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Drug Induced Liver Injury (DILI) Secondary to Homeopathic Drug (Chelidonium Majus) and Literature Review

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Abstract

Background: Drug induced liver injury (DILI) refers to the presence of Acute Liver Damage caused by exposure to a drug or non-infectious toxic agents excluding other causes of liver damage and represents about 50% of cases of acute liver failure in developed countries.

Case presentation: A 32 year old Mexican man was referred for evaluation of new onset of jaundice, nausea, fatigue and dark urine with a>10 fold increase in his transaminase, >50 fold increase in his Bilirubin with elevated alkaline phosphatase with a R factor for Liver Injury of 3.8 (Mixed Pattern). The patient had received a prescription for Greater Celandine (Chelidonium majus) due to Chronic Fatigue approximately 12 weeks prior his evaluation. Hepatic evaluation revealed negative results for acute viral hepatitis, autoimmune disease, metabolic or neoplastic disease. The result of the liver biopsy showed marked centrilobular cholestasis without fibrosis determining a Roussel Uclaf Causality Assessment Method (RUCAM) of 8 points making the diagnosis of DILI secondary to Greater Celandine. The patient was treated with antihistamines, ursodiol and discontinuation of the Homeopathic Drug. His liver enzymes and synthetic function practically normalized 4 weeks after discontinuation of the Greater Celandine.

Conclusión: This case describes the association between a homeopathic drug (Chelidonium majus) and DILI in Mexico. Drug induced liver injury may be difficult to diagnosis since Homeopathic Drugs are not considered a dangerous drugs by patients and its consumption can be omitted by them, so the diagnosis is based on an adequate clinical suspicion, diagnostic tools including the ACG algorithms, causative assessment scales, imaging and histological findings.

Keywords: Drug induced liver injury; Homeopathic drugs; Chelidonium majus; Alternative medicine; Roussel Uclaf causality assessment method

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Introduction

Drug-Induced Liver Injury (DILI) is one of the most common diseases associated with Acute Liver Failure, being reported in some series as the cause of Acute Liver Failure in up to 40-50% of cases. However, it represents one of the main diagnostic challenges for the internist, immunologist and gastroenterologist [1].

The definition of DILI granted by the American College of Gastroenterology (ACG) and by the American Association for the Study of Liver Diseases (AASLD) refers to the presence of Acute Liver Damage caused by exposure to a drug or non-infectious toxic agents excluding other causes of liver damage, while the Working Group of Experts in DILI defined the drug-induced liver damage as: Isolated Increase in levels of AST (Aspartate Transaminase) 5 times above the upper limit of normality (ULN), the increase of AST 3 times over of ULN associated with the elevation of Total Bilirubins (BT) 3 times above the ULN or the increase of Alkaline Phosphatase (FA) above 2 times the ULN associated with the elevation of Gama-glutamyl-Transferase (GLT) in the absence of bone disease [2-4].

Defining 3 patterns of DILI injury: Hepatocellular (40-78% cases), Cholestatic (20-40%) and Mixed (12-20%), being the hepatoceulular pattern characterized with Hepatic Damage Index greater than 5 (Alanine Aminotransferase (ALT)/ALT÷FA/ LS of FA), the cholestatic pattern with a Hepatic Damage Index less than 2 (Elevation of Alkaline Phosphatase over 2 times the ULN) and the mixed pattern with a Hepatic Damage Index between 2 and 5 [5].

The histological patterns found in DILI are: 1) Acute Hepatitis; 2) Chronic hepatitis; 3) Acute Cholestasis; 4) Chronic cholestasis; 5) Cholestatic hepatitis; 6) Granulomatous changes; 7) Steatosis; 8) Steatohepatitis; 9) Coagulative necrosis; 10) Massive / Submassive Necrosis; 11) Vascular injury; 12) Hepatocellular alteration; 13) Regnerative nodular hyperplasia; 14) Mixed injury.

From a pharmacological point of view, two types of DILI can be classified: The first with a Dependent Dose mechanism, with short latency and potentially predictable, correlated with the intrinsic effect of the drug (overdose, side effect or interaction with other drugs) being the most frequent form of presentation. The second pharmacological mechanism associated with DILI is the idiosyncratic characterized by being independent dose, not predictable, not related to the mechanism of action of the drug and linked to factors of immunological or genetic susceptibility of the patient (Decrease in the threshold of action potential of the drug, Deficiencies in the metabolism of the drug, abnormal response to medication by immunological mechanism and immunoallergic reaction to the medication with need for prior sensitization to the drug or toxic agent) [6,7].

