despite their theoretical utility and being validated, these scales are hardly used in clinical practice [22]. To promote its use, it is advisable to have knowledge of the possible agents associated with hepatotoxicity and to reduce subjectivity bias at the time of its application.

5. Hepatotoxic medicines during pregnancy

Twelve hepatotoxic agents were identified as drugs with probability to cause injury in pregnant women are as follows: acetaminophen, alpha-methyldopa, labetalol, methotrexate, saquinavir, nevirapine, propylthiouracil, methimazole, carbimazole, nitrofurantoin, acetylsalicylic acid and piperidolate. Some characteristics associated with these drugs were the time of reaction onset, weeks of pregnancy (between 3 and 36 weeks), risk factors (age and chronic diseases), clinical manifestations (elevation of transaminases, pruritus, vomiting, anorexia and jaundice) and outcomes (liver transplantation and death of mother and/or fetus). In this sense, pregnant women between the second and third decade of age may have an increased risk of liver problems due to the use of medications such as methotrexate, alpha-methyldopa and propylthiouracil. For drugs such as acetaminophen, acetylsalicylic acid, piperidolate, nitrofurantoin, methotrexate and alpha-methyldopa, information about frequency of hepatotoxic reactions during gestation is limited, whereas for antithyroid drugs, the frequency of occurrence of hepatotoxicity can be found between 0.1 and 0.2% of the pregnant population using these drugs [44]. The management in cases of hepatotoxicity in pregnant women must be the suspension of the offending drug, which in most cases afford to improve the symptomatology and prevent fatal outcomes.

6. Pharmacist and prevention of drug-induced hepatotoxicity

Currently, there is a need to discuss about interdisciplinary groups to provide comprehensive patient care; and the pharmacist is a part of this. Through knowledge of the important aspects of hepatotoxicity (hepatotoxic drugs, symptoms, risk factors, pathological antecedents and

patient habits), it is possible for pharmacist to carry out prevention activities and promote the proper use of medications, decreasing deleterious effects on health of patient. Besides, feedback in the interdisciplinary group may optimize the reaction time in a liver injury case.

Identification of liver toxicity is difficult, because it has no specific manifestations; however, having in mind, this health problem may contribute to a fast clinical response. The next actions may help to identify drug-induced liver toxicity:

- In the blood samples, analyze if an alteration of liver tests is present: increase in alanine aminotransferase more than three times and/or increase in alkaline phosphatase more than two times the upper limit of normal.

- Ask treating physician or nurse about pathological antecedents like acute coronary syndrome, autoimmune diseases, previous or underlying liver disease or liver tumors, viral hepatitis, alcohol or substances abuse and blood transfusion, to rule out other causes of liver test alterations.

- Interview the patient or companion and ask about symptoms like abdominal pain, fever, nausea, vomiting, jaundice, dark urine, pale stools, asthenia, loss of weight or appetite; risk factors such as concomitant administration of drugs or herbal remedies, alcohol consumption, pregnancy or tattoos, use of medications at home and self-medication. Besides, it is important to know about the suspected drug, the beginning or cessation time, dose, frequency of use and route of administration.

- To know about the drugs used by the patient; it is recommended to search about adverse reactions in published information.

- Use a causality assessment of drug-induced liver injury scale like RUCAM, to define the causing agent, as propose in **Diagram 1**.

To prevent death or harmful effects, it is necessary to suspend the hepatotoxic drug, monitoring liver test and use other medications such as N-acetylcysteine or corticosteroids (prednisone, prednisolone and betamethasone) to improve the status of patient health [36]. Also, it is important to educate patient in proper use of drugs to prevent the occurrence of hepatotoxicity.

7. Comments and conclusions

Many drugs are hepatotoxic agents, most of these drugs generate idiosyncratic reactions and cause hepatocellular damage in a wide range of patients in different age groups; and moreover, concomitant medications may deteriorate the clinical features of patients. Elevation of liver enzymes, fever and jaundice are common signs and symptoms, with identification and suspension of offending drug, patients present an adequate evolution.

