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Petroselinum crispum, a commonly consumed food, affects sirolimus level in a renal transplant recipient: a case report

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Abstract

Sirolimus is an immunosuppressive drug used to prevent graft rejection. Therapeutic drug monitoring is required as with other immunosuppressive drugs. Previous studies have shown the interactions between sirolimus and drugs that affect the activity of cytochrome P450 3A4 and P-glycoprotein. There is an increasing tendency for the use of herbal remedies in many countries. Medicinal herbs are rich sources of natural bioactive compounds that could interact with drugs. Parsley, *Petroselinum crispum*, is a food, spice, and also a medicinal herb. We report a case of a renal transplant recipient who had a supratherapeutic blood level of sirolimus due to consuming excessive parsley to highlight a possible herb–drug interaction. This is the first case report describing sirolimus–parsley interaction. Herb–drug interactions are especially important for drugs with a narrow therapeutic window. For this reason, healthcare professionals should question all patients, especially transplant patients, about the use of herbs or herbal products and report interactions.

Plain Language Summary

Parsley, a commonly consumed food, affects the level of an important drug in a renal transplant recipient: A case report

Sirolimus is a drug that suppresses the immune response used to prevent organ rejection in people who have had kidney transplants. In order to reach the optimum balance between therapeutic efficacy and adverse effects, sirolimus blood levels should be closely monitored. Previous studies have shown the interactions between sirolimus and drugs that affect the activities of metabolizing enzymes and transporter proteins. Parsley is a food, spice, and also a medicinal herb. Medicinal herbs are rich sources of natural bioactive compounds that could interact with a prescription drug. We report a case of a renal transplant recipient who had a rise in the blood level of sirolimus due to the ingestion of an excessive amount of parsley to highlight possible herb–drug interaction.

Keywords: drug interaction, herb–drug interaction, medicinal herb, parsley, rapamycin, renal transplantation, sirolimus, therapeutic drug monitoring

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Introduction

Sirolimus, a macrolide compound isolated from *Streptomyces hygroscopicus*, was introduced in the late 1990s. The demonstration of the potent immunosuppressive activity of sirolimus has led to its usage for the prevention of graft rejection in kidney transplantation. Sirolimus binds to a protein (FK binding protein-12) and this complex

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inhibits the activation of the mammalian target of rapamycin, which is a key regulatory kinase for cell cycle progression, thus suppressing cytokine-driven T-cell proliferation.[1]

Sirolimus displays a synergistic action with calcineurin inhibitors and a distinctive mechanism of action from calcineurin inhibitors, which are indispensable immunosuppressive agents in kidney transplantation. In addition, sirolimus has some advantages compared with calcineurin inhibitors: sirolimus causes less nephrotoxicity, has anticancer effects, and allows once-daily administration.[2,3]

In recent years, the increasing use of herbs and herbal medicines for primary healthcare and chronic diseases has been widely reported in many countries. One of the important safety concerns with the widespread herbal remedy use is the potential interactions of herbal medicines with prescription drugs that may augment or inhibit the effect of the drugs. This is especially important for drugs with a narrow therapeutic window.[4]

Parsley, *Petroselinum crispum*, is commonly consumed as part of the diet. Parsley, which is also a medicinal herb, is stated to have carminative, antispasmodic, diuretic, emmenagogue, expectorant, antirheumatic, and antimicrobial properties.[5] It was reported to reduce the liver content of cytochrome P450 (CYP P450) isoenzymes in an animal study.[6]

The drug interaction probability scale (DIPS) is a tool to assess the causal relationship between interactions and adverse events. DIPS consists of 10 questions each with three response options to which a score is assigned.[7] A study reported the internal validity of the adapted DIPS for adverse effects associated with dietary and herbal supplements–drug interactions.[8]

PubMed database and Google Scholar were searched using the key terms 'parsley', 'sirolimus', and 'herb–drug interaction' up to 15 October 2020. Articles published in the English language were reviewed.

Herein, we report a possible interaction between parsley and sirolimus in a kidney transplant patient leading to supratherapeutic blood concentrations of sirolimus.

Case report

A 19-year-old woman was diagnosed with chronic kidney disease secondary to juvenile nephronophthisis. In 2013, the patient underwent renal transplantation from her mother. Postrenal transplantation immunosuppressive therapy of the patient comprised a triple drug combination of prednisolone, tacrolimus, and mycophenolate mofetil. The patient's medical history included pseudotumor cerebri and hypophosphatemic rickets. Her other significant medications included enalapril 10 mg once daily, calcitriol 0.5 µg once daily, and 1000 mg elemental phosphorus containing effervescent tablet twice daily.