DILI incidence according to previous published data was between 1 in 10,000 and 1 in 100,000. However in recent population studies, in fact, have shown an annual incidence of 19.1 cases per 100,000 inhabitants in Iceland, of 4.1 cases per 100,000 inhabitants in Italy, and of 13.9 cases per 100,000 inhabitants in France, with hospitalization of 12% and mortality of 6%. The most frequently involved drugs are antibiotics, which according to the DILI Network in the USA, represents about 46% of the DILI cases; similar results have been stemmed from Spanish and Icelandic registries. While in India drugs more involved in episodes of DILI are the anti-tuberculosis drugs (58%), followed by anti-epileptics (11%) and in China antibiotics, Chinese herbal medicine, and cardiovascular system drugs are the most common causes of DILI.

The evaluation of DILI in Latin America comes from the analysis of case reports and series published between 1996 and 2012 report that 90% of the DILI reports in Latin America come from Argentina, Colombia and Chile, while the rest of the 20 countries including Mexico only contribute with 10% of the reports. The results of the Registry are that in LA the main agents associated with DILI are Antibiotics, NSAIDs and sex hormones [8,9].

Physiopathology

In the majority of idiosyncratic reactions the determining mechanism is the absence of a certain cytochrome P450 enzyme (CYP) or the presence of a polymorphism in one or several CYP that would lead to the generation of aberrant reactive metabolites during phase 1 of hepatic biotransformation reactions, mediating a greater production of free radicals or electrophilic compounds, which deplete the glutathione of hepatocytes, covalently bind to proteins, lipids or nucleic acids or induce lipoperoxidation, ultimately resulting in cell death by necrosis or apoptosis.

In a secondary pathway with the increase in the metabolism of toxins, oxidative stress would increase with the subsequent depletion of adenosine triphosphate (ATP), oxidation of sulfhydryl groups of proteins, disorders in ionic hemostasis and a sustained increase in the concentration intracellular calcium eventually leading again to necrosis and cell death.

In the case of immunologically mediated reactions, the drugs are considered foreign antigens, recognized by the HLA binding of a host cell that contains a T cell activating peptide, which triggers the immunological mechanisms for its antigenic processing with the production of proinflammatory cytokines and the subsequent recruitment and activation of neutrophils and lymphocytes.

In the case of Cholestatic DILI, under normal conditions, Biliary Acids are excreted primarily through the canalicular domain using the bile salt export pump (BSEP), from where they promote in concert with the multidrug-resistance protein 3 (MDR3) the release of phospholipids from the canalicular plasma membrane. The basolateral exporters MRP3 and MRP4 may act as salvage systems to lower cytoplasmic levels of potentially hepatotoxic compounds.

While in pathological conditions, defects in the multidrug-resistance protein 3 (MDR3) can lead to the inhibition of the Bile Salts Export Pump (BESP) and increase in the Intracellular Concentrations of Bile salts, resulting in a poor biliary excretion and a disruption of the actin filaments near the bile canaliculi resulting in cholestasis [10-14].

Clinical picture

The clinical symptoms associated with DILI are usually nonspecific, the most common being abdominal pain, jaundice, fever, nausea, vomiting, diarrhea, pruritus. In the forms of hypersensitivity, systemic manifestations such as fever, rash or eosinophilia can be seen. Therefore, the clinical spectrum of this disease varies from asymptomatic individuals to acute liver failure **(Figures 1 and 2)** [15].

Diagnosis

The diagnosis of DILI remains a challenge worldwide due to the absence of ‘‘a gold standard.’’ The specific diagnosis of DILI is a diagnosis of exclusion and the subsequent determination of a causality phenomenon with the substance/agent suspected of liver damage, the clinical history being the key, the time of exposure to the drug/substance. Based on recommendations from the different guidelines in the case of a presentation with a hepatocellular pattern, it is recommended to rule out the presence of hepatotropic viruses (HAV, HBV, HCV, HEV, CMV, EBV and HSV), Autoimmune Hepatitis (HAI), Hepatic Vascular Diseases. (Budd Chiari syndrome) and Wilson's disease. In the case of a cholestatic pattern, the presence of obstruction of the bile duct and subsequently autoimmune diseases (Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis) should be ruled out. Different studies of the Cabinet, antibodies (ANA, AMA, p-ANCA) and finally the Liver Biopsy is necessary when liver enzymes do not fall after 30-60 days of a hepatocelular pattern or after 180 days in a cholestasic pattern, when there is a worsening of liver function after discontinuation of the drug suspected [16] **(Figure 3).**

