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Awareness of the Causes of Drug-Induced Liver Injury: A Case of Hepatotoxicity Resulting from Antipsychotics

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ABSTRACT

Objective: This study attempts to increase awareness of hepatotoxicity caused by antipsychotic drugs and to provide updated information on drug-induced liver injury (DILI) to physicians in Korean medicine (KM) clinics.

Methods: This study presents a detailed case of a female patient diagnosed with DILI attributed to antipsychotic drugs, highlighting the improvement observed through laboratory findings.

Results: A 56-year-old female patient with underlying disorders, including mixed connective tissue disease and depression, was under medical care. One day, she reported experiencing intense fatigue and distressing sensations, prompting the author to order blood tests. The levels of AST and ALT were significantly elevated by more than 2.5-fold, indicating hepatocellular DILI. The RUCAM score for antipsychotic drugs was 9, as no other medications, including herbal medicine, were being taken. Upon discontinuation of the antipsychotic drugs, the patient's laboratory findings returned to normal levels within 2 weeks, accompanied by a recovery of subjective symptoms.

Conclusion: This study presents a noteworthy case of hepatotoxicity caused by antipsychotic drugs, serving as an illustrative example that highlights the crucial need for awareness among doctors of KM in clinical settings.

Key words: drug-induced liver injury, hepatotoxicity, antipsychotics drug, traditional Korean medicine

Ⅰ. Introduction

Drug-induced liver injury (DILI) represents a significant concern as it stands as the leading cause of acute liver failure, accounting for approximately 10% of all cases of acute hepatitis[1,2]. The spectrum of DILI manifestations varies widely, ranging from asymptomatic mild elevation of biochemical parameters to severe hepatitis with jaundice that can ultimately result in mortality[3]. Typically, around 80% of DILI patients experience complete recovery upon discontinuation of the suspected drug. Nevertheless, it is important to note that approximately 10 to 15% of DILI cases exhibit persistently abnormal

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laboratory values for over a duration of six months[4].

The commonly implicated agents in DILI encompass acetaminophen, troglitazone (an antidiabetic drug), anticonvulsants, analgesics, antibiotics, and anti-cancer drugs[5]. However, the hepatotoxicity can potentially arise from any type of medication, including over-the-counter drugs, herbal products, and dietary supplements, operating through various mechanisms[6]. In contrast to general adverse drug reactions (ADRs) that typically exhibit a dose-dependent and predictable nature, DILI mainly manifests as idiosyncratic metabolic responses that are independent of dosage and display an unpredictable pattern[7]. Consequently, the prevention and early detection of DILI pose significant challenges in clinical practice, representing complex and intricate issues[8].

A nationwide multicenter study in Korea reported an incidence rate of approximately 0.6% for herb-induced liver injury (HILI), which is significantly lower, by at least 2-3 times, than that associated with conventional drugs[9]. However, the risk attributed to HILI has been overestimated thus far. Considering that patients visiting Korean Medicine (KM) clinics commonly receive treatment with Western drugs, it is crucial for KM physicians to be aware of the potential occurrence of DIL) caused by conventional drugs.

The objective of this study is to present a case of DILI induced by antipsychotic drugs in a woman, providing a typical example of DILI that highlights the necessity for awareness among practitioners in Korean medicine (KM) clinics. This study aims to report a woman case with a DILI by antipsychotics, which provides a typical DILI example for an awareness requirement in clinics of Korean medicine (KM).

Ⅱ. Case presentation

1. Medical history and examination

A 56-year-old woman has been grappling with mixed connective tissue disease and major depressive disorder for the past 5 years. Despite receiving ongoing treatment with both immunosuppressants and antidepressants, her symptoms have exhibited frequent fluctuations. The patient previously admitted to my clinic, where her condition gradually improved, with no episodes of severe deterioration. The treatment primarily involved the utilization of acupuncture (mainly at both HT7, ST36, LI4, and LR3), and an indirect moxibustion (at Ki1) once a week, contributing to the gradual enhancement of her overall well-being.