The patient received tacrolimus-based immunosuppression until April 2016, and then the treatment was switched from tacrolimus to sirolimus due to evident tremors. Immunosuppressive treatment of the patient was under control with sirolimus 1.5 mg twice daily, mycophenolate mofetil 540 mg twice daily, and prednisolone 10 mg once daily since 2016. In July 2020 at an out-patient follow-up visit, the patient's blood level of sirolimus (14.8 ng/ml) was seen to be high. Previous blood sirolimus levels ranged from 2 ng/ml to 4 ng/ml. The concentration–time profile is shown in Figure 1. At that time the serum creatinine level was 74.27 µmol/L and was stable. Other factors that could increase the sirolimus level were questioned and ruled out. No new drug that could influence the sirolimus levels had been administered. The next day testing of the blood sirolimus level (14.6 ng/ml) confirmed that there was no laboratory mistake. A more detailed history was taken from the patient. It was learned that she regularly made a juice of parsley and consumed the parsley juice daily to lose weight and promote her health. The juice, which contained about 30 g of parsley, was consumed by the patient for 7 days.

She was asked to pay attention to a balanced diet and avoid consuming excessive amounts of a single vegetable, fruit, and herb for a week. A week later, the patient's sirolimus level (4.6 ng/ml) was seen in the normal range. No alternative causes for the rise in sirolimus exposure were found. Assessment with DIPS was found to be five, which showed this interaction to be probable.

In addition, the patient's low-density lipoprotein and triglyceride levels showed a spontaneous decline by 6% and 17%, respectively, 3 months

after the peak level of sirolimus, which implied that sirolimus levels were associated with an elevation in cholesterol and triglyceride. The probability of this reaction to sirolimus is 'probable' based on Liverpool Adverse Drug Reaction Causality Assessment Tool.[9]

Discussion

In this patient, we reported the possible effect of parsley juice on the level of sirolimus. We propose that in this patient blood concentration of sirolimus increased because of the parsley juice she had used intensively to lose weight. The normalization of the drug level when parsley juice was stopped also supports this consideration. In addition, DIPS was performed and expert opinions were received. According to these data the probability of herb–drug interaction is reasonable.

Experimental animal and clinical data have shown that sirolimus is a critical-dose drug requiring therapeutic drug monitoring to minimize drug-related toxicities and maximize efficacy. For this reason, close therapeutic drug monitoring is recommended for sirolimus, which has a narrow therapeutic window similar to other immunosuppressive drugs.[2,10] The factors that could affect the exposure of sirolimus are age, sex, ethnicity, presence of hepatic failure, and administration of the drug with food. In addition, drug interaction studies reported pharmacokinetic alteration of sirolimus when some drugs are co-administered with sirolimus, which is a substrate for both CYP P450 3A4 enzyme (CYP3A4) and P-glycoprotein (P-gp), and undergoes extensive first-pass extraction. Drugs that are known to inhibit or induce these proteins located at the gut mucosa and liver may potentially affect sirolimus exposure.[11]

Some known inhibitors of CYP3A4 and P-gp, such as voriconazole,[12] ketoconazole,[13] and diltiazem,[14] were reported to increase the concentration of sirolimus. The Food and Drug Administration (FDA) prescribing information indicates that co-administration of voriconazole increases the area under the concentration curve (AUC) and the maximum plasma concentrations of sirolimus an average of 11-fold and 7-fold, respectively, and concomitant use of voriconazole with sirolimus stated contraindicated.[12] A pharmacokinetic study has shown that ketoconazole causes a 10-fold increase in the bioavailability of sirolimus.[13] The interactions between the azole antifungals and