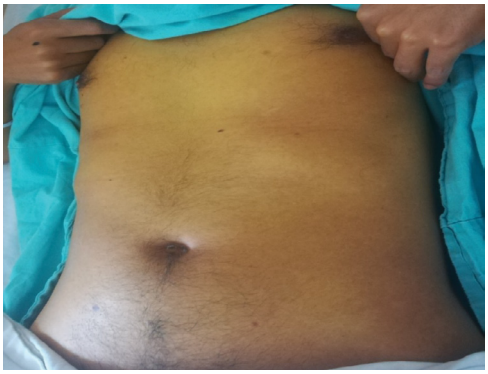

Figure 1 Clinical picture: Generalized jaundice without signs of portal hypertension.

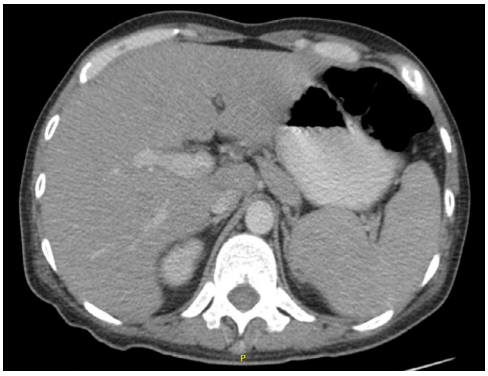

Figure 2 Contrast CT axial image: Hepatic steatosis, moderate hepatomegaly, without nodular lesions or changes of density in hepatic parenchyme.

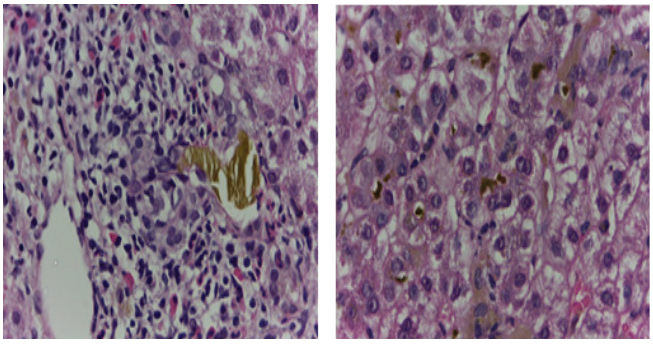

Figure 3 Liver biopsy: Ballooned hepatocytes and numerous pigmented Kupffer cells (asterix) are present in portal tracts consistent with injury. Marked centrilobular cholestasis is present, with otherwise normal bile duct structure and no evidence of hepatic fibrosis HE × 400.

For the causality determination of the drug/substance there are different association models that offer high sensitivity and specificity, the main models being the Roussel Uclaf Causality Assessment Model (RUCAM), also known as CIOMS (for its acronym in English, Council for International Organizations of Medical Sciences) and the model of María and Vitorino (MyV). The RUCAM model involves 4 main items (chronological relationship between drug administration and injury, risk factors, exclusion of other causes and the existence of previously reported injury) **(Table 1)** [17,18].

The prognosis associated to DILI is uncertain because although the literature refers 90% presents a partial recovery when discontinuing the drug / substance, it is also estimated that 10% of patients dies of this disease or requires a liver transplant and even 20% can develop chronic liver disease, being the TB, AST and ALT the main predictors of mortality [19].

Treatment

The main treatment in DILI is the identification of the drug/substance and its suspension. Within the use of specific drugs only the use of antidotes such as N-Acetylcysteine in the case of Acetaminophen, the use of Folinic Acid in the DILI associated with Methotrexate and the use of L-Carnitine in the DILI associated with Valproate have been shown to be effective and increase long-term survival [20].

The use of Ursodeoxycholic Acid has no support in the literature in patients with cholestatic DILI and clinical trials have not proven it effectiveness or their cost/benefit in DILI.

The use of systemic steroids has only shown efficacy in the concept of DILI induced with Autoimmune Hepatitis and the presence of hypersensitivity to the drug [21,22].