One day, the patient's psychological well-being deteriorated due to stress related to her family, which resulted in disrupted sleep and a decline in her overall condition. Consequently, her psychiatric doctor adjusted her medication regimen. However, after 7 days of the new prescription (Table 1), she began experiencing severe malaise, fatigue, and distressing sensations. In order to ascertain the absence of any objective disorders, I conducted laboratory tests including chemistry and complete blood count. The results unexpectedly revealed significantly elevated levels of serum alanine aminotransferase (ALT) at 103 IU/L and aspartate aminotransferase (AST) at 106 IU/L, while the levels of gamma glutamyl transpeptidase (GGT, 14 IU/L), alkaline phosphatase (ALP, 71 IU/L), and total bilirubin (0.38 mg/dl) fell within the normal range. The Institutional Review Board had approved this case study.

Table 1. Summary of Prescriptions

Name of product (dose per day)	Active ingredient	Main action	Warning for liver injury
Quaichi Tab. (12.5 mg once)	Quetiapine	Atypical anti-psychotic for schizophrenia and bipolar	AST, ALT elevation[19]
Depro Tab (10 mg once)	Escitalopram (SSRI)	Anti-depressant	A case report[20]
Azolac Tab (0.4 mg twice)	Alprazolam	Anti-anxiety	A case report[12]

2. Treatments and clinical outcome

Based on the absence of any other potential causes, such as hepatitis B virus (HBV) infection, and the previous normal results of liver-related enzyme tests conducted at the author's hospital, the elevations in both ALT and AST levels, exceeding 2.5 times the upper normal limit (UNL), were indicative of drug-induced liver injury (DILI). Consequently, I strongly advised the patient to discontinue the use of psychiatric medications. Subsequently, the patient experienced a rapid disappearance of subjective complaints (severe malaise, fatigue, and distressing sensations) within 5 days. Additionally, the follow-up test conducted at 14 days demonstrated a return of AST and AST serum levels to the normal range, measuring 36 IU/L and 31 IU/L, respectively (Fig. 1).

Given the prompt recovery of AST and AST levels, there was no necessity for liver-focused radiologic examinations such as abdominal ultrasonography in this case. Apart from regular acupuncture and moxibustion, I refrained from prescribing any conventional or herbal medications for DILI of the patient.

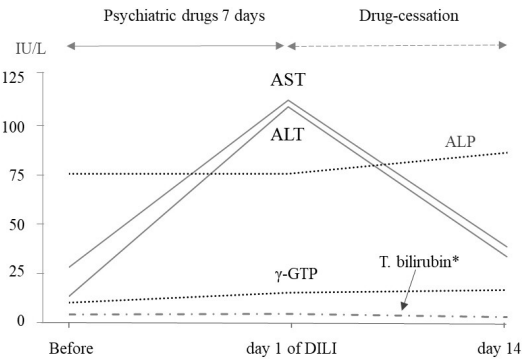

Fig. 1. Summary for changes of serum hepatic enzymes.

The upper normal limits are follows; 40 IU/L for AST and ALT, 64 IU/L for GGT, 120 IU/L for ALP. *For the readability, the total bilirubin (normal 0.1~1.2 mg/dL) value was 10-folded in this figure.

Ⅲ. Discussion and conclusion

In general, the majority of DILI cases is characterized by idiosyncratic metabolic responses, displaying patterns that are independent of dosage and unpredictable[7]. Among the commonly encountered drug groups, anti-tuberculosis (anti-TB) medications are well known to induce idiosyncratic DILI, accounting for an estimated 5% to 28% of hepatotoxicity cases among individuals undergoing anti-TB treatment[10,11]. Additionally, certain antibiotics such as amoxicillin-clavulanate and flucloxacillin have been frequently associated with cases of idiosyncratic DILI worldwide[12].

The patient in this case had been prescribed

three different antipsychotic drugs: quetiapine, escitalopram, and alprazolam. These medications are typically prescribed for individuals with conditions such as schizophrenia, bipolar disorder, depression, or anxiety. Shortly after initiating the administration of these newly prescribed drugs for 7 days, the patient experienced novel symptoms including severe malaise, fatigue, and distressing sensations. Based on the significant elevation of hepatic enzymes (ALT and AST) to over 2.5 times UNL, the absence of other liver disorders such as viral hepatitis, and the rapid normalization of enzyme levels after discontinuing the drugs, there was a strong suspicion of DILI. In addition, her subjective symptoms of malaise, fatigue, and distress rapidly disappeared after drug-cessation. In terms of withdrawal symptoms, I had provided a warning to the patient, but no withdrawal symptoms were observed. The Roussel Uclaf Causality Assessment Method (RUCAM)[13] was employed to evaluate the causality, yielding a RUCAM score of 9 for this case, indicating a classification of "highly probable" for DILI.

