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Antipsychotic Drugs and Liver Injury

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Summary: In October 2015, the drug-induced liver diseases group of the Chinese Society of Hepatology drafted and published the first Diagnosis and Treatment Guidelines on Drug-induced Liver Injury in China, giving suggestions on the diagnosis and treatment of drug-induced liver injury (DILI). As a psychiatrist, I have found that in clinical practice both typical and new antipsychotic drugs can induce liver injury to varying degrees. Therefore, it is necessary to quickly and accurately determine the cause of liver injury and the type and severity of injury and establish a solution. This article reviewed relevant literature including the common pathogenesis and clinical manifestations of drug-induced liver injury caused by antipsychotic drugs, laboratory tests, diagnostic criteria and classification, and clinical management strategies. This paper also includes a summary and a perspective on liver injury caused by antipsychotic drugs.

Key words: antipsychotic drugs, drug-induced liver injury

[*Shanghai Arch Psychiatry*. 2018; **30**(1): 47-51. doi: http://dx.doi.org/10.11919/j.issn.1002-0829.217090]

Drug-induced liver injury (DILI) refers to liver injury caused by various prescription or non-prescription chemical drugs, biological agents, traditional Chinese medicine (TCM), natural medicine (NM), health care products (HP), dietary supplements (DS), and their metabolites and even excipients.[1] It was reported that DILI accounted for 10 - 15% of adverse drug effects.[2] The incidence rate of DILI is approximately 1/10,000 to 1/100,000 per year.[3] Among the main drugs causing DILI in our country, sedatives and neuropsychiatric drugs accounted for 2.6%.[4] Systematic reviews have found that[5] all patients treated with conventional antipsychotic therapy have an increased risk of hepatic dysfunction. The median percentage was 32% (range: 5 - 78%). The median percentage of significant abnormalities in these patients was 4% (range: 0-15%). The risk factors for DILI were host factors (including genetic factors, age, gender, pregnancy, underlying diseases), drug factors (including chemical properties of drugs, interactions, pollution in the course of planting and processing the traditional Chinese medicinal materials), and environmental factors (excessive drinking and smoking etc).[1] The pathogenesis of DILI is complicated, and it is often the result of successive or combined effects of various mechanisms that have not yet been fully clarified. The clinical manifestations were mostly asymptomatic transaminase elevation and it happened in the initial 6 weeks of using antipsychotic drugs. Abnormal liver function can be stabilized or improved via treatments and fatal hepatitis rarely happens. It is necessary to point out that chlorpromazine often triggers cholestatic liver injury. This injury is generally regarded as a relatively severe liver injury.

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1. Pathogenesis and pathological changes of drug-induced liver injury

DILI has a complex pathogenesis that can be summarized into direct hepatotoxicity and idiosyncratic hepatotoxicity reactions to drugs. The process involves the upstream events caused by drugs and their metabolites, and the downstream events constituted by the imbalances in hepatic target cell damage pathways and protective pathways. Direct hepatotoxicity of drugs refers to the drugs ingested into the body and/or the direct damage of its metabolites to the liver and was often dose-dependent, usually predictable, and also called intrinsic DILI. Direct hepatotoxicity of drugs can further induce other liver injury mechanisms such as immunity and inflammatory response. The pathogenesis of idiosyncratic hepatotoxicity has been a hot topic in research in recent years. Gene polymorphisms of the drug-metabolizing enzymes, transmembrane transporters and solute transport proteins, and human leukocyte antigen systems (HLA) result in adaptive immune responses to some drugs relatively easily, increasing the host's susceptibility to DILI. Hepatic mitochondrial damage and oxidative stress induced by drugs and active metabolites can cause hepatocyte damage and death through a variety of molecular mechanisms. Persistent and excessive endoplasmic reticulum stress response (ERSR) broke the alleviating effect of the unfolded protein response (UPR) on stress, facilitating the progress of DILI. Drugs and their metabolites are capable of activating a variety of death signaling pathways, promoting the occurrence of cell necrosis and autophagic cell death. Adaptive immune attack may be the last common event of DILI. [4]