The use of antihistamines is reserved as a symptomatic treatment against pruritus and has not been shown to modify the natural history of the disease or reduce long-term complications [23].

Liver transplantation is the therapy of choice in the presence of DILI associated with Acute Hepatitis, while all cases MARS (Molecular Adsorbent Recirculation System) as an extracorporeal detoxification system is presented as a great treatment alternative, however at this moment, there are no clinical trials that demonstrate their efficacy or their cost / benefit in DILI [24,25].

Clinical case

A 32 year old Mexican male presented to the hospital with painless jaundice associated with dark urine. No significant antecedents and without previous alcohol consumption. The Physical examination revealed scleral icterus, generalized jaundice and hepatomegaly. His blood test revealed an Aspartate Aminotransferase (AST/TGO) level of 780 Units/liter, Alanine Aminotransferase (ALT/TGP) levels of 573 Units/liter, Alkaline Phosphatase 450 Units/liter, Total Bilirubin of 50.2 milligram/deciliter, Direct Bilirubin of 47.8 milligram/deciliter, Lactic Dehydrogenase (LDH) of 228 Units/liter, White Blood Count of 7800/liter, hemoglobin level of 14..5 gram/deciliter and platelet count of 425000/liter determining a R Factor for Liver Injury of 3.8 and classifying the liver injury with a mixed pattern.

Blood cultures, urine analysis, chest X-ray, abdominal ultrasound, Magnetic Resonance Cholangiopancreatography, Viral serologies (hepatitis A, B, C, and E, HIV, cytomegalovirus), ferritin levels, ceruloplasmin Antinuclear antibody, Anti-smooth muscle, anti-liver/kidney microsomal, and anti-mitochondrial antibodies results were negative. The Computed Tomography scan only evidenced hepatomegaly, without nodular lesions or changes of density in hepatic parenchyma.

In this stage of the diagnostic protocol, the patient reports having

Table 1 Causality assessment scale drug/substance cioms or rucam.

Enzyme Pattern	Hepatocellular			Cholestatic		
Exposure	Initial	Subsequent	Score	Initial	Subsequent	Score
Time Frame of Latency Period	May-90	Jan-15	2	May-90	Jan-90	2
	<5 OR >90	>15	1	<5 O >90	>90	1
From Cessation of the Drug/Substance:	<15	<15	1	<30	>30	1
Disease Course	Recurrent ALT increase Difference between maximum ALT value and Upper Normal Limit			Recurrent ALP increase Difference between maximum ALP value and Upper Normal Limit		
After Stopping the Drug:	Decrease ≥ 50% within 8 days		3	Decrease ≥ 50% within 180 days		2
	Decrease ≥ 50% within 30 days		2	Decrease <50% within 180 days		1
	No information or decrease ≥ 50% after 30 days		0	Persistence or increase or no information		0
	Decrease <50% after 30 days OR Recurrent increase		-2			
Risk Factors:	Presence of Ethanol		1	Presence of Ethanol or Pregnancy		1
	Absence of Ethanol		0	Absence of Ethanol or Pregnancy		0
Age	>55 years		1	>55 years		1
	<55 years		0	<55 years		0
Concomitant Drug(S):	None or no information or concomitant drug with incompatible time to onset					0
	Concomitant drug with suggestive or compatible time to onset					-1
	Concomitant drug known to be hepatoxic with a suggestive time to onset					-2
	Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)					-3
Exclusion of Other Causes of Liver Injury:	**Group I (6 causes):** Acute viral hepatitis due to HAV (IgM anti-HAV), or HBV (HBsAg and/or IgM anti-HBc), or HCV (anti HCV and/or HCV RNA with appropriate clinical history) Biliary obstruction (By imaging) Alcoholism (History of excessive intake and AST/ALT ≥ 2) Recent history of hypotension, shock or ischemia (within 2 weeks of onset) **Group II (2 categories of causes):** Complications of underlying disease(s) such as autoimmune hepatitis, sepsis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis; or Clinical features or serologic and virologic tests indicating acute CMV, EBV, or HSV.			All causes in Group I and II ruled out		2
				The 6 causes of Group I ruled out		1
				Five or 4 causes of Group I ruled out		0
				Less than 4 causes of Group 1 ruled out		-2
				Non drug cause highly probable		-3
Previous Information on Hepatotoxicity of the Drug	Reaction labeled in the product characteristics					2
	Reaction published but unlabeled					1
	Reaction unknown					0
Response to Readministration	Positive	Doubling of ALT with drug alone		Doubling of Alk P (or bilirubin) with drug alone		3
	Compatible	Doubling of the ALT with the suspect drug combined with another drug		Doubling of the Alk P (or bilirubin) with the suspect drug combined with another drug		1
	Negative	Increase of ALT but less than ULN with drug alone		Increase of Alk P (or bilirubin) but less than ULN with drug alone		-2
	Not done or not interpretable	Not done or not interpretable		Not done or not interpretable		0
Interpretation of the score: Highly probable>8; Likely 6 to 8; Possible 3 to 5; Unlikely 1 to 3; <0 is excluded						

