Pharmaceutical care of vascular dementia patients with drug-induced liver injury caused by the Compound Congrong Yizhi Capsules: a case report


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Abstract. – BACKGROUND: Drug-induced liver injury (DILI) is a newly discovered adverse drug reaction of Compound Congrong Yizhi Capsules (CCYC) in the treatment of vascular dementia (VD), and targeted pharmaceutical care is urgently needed to be explored.

CASE REPORT: DILI was found in a patient who was admitted to the hospital with a diagnosis of VD after treatment with Compound Congrong Yizhi Capsules. According to the guidelines, the patient was initially treated with magnesium isoglycyrrhizinate injection. After 4 days, the clinical pharmacist monitored liver function: alanine aminotransferase (ALT): 153 IU/L, aspartate aminotransferase (AST): 160 IU/L, total bilirubin (TBil): 4.5 µmol/L, and alkaline phosphatase (ALP): 551 IU/L, which indicated that DILI was further aggravated. In addition, the increased blood pressure (156/65 mmHg) indicated the requirement to adjust the medication. Then, the hepatoprotective drugs were adjusted with reduced glutathione combined with ursodeoxycholic acid. After 12 days of treatment, the liver function was significantly improved, the clinical treatment was effective, and the blood pressure was controlled stably with no obvious adverse drug reactions.

CONCLUSIONS: With pharmaceutical care guided by clinical pharmacists, the DILI caused by Compound Congrong Yizhi capsules could be reversed to improve the clinical outcome and avoid the occurrence of serious complications.

Key Words: Compound Congrong Yizhi Capsules, Clinical pharmacists, Drug-induced liver injury, Pharmaceutical care, Vascular dementia.

Introduction

Vascular cognitive impairment (VCI) refers to a group of syndromes ranging from mild cognitive impairment to dementia. The American Diagnostic and Statistical Manual of Mental Disorders V edition classifies VCI into mild (vascular cognitive impairment no dementia) and vascular dementia (VD) according to the severity of cognitive impairment. With the accelerating process of population aging in China, the incidence, prevalence, disability and mortality of VCI are increasing continuously, which brings heavy care and economic burdens. At present, there is no definite and effective Western medicine for the intervention of early cognitive impairment or dementia.

VCI belongs to “forgetfulness and dementia” in the category of traditional Chinese medicine. The disease is located in the brain, and its target is blood stasis and phlegm obscure clear orifices, resulting in insufficiency of the mind. Traditional Chinese medicine emphasizes the importance of disease prevention and attaches great importance to early intervention, delays disease progression, and treats individuals based on syndrome differentiation, holistic treatment, and fewer adverse reactions. With the aim of treating VCI, Compound Congrong Yizhi Capsules (CCYC) were developed with the composition of Shouwu, Cistanche deserticola, Dilong, lotus leaf, and Radix rhapontici to nourish intelligence and liver, promote blood circulation and remove turbidity. The combination can improve clinical symptoms such as mental retardation, slow thinking, sluggish expression, and forgetfulness and achieve the effect of increasing intelligence. In addition, clinical studies have shown that Compound Congrong Yizhi Capsules can increase brain blood flow, reduce blood viscosity, improve energy load and cognitive function.

The adverse reactions of CCYC are mainly gastrointestinal reactions, which can be relieved without special treatment or domperidone. Drug-induced liver injury (DILI) is a newly discovered adverse drug reaction of Compound Congrong Yizhi Cap-
sules	extsuperscript{10}, and targeted pharmaceutical care urgently needs to be established. In this paper, we conducted pharmaceutical care on a case of VD patients with DILI caused by the CCYC to ensure drug safety.

**Case Presentation**

A 79-year-old female was admitted to the hospital on March 10, 2021, with the symptom of “seeing things out of thin air, nervousness and afraid for more than a year, and aggravation for a week”. The patient began to talk to herself for no apparent reason or inducement and often stood in front of the window in a daze for one year. In March 2020, the patient began to see things out of thin air and saw cats, dogs, and gods in the house. She felt nervous and scared and said that something would climb in through the window at night. Then, the patient was diagnosed with “dementia” and treated with “sleeping pills” (unknown). The condition did not improve after taking medicine irregularly. The patient was admitted to our hospital for the first time in September 2020, diagnosed with VD, and discharged after treatment with quetiapine. After that, the patient was able to adhere to the medication, and the condition was stable and controlled. In the past week, the condition worsened again without sleeping all night. Then, the patient was brought to our hospital again to request hospitalization. The patient had a history of hypertension for more than 10 years, and her blood pressure reached 193/82 mmHg, which could be controlled smoothly by taking metoprolol succinate sustained-release tablets and benazepril hydrochloride tablets. Disease history: gastric ulcer and gastric bleeding for more than 30 years and left side facial paralysis 10 years ago. There was no special personal history, family history, or bad habits, such as tobacco and alcohol use.