Most antipsychotic drugs (except sulpiride, amisulpride, risperidone, and paliperidone) are metabolized through the cytochrome P450 (CYP) system. The majority of antipsychotic drugs mainly metabolize through CYP2D6 and CYP3A4 and some antipsychotic drugs were through CYP1A2 (such as clozapine and olanzapine).[6] There may be three main mechanisms underlying the hepatic injury induced by antipsychotic drugs: firstly, phenothiazines (especially chlorpromazine) or their metabolites can affect bile secretion and excretion, resulting in cholestasis, which may be related to immune-mediated hypersensitivity.[7] Secondly, the direct toxic effects of the drugs or their metabolites attack hepatocytes; the delayed toxic effect is caused by a gradual accumulation of small toxic metabolites.[7] Although the drug continues to damage the hepatocytes, the hepatocyte can adapt to this change by up-regulation of antioxidant genes or chaperone proteins.[8] Thirdly, antipsychotic drugs indirectly affect the liver by increasing the risk of metabolic syndrome, leading to an increased risk of non-alcoholic fatty liver disease.[9] Some studies have found that clozapine and olanzapine increase the risk of non-alcoholic fatty liver disease compared with other novel antipsychotic drugs[10] (clozapine OR 34.6; 95% CI 2.8 - 824.9; olanzapine OR 18.6; 95% CI 2.8-68.4) and there were 2 case reports regarding acute liver damage after using clozapine. Clozapine, [11] olanzapine, quetiapine and risperidone[12,13] resulted in 40%, 30%, 27%, and 31% of asymptomatic elevation of aminotransferase respectively. Generally, it takes place in the first few days to weeks of taking the medication. The target cells of DILI are mainly the hepatic cells, bile duct epithelial cells, and vascular endothelial cells in the hepatic sinusoid and hepatic vein system. The injury modes are complex and diverse; the pathological changes cover almost all the areas of liver pathological changes. Most of the pathological changes caused by antipsychotics are mainly in the form of acute cellular lysis.[14] The hepatotoxicity induced by conventional antipsychotic drugs is represented by phenothiazine. Especially liver injury caused by chlorpromazine is manifested as acute cholestasis. The hepatic injury modes of the novel antipsychotics are diverse. Studies[14] have shown that clozapine can cause acute necrotic hepatitis, cholestatic hepatitis with necrosis of a single hepatocyte, and eosinophil infiltration; risperidone usually results in cholestatic hepatitis and rare allergic symptoms; olanzapine induces hepatocyte damage, accompanied monocytes, centrolobular necrosis of lymphocytes, and eosinophils infiltration in the portal area; quetiapine is the leading cause of hepatocyte damage, extensive necrosis of hepatocytes, and nonspecific inflammatory infiltration; ziprasidone usually causes hepatocyte damage, hypersensitivity, eosinophilic and systemic symptoms drug-induced reaction syndrome; aripiprazole, paliperidone, aripiprazole, amisulpride have no relevant reports.

2. Clinical manifestations of drug-induced liver injury

The clinical manifestations of acute DILI are usually non-specific. The incubation period varies considerably in that it can last as short as one to several days and up to several months. Most patients had no obvious symptoms with only an increase of varying degrees on hepatic biochemical indicators such as serum ALT, AST and ALP, GGT, and so forth. Some patients may have digestive symptoms such as fatigue, loss of appetite, distending pain in the liver area, and epigastric discomfort. People with cholestasis can have yellow skin over the entire body, pale stool color, itching, and so forth. A small number of patients may have allergic reactions such as fever, rash, eosinophilia, and even arthralgia, and possibly be accompanied with manifestations of other extrahepatic organ injuries. Acute liver failure (ALF) or subacute liver failure (SALF) may be present in severe cases. Studies have found that new antipsychotic drugs rarely showed hepatic injury that was accompanied with jaundice in clinical practice, and the cause was unknown.[1] Chronic DILI in clinical practice can be manifested as chronic hepatitis, hepatic fibrosis, compensated and decompensated cirrhosis, autoimmune-like hepatitis (AIH) DILI, chronic cholestasis, vanishing bile duct syndrome (VBDS),

and so forth. It is relatively easy for cholestatic DILI to develop into a chronic condition.[15]

The severity of DILI was graded according to clinical features and laboratory indexes ALT, ALP, TBil, and INR (international normalized ratio). It is divided into 5 grades, including no liver injury, mild, moderate and severe liver injuries, ALF, and fatal. [4]