DILI can be classified into three distinct patterns: hepatocellular, cholestatic, or mixed type. The specific pathological pattern observed in a DILI case is determined by calculating the R ratio, which is derived from the ratio of ALT value to the UNL, divided by the ratio of ALP value to the UNL[14]. A R ratio greater than 5 indicates a hepatocellular pattern, while a ratio below 2 suggests a cholestatic pattern, and values between 2 and 5 are indicative of a mixed pattern. Alternatively, an ALT value equal to or greater than 2 times the ULN with a normal range of ALP level is suggestive of a hepatocellular pattern, whereas an ALP value equal to or greater than 2 times the ULN with a normal range of ALT level points towards a cholestatic pattern[15].

Although the prescription of antipsychotic drugs or antidepressants is generally considered safe[16], the worldwide increase in the use of psychotropic drugs, along with long-term use, polypharmacy, and the presence of common comorbidities such as metabolic disorders, has led to an increased incidence of psychotropics-induced drug-induced liver injury (DILI) in psychiatric patients[17]. According to a systematic review, approximately 1.3% of patients taking antipsychotic medications exhibited clinically significant abnormal liver function tests (3-fold> UNL for ALT, AST and GGT, and 2-fold>ALP level)[18]. The current case patient had been receiving medication for her mixed connective tissues disease and major depressive disorder for over 5 years, with no abnormalities observed in her liver function tests. There is no information of the extent how the hepatotoxicity can raise by three drugs taken by the patient either in Korea or worldwide. However, there have been case reports associated with the those drugs: fulminant hepatic failure with quetiapine[19], and liver injury with escitalopram and alprazolam[20,21], respectively. These reports highlight the potential risk of hepatotoxicity related to these medications regardless the general belief of safety of antipsychotic drugs.

Early detection and prompt withdrawal of suspected drugs are essential principles in the management of DILI[3]. In the present case, the DILI was identified at an early stage due to the unusual manifestations reported by the patient and the author's suspicion, facilitated by the availability of laboratory testing in the medical environment. It is worth mentioning that there is sometimes an excessive focus on the risk of herbal drug-associated DILI, which can lead to a distorted

reputation for herbal medicine in Korea[22]. Furthermore, the author cautiously hypothesizes the possibility of pre-existing DILI or the development of DILI caused by chemical drugs during the treatment with herbal drugs. While it is unfortunate that not all Korean medicine (KM) clinicians have access to laboratory facilities for timely diagnosis, it is crucial for KM clinicians to remain aware of the potential occurrence of DILI caused by conventional drugs. By being mindful of this possibility, KM clinicians can take appropriate precautions and closely monitor patients for any signs of hepatotoxicity.

In summary, this case report highlights the importance of raising awareness among doctors in the KM field regarding conventional drug-induced hepatotoxicity. Through the example of DILI induced by antipsychotic drugs having the increase in the clinical use, it emphasizes the need for doctors in the KM field to be vigilant and informed about the potential risks associated with antipsychotic medications.

References

1. Pandit A, Sachdeva T, Bafna P. Drug-Induced Hepatotoxicity: A Review. *J Appl Pharma Science* 2012;2(5):233-43.
2. Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* 2005;42(6):1364-72.
3. Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. *World J Gastroenterol* 2008;14(44):6774-85.
4. Fontana RJ, Bjornsson ES, Reddy KR, Andrade RJ. The Evolving Profile of Idiosyncratic Drug Induced liver Injury. *Clin Gastroenterol Hepatol* 2023;21(8):2088-99.
5. Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. *Dig Liver Dis* 2006;38(1):33-8.
6. Zheng EX, Navarro VJ. Liver Injury from Herbal, Dietary, and Weight Loss Supplements: a Review. *J Clin Transl Hepatol* 2015;3(2):93-8.
7. Au JS, Navarro VJ, Rossi S. Review article: Drug-induced liver injury its pathophysiology and evolving diagnostic tools. *Aliment Pharmacol Ther* 2011;34(1):11-20.
8. Tran T, Lee WM. DILI: New Insights into Diagnosis and Management. *Curr Hepat Rep* 2013;12(1):53-8.
9. Cho JH, Oh DS, Hong SH, Ko H, Lee NH, Park SE, et al. A nationwide study of the incidence rate of herb-induced liver injury in Korea. *Arch Toxicol* 2017;91(12):4009-15.
10. Ramappa V, Aithal GP. Hepatotoxicity Related to Anti-tuberculosis Drugs: Mechanisms and Management. *J Clin Exp Hepatol* 2013;3(1):37-49.
11. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137(12):947-54.
12. Teschke R. Idiosyncratic DILI: Analysis of 46,266 Cases Assessed for Causality by RUCAM and Published From 2014 to Early 2019. *Front Pharmacol* 2019;10:730.
13. Lucena MI, García-Cortés M, Cueto R, Lopez-Duran J, Andrade RJ. Assessment of drug-induced liver injury in clinical practice. *Fundam Clin Pharmacol* 2008;22(2):141-58.
14. Madariaga MG. Drug-related hepatotoxicity. *N*