On the other hand, it is important to have in mind that some patients are asymptomatic and the liver injury identification is based only on the elevation of liver enzymes; therefore, monitoring of liver tests is important to prevent serious effects. In addition, knowing the risk factors and habits of patient can improve the response time in a possible case.
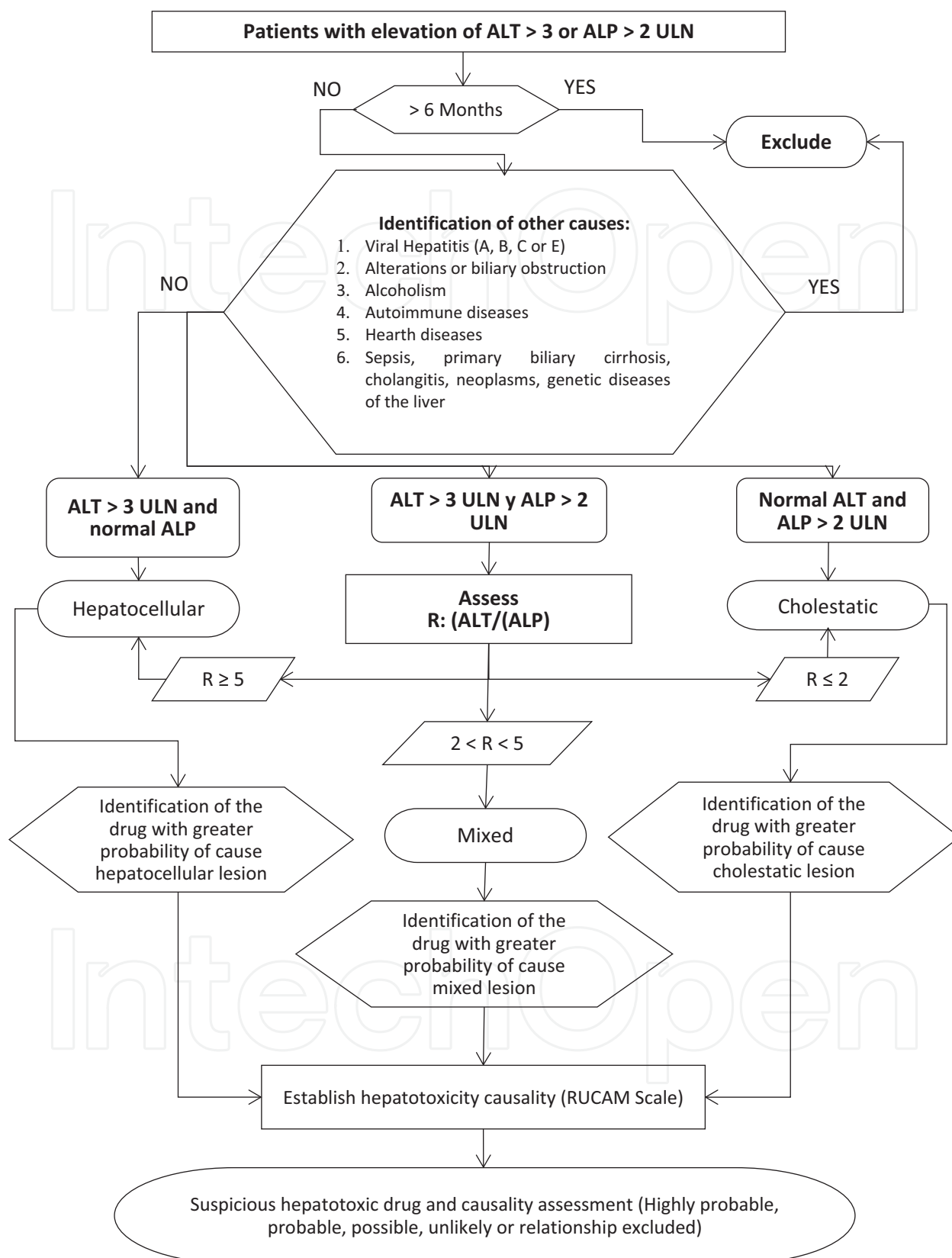
ALT: alanine-aminotransferase; ALP: alkaline phosphatase; ULN: upper limit of normal

Diagram 1. Identification of hepatotoxicity.

It is advisable to use RUCAM scale to obtain a correct judgment when the probability of hepatotoxicity or any doubt exists. While there are other scales present, RUCAM allows discern when confusing factors or concomitant drugs are present.

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