3. Laboratory and auxiliary examinations of drug-induced liver injury

Laboratory tests mostly showed asymptomatic aminotransferase elevation. We believe that it is a non-specific liver injury and a relatively sensitive biomarker of liver injury when alanine aminotransferase (ALT) is 3 times higher than the normal limit or the increase of alkaline phosphatase (ALP) is 2 times higher than the normal value, or TB (total bilirubin)> 2mg/dl. Therefore, the laboratory examination mainly showed enzymology change and bilirubin excretion disorders, and Liver enzymology was positively correlated with bilirubin. In addition, most patients had no significant change in blood routine compared with the baseline period. Patients with allergic diathesis may present with eosinophilia (> 5%) and attention should be paid to the influence of underlying diseases on blood routine. Other than ALT, AST, and ALP, change of TBil is the primary laboratory indicator for determining the presence of liver damage and diagnosing DILI. The diagnostic sensitivity and specificity of serum GGT to cholestatic/ mixed DILI could not be less than ALP. Elevated serum TBil, decreased albumin levels, and the decrease of blood coagulation function suggest severe liver injury. The prothrombin time international normalized ratio (INR) ≥ 1.5 is usually used to determine the decrease of the blood coagulation function. In patients with acute DILI, the liver ultrasound showed no obvious changes or only mild swelling. Patients with drug-induced ALF could have a reduction of hepatic volume. A small number of patients with chronic DILI may have imaging findings of cirrhosis, splenomegaly, and enlargement of the portal vein diameter. The intrahepatic and extrahepatic bile duct usually have no obvious dilatation. Currently, the new studies on serum, biochemistry, and histological biomarkers were mostly related to DILI; however, they all lacked specificity.[1]

4. Diagnostic criteria and types

At present, the diagnostic criteria commonly used for drug-induced liver injury (DILI) in the world are: the Japanese Diagnostic Criteria for Drug-induced Liver Injury developed by the Japanese Liver and Drug Research Society in 1978; the European Consensus Meeting Criteria for Acute Drug-induced Liver Injury developed by Danan and colleagues in 1988; the ICM standard developed by the Council for International Organization of Medical Sciences (CIOMS) in 1993 (this had improvements to the Danan standards); the Maria Diagnositc Criteria developed by Maria in 1997; the DDW Japan criteria developed by the Japanese Society of Hepatology in 2004. In our country, the most commonly used set of criteria was the one that used medical history, symptoms, and signs combined with laboratory markers as the diagnostic criteria for DILI.[16]

The clinical manifestations and histological features of drug-induced liver injury were similar to most types of liver diseases, and the same drug can present different characteristics (including clinical features, pathological manifestation, and latency manifestation). Additionally, the diagnosis of DILI is not convincing enough at present due to the lack of specific biological indicators (laboratory, radiological, imaging or histological manifestations).[14] Therefore, some studies[14] have proposed a train of thought for diagnosis: 1) establishing diagnostic procedures: there is a need for understanding comprehensively the relationship between patients' medication use situation and liver injury in clinical practice, awareness of the risk of liver injury caused by drugs, knowing the liver injury risk caused by drugs, and excluding other factors that could lead to liver injury (for example, viruses, infections, autoimmune diseases, and ischemic and metabolic diseases). 2) Observing the clinical manifestations and evaluating risk factors: acute and chronic liver injuries can have all kinds of clinical manifestations, mainly in the form of acute cytolysis; hepatocellular injury, being female, high total bilirubin, high AST, and AST/ALT > 1.5 are the risk factors for developing acute liver injury. 3) Evaluating the biochemical markers of liver at baseline: weight gain and metabolic syndrome caused by new antipsychotic drugs impair the liver function indirectly. Therefore, it is necessary to define the type of liver injury and, more importantly, to record the patients' liver and other metabolic markers before taking medication. 4) Age: age can determine the biochemical expression of hepatotoxicity. Elderly patients have a strong relationship with cholestatic or mixed liver injury. It is more common to express as hepatocellular toxicity in young patients. 5) Comorbidity and concomitant medication: psychiatric patients have more comorbidity and concomitant medication situations. The past history, medication history, including the use of traditional Chinese medicine and dietary supplements of this kind of patients should be known. In addition, it should be noted that the recent use of drugs does not necessarily mean it is relevant to liver injury.

According to the preliminarily established and posteriorly revised DILI classification criteria by the Council for International Organization of Medical Sciences (CIOMS), DILI was classified into 3 types: liver cell type, intrahepatic cholestasis type and mixed type. Liver cell type: ALT≥ 3 normal upper limit (ULN), and R≥ 5 [R= (ALT measured value/ ALT ULN) / (ALP measured value/ ALP ULN)]; cholestatic type: ALP≥ 2 ULN, and R≤

2; mixed type: ALT≥ 3 ULN, ALP≥ 2 ULN, and 2< R<5. If ALT and ALP do not meet the above criteria, they are called the abnormal liver biochemical test. The cholestatic type DILI accounts for approximately 30% of DILI.