Physical examination: conscious, body temperature 36.7°C, pulse 72 beats/min, respiration 16 beats/min, blood pressure 165/87 mmHg, soft neck, no dry or wet rales on auscultation of both lungs, heart rate 72 points, normal heart rhythm, no pathological murmur, soft abdomen, no tenderness, rebound tenderness, liver and spleen subcostal, normal muscle strength and muscle tone of limbs, involuntary tremor of both upper extremities, and physiological reflexes exist, but pathological reflexes were not elicited.

Mental examination: clear consciousness, accurate orientation, contact and cooperation, answer to the topic, coherent thinking, elicited hallucinations, no delusions detected, emotional nervousness, acceptable near and far memory, and impaired instantaneous memory.

Intelligent examination: acceptable comprehension, reasoning and judgment ability, reduced calculation ability, and no insight.

Laboratory examination: normal thyroid function, sex hormones, coagulation function, HIV, Treponema pallidum specific antibody, blood routine, tumor biomarkers; electrocardiogram showed sinus rhythm and left ventricular high voltage. Troponin T: 0.021 µg/L, mildly high with no discomfort, such as palpitations and chest tightness. Blood biochemistry showed alanine aminotransferase (ALT) 8 IU/L, aspartate aminotransferase (AST) 10 IU/L, alkaline phospahtase (ALP) 106 IU/L, and total bilirubin (TBil) 5.3 µmol/L, and the level was normal.

Admission diagnosis: VD, grade 3 hypertension, lacunar cerebral infarction, old rib fracture.

**Treatment Process and Pharmaceutical Care**

*Initial treatment*

After the patient was admitted to the hospital, the clinical pharmacist assisted in evaluating the condition of conducting pharmaceutical care. According to the guidelines	extsuperscript{11}, quetiapine 25 mg (once per night) was applied as oral antipsychotic therapy. Considering the acceptable near-distance memory, impaired instantaneous memory, acceptable comprehension ability and reasoning and judgment ability, Compound Congrong Yizhi Capsules 1.2 g (3 times a day) were applied orally to improve intelligence. Betaloc sustained-release tablets (47.5 mg, once a day) and benazepril hydrochloride tablets (10 mg, once a day) were continuously given orally to lower blood pressure.

*Hepatoprotective therapy*

On the 6th day after admission, the result of the blood biochemical examination suggested that the liver function index was significantly higher than that at admission.

Combined with the medication history and the development of liver function damage after adding CCYC, the possibility of DILI was considered. According to the guidelines	extsuperscript{11}, it was recommended to avoid continuous application of liver-damaging drugs, and liver-protecting drugs should be added. The clinician accepted the suggestion to give 5% glucose injection 250 ml + magnesium isoglycyrrhizinate injection 100 mg (once a day) intravenous infusion of hepatoprotective therapy, stop CCYC, and monitor liver function.
**Adjustment of Hepatoprotective Therapy**

On the 9th day after admission, the liver function had not improved. The clinical pharmacist considered a history of hypertension. Magnesium isoglycyrrhizinate injection could cause pseudoadosteronism, and there is a risk of increased blood pressure, so it should be contraindicated in patients with hypertension. According to clinical acceptance, it was recommended to use 5% glucose injection 250 ml + reduced glutathione 1.8 g (once a day) for intravenous infusion of hepatoprotective therapy.

Based on the guidelines12,13, quantitative evaluation based on the causality scale-RUCAM scoring system was performed and suggested that the liver injury was mildly cholestatic. It has been reported that ursodeoxycholic acid (UDCA) is effective in the treatment of cholestatic DILI14,15. According to the Consensus on the Diagnosis and Treatment of Cholestatic Liver Diseases (2015)16, clinical pharmacists recommended the addition of 300 mg UDCA tablets (twice a day) on the basis of reduced glutathione for oral hepatoprotective therapy. On the 20th day, the liver function improved significantly. The details can be found in Table I.