CIOMS: Council for International Organizations of Medical Sciences; RUCAM: Roussel Uclaf Causality Assessment Model.

been consuming homeopathic medication due to chronic fatigue for three months, requesting the product with family, resulting to be Greater Celandine (Chelidonium majus), determining the need in conjunction with the gastroenterology service to perform liver biopsy finding marked centrilobular cholestasis without fibrosis determining a Roussel Uclaf Causality Assessment Method (RUCAM) of 8 points making the diagnosis of DILI secondary to Greater Celandine. Deciding to start treatment with antihistamines, ursodiol, intensive fluid therapy and surveillance reducing bilirubin levels to 10.8 milligram/deciliter, Alanine Aminotransferase (ALT/TGP) to 290 Units/liter after 15 days of treatment and after 28 days of stopping homeopathic drug.

Discussion

Complementary and alternative medicine in the form of herbal and homeopathic medications have been used dating as far back as 2100 BC in ancient China and India. In Europe and United States, homeopathy is the complementary medicine most commonly used. In Mexico Homeopathy is approved since the year of 1850, and is the most commonly used complementary and alternative medicine, finding in some reports up to 78% of use in allergic diseases and 30% in rheumatological diseases [26].

In Mexico like in many other countries, the regulation of homeopathy drugs including composition, dosage, and quality is often lacking or incomplete so manufacturers and homeopathic doctors are not always obliged to declare a description of the marketed products. On the other hand, most controlled studies with random distribution did not show any solid evidence that homeopathy is effective for any specific condition. For these reasons, safety and effectiveness of Homeopathic drugs is not always ensured, and occurrence of toxicity is, therefore, not a rare event. Based on the DILIN registry, Herbolary and Dietary supplements are responsible for 20% of the observed DILI being the second most frequent class and based on the latest LATIN DILI report, its frequency is close to 9%.

The Chelidonium majus is a Homeopathic remedy based on Greater Celandine, a plant of the family Papaveraceae, which grows wild in part of Asia, Central and Southern Europe, in the Azores and North America. It has been used for a long time in hepatobiliary disorders: gall bladder and digestive dysfunctions; dyspeptic complaints and spasms in phytotherapy and traditional medicine [27].

The protective potential of chelidonine (the major active component of Chelidonium majus) derives from the reduction of cadmium chloride, decreasing lipid peroxidation levels, oxidative stress and restoring glutathione levels. However, in animal studies it has been proved that the plant contains quaternary benzo [c] phenanthridine alkaloids that offer greater difficulty in passing through the mitochondrial membrane, being Berberine the alkaloid with the greatest potential for hepatotoxicity. Also European studies show cholestatic type hepatotoxicity with CM [28,29].

Hepatic damage secondary to Chelidonium has been reported in multiple case reports by several authors [30,31]. The diagnosis of DILI should always be made by the doctor's suspicion, without forgetting the use of homeopathic medicines is an important cause of this disease.

Conclusion

However, despite all the case reports, the use of homeopathic medicines and herbal medicine is increasing in the belief that they are harmless. However, like any other substance or medication, there are adverse reactions (idiosyncratic) that depend on the susceptibility of the patient, which are not preventable and can have fatal consequences. Therefore, this case report is elaborated to suggest a greater regulation in its use, preparation, distribution and sale and have a better diagnostic and treatment approach for DILI.

We know that the use of Homeopathy, Herbolary and Dietary Supplements in Mexico is very common, but there are no data about frequency of use, incidence of liver injury, type of products, similarities and differences with those reported in other countries. Research in alternative medicine toxicity represents compelling challenges and it is a priority issue. This is one of the first cases of DILI secondary to homeopathic medication in Mexico with a proven causality phenomenon.

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