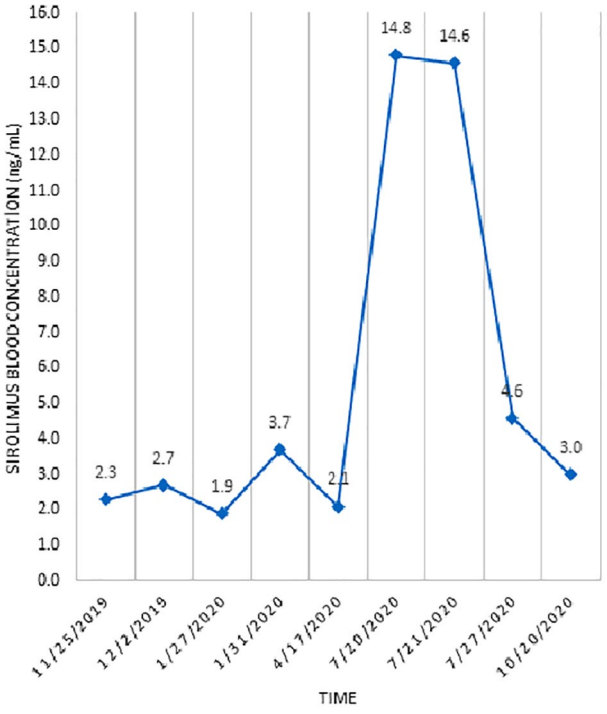

Figure 1. Sirolimus blood concentration *versus* time.

sirolimus are established and of clinical importance. Manufacturers recommend therapeutic drug monitoring and a possible dose adjustment for sirolimus if some drugs like diltiazem, which inhibits CYP 3A4 and P-gb activity weakly or moderately, are used concurrently with sirolimus.[15]

Due to being natural, herbs and herbal products are thought safer and more efficacious than pharmaceutically derived medications. Contrary to this safety perception, herb–drug interactions could lead to serious adverse effects.[16] For example, more than 85 drugs have been reported that may interact with grapefruit, which contains a complex mixture of several hundreds of ingredients including furanocoumarins and flavonoids. Most clinically important interactions of grapefruit result in an increase in drug exposure and adverse events of which more than half are serious.[17]

There are a few studies that state interactions between sirolimus and herbs. A phase I study reported grapefruit juice increased sirolimus AUC approximately 350%.[18] A pharmacokinetic study with 112 Chinese adult renal transplant recipients stated clearance of sirolimus decreased

in those patients with abnormal alanine aminotransferase (ALT) values who were taking herbal formulations containing glycyrrhizin, which is a constituent of *Glycyrrhiza glabra* (liquorice) root or silymarin, which is a standardized extract of the milk thistle seeds.[19] A pharmacokinetic study in healthy volunteers given *Schisandra chinensis* extract, a traditional Chinese medicine, reported the oral bioavailability of sirolimus increased almost 2-fold.[20]

The pharmacological and toxicological properties of parsley are primarily associated with the volatile oil (apiole, myristicin), flavonoid, and furanocoumarin constituents.[5] Apigenin, the dominant type of flavonoid in parsley, has been reported to possess the ability to inhibit CYP3A4 and P-gp and thus, it may be involved in drug interactions.[21] There is scarce information about parsley–drug interactions. Lithium toxicity has been reported in one patient taking a herbal diuretic containing parsley.[22] Another patient taking warfarin was observed to increase the international normalized ratio (INR) after stopping a supplement containing various herbs, including parsley.[23] A study in mice found that parsley potentiated and prolonged the effects of aminophenazone, paracetamol, and pentobarbital. Parsley extract reduced the liver content of CYP 450, which is the most important enzyme family for drug metabolism.[6] Treatments with doxorubicin, parsley leaf juice, and their combination were reported to significantly reduced the content of CYP P450 in an animal study.[24] Enzyme inhibition could result in the reduced metabolism of an affected drug, so that it may begin to accumulate within the body. Unlike enzyme induction, which may take several days or even weeks to develop fully, enzyme inhibition can occur within 2–3 days, resulting in the rapid development of toxicity.[25] In our patient, blood sirolimus level was increased unexpectedly, despite the daily dosage of sirolimus being the same as at the previous visit. The only change was the parsley-containing drink she started to lose weight. Also, the time course of drug level increase is consistent with enzyme inhibition.

Conclusion

Herb–drug interactions could represent a serious clinical problem during the management of patients treated with some drugs. These interactions, which could lead to drug toxicity or graft function loss, are especially important for some special patient populations like transplant patients. There is a lack of clinical research assessing the efficacy and safety of medicinal herbs including parsley. Parsley should not be consumed in a quantity that markedly exceeds the amounts used in a regular diet, as excessive ingestion may result in drug interactions and toxicity. There is little known about herb–drug interactions so it is logical to be alert about medicinal herbs and herbal supplementations that may have pharmacological effects. Further researches, including prospective studies on medicinal herbs, are needed to investigate interactions with drugs.

Author contributions

MK drafted the initial and final versions of the manuscript. MSA drafted the initial version of the manuscript. NSK provided intellectual review of the manuscript as well as involvement in the care of this patient. TY, SRY, and YE were involved in patient care as nephrologists and contributed towards the intellectual review of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Informed consent

Written informed consent for patient information was provided by the patient.

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