**Discussion**

DILI refers to all kinds of prescription or non-prescription chemical drugs, biological preparations, traditional Chinese medicines, natural medicines, health products, dietary supplements and their metabolites, and even excipients17-19. In recent years, DILI has attracted increasing attention, and it has become not only one of the common diseases causing liver injury in clinical practice but also the main reason for the withdrawal of drugs from the pharmaceutical market and the development of new drugs20. The Compound Congrong Yizhi Capsule is a Chinese patent medicine composed of several Chinese medicines. Searching domestic and foreign literature, only one case report of liver injury caused by the drug was found21. The report showed that the main component of the drug is *Polygonum multiflorum*, and its related preparations have been determined to have specific liver toxicity22,23. After admission, Compound Congrong Yizhi Capsules were added to symptomatic treatment, and liver function indexes were obviously abnormal after taking the medicine for 6 days. Using the RUCAM scale24 to help assess the possibility of DILI, it was determined that the patient was likely to have acute cholestatic DILI caused by the polygonum multiflorum in Compound Congrong Yizhi Capsules, with RUCAM score 6 (very likely) and severity 1 (mild).

Considering the acceptable far-near memory, impaired instantaneous memory and computing ability, and lack of insight, the liver function damage drug, Compound Congrong Yizhi Capsules, was discontinued. At the same time, anti-inflammatory liver protection and prevention of liver fibrosis treatment were added. The patient was initially treated with magnesium isoglycyrrhizinate injection, which is a glycyrrhizic acid preparation with anti-inflammatory and hepatoprotective effects. It can significantly improve the abnormality of elevated serum transaminase levels caused by various types of hepatitis, reduce the pathological damage of the liver, improve the function of damaged liver cells, and have a good effect on DILI25,26. After the patient was treated with magnesium isoglycyrrhizinate injection for 4 days, the DILI was further aggravated. In addition, the increased blood pressure, serum potassium, and sodium concentrations.

### Table I. Drug regimens and pharmaceutical care for patients with DILI.

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug</th>
<th>Dosage</th>
<th>Pharmacy monitoring</th>
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<tr>
<td>6th-9th days</td>
<td>Magnesium Isoglycyrrhizinate Injection</td>
<td>100 mg (once a day) intravenous infusion</td>
<td>ALT: 153 IU/L&lt;br&gt;AST: 160 IU/L&lt;br&gt;ALP: 551 IU/L&lt;br&gt;T Bil: 4.5 umol/L&lt;br&gt;Monitor patient blood pressure, serum potassium, and sodium concentrations.</td>
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<tr>
<td>9th-20th days</td>
<td>Reduced glutathione UDCA Tablets</td>
<td>1.8 g (once a day) intravenous infusion 300 mg (2 times a day) orally</td>
<td>ALT: 24 IU/L&lt;br&gt;AST: 27 IU/L&lt;br&gt;ALP: 129 IU/L&lt;br&gt;T Bil: 6.2 umol/L&lt;br&gt;Monitor for rash, anaphylactic shock, gastrointestinal reactions. Monitor platelet count, constipation, allergies, tachycardia.</td>
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pressure (156/65 mmHg) indicated the requirement of adjusting the medication. After reviewing the literature and related guidelines, the clinical pharmacist found that UDCA was recommended for the treatment of cholestatic DILI. Therefore, the hepatoprotective drugs were adjusted with reduced glutathione combined with UDCA.

Conclusions

This study found that the Chinese patent medicine Compound Congrong Yizhi Capsules contain *Polygonum multiflorum*, which can cause DILI. It is recommended to add a liver injury warning in the drug insert of Compound Congrong Yizhi Capsules. At the same time, in the process of diagnosis and treatment, regarding the DILI caused by CCYC, the clinical pharmacist should actively communicate with physicians, consult relevant literature, analyze the causes of liver damage, and promptly advise physicians to stop the suspected drugs with the potential of liver injury, participate in the formulation of the hepatoprotective therapy, and conduct pharmaceutical care throughout the process to re-adjust the hepatoprotective therapy according to the individual situation to improve the clinical outcome and avoid the occurrence of serious complications.

Authors’ Contributions

Conceptualization, Zhiqiang Du and Yuan Shen; methodology, Ying Jiang, Rongrong Lu, Qin Zhou and Hao Hao Zhu; writing—original draft preparation, Zhiqiang Du and Hao Hao Zhu; writing—review and editing, Yuan Shen and Hao Hao Zhu. All authors have read and agreed to the published version of the manuscript.

References

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