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LETTER TO THE EDITOR

An unwanted complement: Rare case of potential liver injury induced by an interaction between ginseng and atorvastatin

We read with interest the recent article by Kim et al[1] on the influence of fermented red ginseng on cytochrome P450 enzymes. We would like to bring to attention how ginseng ingestion can potentially result in drug-induced liver injury (DILI) by mechanisms other than direct injury. This clinically relevant phenomenon can be easily identified in order to prevent life-threatening complications.

We present a case of an 82-year-old male with likely secondary atorvastatin DILI after longstanding atorvastatin, which was precipitated only after concomitant ginseng intake. The patient had a background of ischaemic heart disease, carotid artery disease, and hypercholesterolaemia. His regular medications, which have not changed for 5 years, were atorvastatin 80 mg nocte, atenolol 50 mg mane, and aspirin 100 mg mane. Baseline liver tests (LTs) were all within normal range. Routine blood tests performed 6 months later revealed markedly elevated LTs with alanine aminotransferase 931 U/L (normal <55 U/L), aspartate aminotransferase 658 U/L (<55 U/L), alkaline phosphatase 253 U/L (<110 U/L), gamma-glutamyl transpeptidase 1,477 U/L (<60 U/L), bilirubin 40 μmol/L (<21 μmol/L), and albumin 35 g/L (33-48 g/L). His international normalised ratio was normal at 1.1. His creatine kinase (CK) was also elevated at 350 U/L (<250 U/L). Symptomatically, the patient experienced lethargy, myalgias, and early satiety. He had no abdominal pain, rash, or fever. His physical examination found no stigmata of chronic liver disease, organomegaly, or hepatic decompensation.

The patient was initially referred to a gastroenterologist who investigated for secondary causes of liver injury. This revealed previous exposure to hepatitis B, but the remainder of the viral hepatitis serology and autoimmune liver disease markers were negative. In the setting of significant hepatitis, his serum ferritin was elevated at 7,240 μg/L (normal <400 μg/L), with a transferrin saturation of 76% (normal 15%-50%). However, his haemochromatosis gene tests for C282Y, H63D, and S65C mutations were negative. An abdominal ultrasound revealed a normal appearance of the liver with a mildly dilated common bile duct and pancreatic duct. This was further assessed with computed tomography, magnetic resonance cholangiopancreatography, and endoscopic ultrasound, which excluded obstructing lesions or masses.

After 18 months of persistently deranged LTs and the above investigations not yielding a diagnosis, the patient was referred to a hepatologist. A thorough medication history discovered that he had commenced an over-the-counter complementary medication consisting of a combination of Siberian ginseng and silymarin 1 week prior to his LTs becoming deranged. Given the temporal relationship between the patient's laboratory abnormalities and commencement of the complimentary medication, DILI was suspected. The patient scored 7 on the mixed liver injury RUCAM scale, consistent with a probable adverse drug reaction.[2] The RUCAM score for atorvastatin was also 7, while the scores for aspirin and atenolol were both consistent with an unlikely drug reaction. After cessation of both the complementary medication and atorvastatin, there was resolution of the patient's symptoms as well as complete and rapid normalisation of his LTs, CK, and iron studies within 2 months. This patient provided verbal and written informed consent to report his case.

Ginseng is a popular herbal medication and extract derived from the roots of a plant in the genus *Panax*. Silymarin is an extract from the herb *Silybum marianum* (milk thistle), which has been used widely to treat liver disease. Although both herbs have been used for centuries, there have been no published reports of either ginseng or silymarin causing DILI when used alone. Indeed, many components of ginseng have exhibited hepatoprotective effects, while silymarin is an accepted antidote for patients with hepatotoxicity after *Amanita phalloides* ingestion.[3]

Several complementary medications are known to have an inhibitory effect on CYP3A4, including grapefruit juice and green tea extract (*Camellia sinensis*). Ginseng also causes inhibition of CYP3A4, particularly via its intestinal metabolites.[4] Although silymarin has been found to inhibit CYP3A4 in vitro, in vivo studies have not shown convincing enzyme inhibition.[5] Therefore, ginseng is likely to only cause DILI when taken concomitantly with a potentially hepatotoxic medication that is metabolised by CYP3A4. Such interactions with imatinib and raltegravir have previously been reported.[3] Atorvastatin is metabolised by CYP3A4 in the liver and intestine and eliminated via the OATP1B1 transporter.[6] Inhibition of hepatic CYP3A4 is proposed to increase the plasma area under the curve of atorvastatin by 3.3-fold, which can result in hepatotoxicity and myositis, as seen in our patient.[6] There is also some data that ginseng inhibits the OATP1B1 transporter, which may result in similar toxicity because of impaired elimination of atorvastatin.[7] In our patient, it is difficult to ascertain whether the inhibition of CYP3A4 or OATP1B1 (or both) was responsible for hepatotoxicity. Nonetheless, since the patient had tolerated atorvastatin for at least 5 years without toxicity prior to commencing ginseng, this suggests a likely herb-drug interaction. As alternatives, rosuvastatin, fluvastatin, and pravastatin are minimally metabolised by CYP3A4, thus have lower risk of significant pharmacokinetic drug interactions.[6]

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We hope this case serves as a valuable reminder of the importance of taking a thorough medication history, including over-the-counter drugs and herbal supplements. This case also highlights another mechanism of DILI from herbal medications occurring due to herb-drug interactions on other concomitant medications, rather than direct hepatotoxicity.

COMPETING INTERESTS

There are no competing interests to declare.

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