Engl J Med 2006;354(20):2191-3.
15. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases. Roussel Uclaf Causality Assessment Method (RUCAM) in Drug Induced Liver Injury [Internet]. Available at https://www.ncbi.nlm.nih.gov/books/NBK548272/
16. Werner FM, Coveñas R. Safety of antipsychotic drugs: focus on therapeutic and adverse effects. *Expert Opin Drug Saf* 2014;13(8):1031-42.
17. Todorović Vukotić N, Đorđević J, Pejić S, Đorđević N, Pajović SB. Antidepressants- and antipsychotics-induced hepatotoxicity. *Arch Toxicol* 2021;95(3):767-89.
18. Marwick KF, Taylor M, Walker SW. Antipsychotics and abnormal liver function tests: systematic review. *Clin Neuropharmacol* 2012;35(5):244-53.
19. Al Mutairi F, Dwivedi G, Al Ameel T. Fulminant hepatic failure in association with quetiapine: a case report. *J Med Case Rep* 2012;6:418.
20. Ng QX, Yong CSK, Loke W, Yeo WS, Soh AYS. Escitalopram-induced liver injury: A case report and review of literature. *World J Hepatol* 2019;11(10):719-24.
21. Judd FK, Norman TR, Marriott PF, Burrows GD. A case of alprazolam-related hepatitis. *Am J Psychiatry* 1986;143(3):388-9.
22. Park HM, Jang IS, Lee SD. Hepatotoxic Events Associated with Herbal Medicinal Products, Folk Remedies and Food Supplements in Korea. *J Korean Oriental Med* 2005;26(2):152-65.

사례로 본 한방임상에서 양약으로 인한 약인성간손상에 대한 인식 필요성

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초 록

목적: 본 연구는 임상에서 많은 빈도로 사용되고 있는 향정신성 약물이 간독성을 발생시킬 수 있음을 임상 예를 통해 보여줌으로써, 한의진료현장에서 이에 대한 경각심과 더불어 약인성간손상에 대한 최신 정보를 제공하고자 한다.

방법: 본 임상 예의 논문은 향정신성 약물을 사용한 후 약인성간독성의 의심과 진단 및 약물의 중단 후 증상과 간손상 효소의 개선과정을 자세히 제시하였다.

결과: 평소 혼합결합조직병으로 한방병원에서 수년 동안 침과 뜸 치료 등으로 잘 유지되고 있던 56세의 여성 환자가, 어느 날부터 갑자기 심한 피로감과 전신적 불편편함을 호소하였다. 혈액검사를 시행한 결과, 혈청 AST, ALT가 정상 경계의 2.5-배 이상 증가하였고, 최근 복용한 향정신성약물에 대한 RUCAM score가 9점으로 약인성간손상 진단에 부합하였다. 이 의심 약물들을 중지한 뒤에 주관적 불편함이 빠르게 개선되었으며, 혈청 간손상 효소 수치 또한 2주 안에 정상화되었다.

결론: 본 증례는 향정신성약물로 생길 수 있는 간손상의 전형적인 임상 예로서, 향정신성약물의 일반화된 상황에 비추어 한의원에서 환자의 진료 과정에서 하나의 중요한 고려사항을 암시한다.

중심어: 약인성간손상, 간독성, 향정신성약물, 한의학