5. Clinical management strategy

The basic treatment principle of DILI is: 1) stop using the suspected liver injury drugs promptly and try to avoid using suspicious or similar drugs again; 2) one should weigh the progression of primary diseases after stopping medication and the risk of aggravating liver injury caused by continuous use of medication; 3) choosing appropriate medication treatment according to the clinical type of DILI; 4) patients with acute liver failure / subacute liver failure can consider emergency liver transplantation when necessary.

Currently, there is no clear guideline for the impairment of liver function caused by antipsychotic drugs in clinical practice and it is still based on clinical recommendations, or guidelines from various centers. A more consistent suggestion is that liver function tests should be performed prior to the use of antipsychotic drugs,[17] to understand the patient's baseline period status. Once liver function impairment is found in the baseline period, it is recommended to use antipsychotic medication that has low doses or metabolize less through livers (for instance, sulpiride, amisulpride, and paliperidone). Patients with liver injury should avoid using phenothiazines. Some common adverse drug reactions (such as excessive sedation or constipation) can also aggravate the impairment of liver function. For those who had liver injury before the use of antipsychotic drugs, liver function tests should be performed at least once a week in the early stage.[18] If the patient has normal liver function at baseline, regular liver function tests are needed even after using antipsychotic medication.[18] It is recommended to have the exam at least once a year (patients who take clozapine have the test every six months). Some centers believe that liver function should be evaluated frequently (usually every three months) during the first year of using antipsychotic drugs (especially with patients with alcohol or drug use). Patients with clinical symptoms, (such as jaundice, nausea, vomiting, anorexia, weakness, pale urine, or black stool) should increase the number of liver function tests. Once the patient was found to be suffering from liver damage due to the use of antipsychotic drugs (ALT≥ 3 times ULN or ALP≥ 2 times ULN or TB> 2mg/dl), it is suggested to stop the medication treatment as soon as possible,[8] receive liver-protecting treatment, or get a referral to a general hospital. If mild and asymptomatic liver injuries occur and they do not meet the above criteria, whether there is alcohol or substance use should be assessed including other possible risk factors. Clinical observation should be strengthened without the discontinuation of antipsychotic drugs.[8] If patients suffer from transient liver damage that mostly had a low correlation with antipsychotic drugs, clinical and laboratory monitoring can be strengthened without discontinuation of antipsychotic drugs.[8]

6. Conclusions

The mechanism of liver injury induced by antipsychotic drugs is different. The liver injuries induced by typical antipsychotic drugs that represented by chlorpromazine are mostly presented as cholestasis type. Novel antipsychotics primarily cause liver injury indirectly through adverse events associated with metabolism (weight gain, obesity, metabolic syndrome, etc.). Liver function monitoring is still necessary before and after treatment. It is necessary to continue the promotion of clinical and basic research on DILI induced by antipsychotic medication in the future, including applied genomics, transcriptomics, proteomics, metabonomics and other "omics" techniques assessing the incidence of DILI before and after onset and genetics between individuals, as well as studies of immunology, molecular biology, the change of biochemistry and such events, conducting big data analysis, and promoting the study of pathogenesis. These will all serve to identify patients' susceptibility, adaptability, and tolerance to specific antipsychotic drugs in the early stage, thereby improving prevention of DILI.

Funding statement

The National Natural Science Foundation of China (project code: 81671326);

National Basic Research Program of China (project code: 2016YFC0906402);

Shanghai Mental Health Center Program (project code: 2017-YJ-01, 2015-YJGJ-03);

The Fundamental Research Funds for the Central Universities (project code: 16JXRZ06);

The Shanghai Science and Technology Commission Foundation (project code: 17411970000)

Conflict of interest statement

The authors report no conflict of interest related to this manuscript.

Authors' contributions

Qinyu LV reviewed relevant literature and wrote the first draft. Zhenghui Yi checked all the information. Kaida Jiang provided guidance on the writing. All authors read and finalized the manuscript.

抗精神病药物与肝损伤

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概述：2015 年 10 月中华医学会肝病学分会药物性肝病学组起草并推出了中国首部《药物性肝损伤诊治指南》，对药源性肝损伤（DILI）临床诊治提出了建议。作为精神科医生，临床也发现无论是典型还是新型抗精神病药物均会不同程度引起肝脏损伤，因此需要快速准确的判断肝损伤发生的原因，损伤的类型和程度，确立解决方案。本文复习了相关文献，包括抗精神病药物所致药源性肝损伤常见的发病机制和临床表现、实验室检查、诊断标准和分型、临床管理策略，最后对抗精神病药物所致肝损伤进行了总结和展望。

关键词：抗精神病药物；药源性肝损伤

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