Case Reports

Journal of INTERNATIONAL MEDICAL RESEARCH

The influence of excessive consumption of liquorice on phenprocoumon (Marcumar®): a case report

Journal of International Medical Research
49(11) 1–6

DOI: 10.1177/03000605211049649
journals.sagepub.com/home/imr
SAGE

Hermann Casper Roemer, Luisa Kunz and Suzan Botzenhardt

Abstract

Here, the case of a 92-year-old female patient, who was diagnosed with atrial fibrillation and treated with phenprocoumon (Marcumar®), is reported. Pre-existing comorbidities were arterial hypertension, coronary heart disease, diabetes mellitus type 2, mild senile dementia and renal insufficiency. Despite treatment with phenprocoumon (Marcumar®), the patient experienced an ischaemic stroke. Her measured international normalized ratio (INR)-values during the months before the stroke were within the therapeutic range of 2–3, then suddenly decreased to 1.25. A retrospective inquiry failed to identify any significant changes in behaviour or therapy adherence, other than the consumption of 1.5 kg (3.3 lb) of hard-boiled candy liquorice in the days leading up to the stroke. The sudden decrease in INR-values may be explained by the influence of liquorice and its compounds on the pharmacokinetics of phenprocoumon (Marcumar®). In this context, the most important factors are the susceptibility of vitamin K antagonists to nutrition or metabolic irregularities, the influence of liquorice on the function of isoenzymes of the cytochrome P450 family that may lead to reduced bioavailability of phenprocoumon, and the influence of liquorice on peroxisome proliferator-activated receptor alpha transactivation.

Keywords

Liquorice, phenprocoumon, ischaemic stroke, cytochrome P450, case report, vitamin K antagonists, PPARα

Date received: 28 May 2021; accepted: 9 September 2021

Institute for General Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany

Corresponding author:
Suzan Botzenhardt, Institute for General Medicine, University Hospital Essen, University Duisburg-Essen, Pelmanstrasse 81, 45131 Essen, Germany.
Email: Suzan.Botzenhardt@uk-essen.de

Introduction

Liquorice is a herbal substance found in the root of *Glycyrrhiza glabra* that has long been recognised for its medicinal properties.[1] Beside potentially valuable pharmacological effects in inflammation, cardiovascular diseases, peptic ulcers and antitumor treatments,[2] a lot of research has been conducted to systematically analyse both the beneficial and adverse effects associated with liquorice.[3] A review investigating the toxic effects of liquorice and glycyrrhizin, including cytotoxicity, genotoxicity, mutagenicity, carcinogenicity and developmental toxicity, in different acute and chronic states, reported that liquorice and glycyrrhizin salts are moderately toxic.[4] The most important side effects were found to be hypertension and hypokalaemic-induced secondary disorders, and side-effects were further increased by factors including hypokalaemia, hypertension, old age, female sex, and decreased 11-beta-hydroxysteroid dehydrogenase type 2 activities. By inhibiting 11-beta-hydroxysteroid dehydrogenases, glycyrrhizin increases the half-life of corticosteroids, initiating hyperaldosteronism and hypercortisolism.[4]

Interactions between herbal substances and medications in humans have been widely discussed;[5] however, to the best of the present authors' knowledge, interactions between liquorice and phenprocoumon (Marcumar®) have not been described to date. Phenprocoumon belongs to the group of 4-hydroxycoumarins that also includes warfarin.[6] Coumarin anticoagulants, including phenprocoumon, are vitamin K antagonists that exhibit their anticoagulant effect by inhibition of vitamin K epoxide reductase, thereby inhibiting the synthesis of functional prothrombin and factors II VII, IX and X in the liver. Phenprocoumon is mainly indicated for use in stroke prevention in cases of atrial fibrillation, but is also used in the treatment and prophylaxis of thrombosis and embolism, in heart valve replacement, and for the long-time treatment of myocardial infarction when there is an increased risk of thromboembolic complications.[6,7]

Case report

The present report describes the case of a 92-year-old female patient who was diagnosed with atrial fibrillation in 2009 and was being treated with phenprocoumon (Marcumar®) for stroke prevention. Pre-existing comorbidities were arterial hypertension, coronary heart disease, diabetes mellitus type 2, mild senile dementia and renal insufficiency. Ongoing treatment of comorbidities comprised the following: 95 mg metoprolol succinate, twice daily; 10 mg torasemide, once daily; 20 mg omeprazole, once daily; 2 mg glimepiride, once daily; 20 mg furosemide, once daily; and 80 mg febuxostat, once daily; combined with speech therapy and physiotherapy. Despite being treated with phenprocoumon (Marcumar®), the patient experienced an ischaemic stroke in 2016. The patient presented at Philippusstift Hospital, Hülsmannstrasse 17, 45355 Essen, Germany in August 2016 with the first clinical signs of stroke (hemiplegia, gaze turn to the right, anarthria, and National Institutes of Health Stroke Scale score of 13). Cranial computed tomography confirmed occlusion of the right middle cerebral artery in the distal M1 segment. Lysis of the thrombus using systematic treatment was not performed. Her measured international normalized ratio (INR) values during the months prior to stroke were within the therapeutic range of 2–3, but on the first day of hospitalisation due to stroke, her INR was found to have decreased to 1.25. During hospitalization, the patient's INR values normalized (Table 1).

The patient's sodium and potassium levels were within normal range throughout

Table 1. International normalized ratio (INR) values during hospitalization in a 92-year-old female patient treated with phenprocoumon who had experienced an ischaemic stroke.

	Date						
Parameter	29 August	25 September	26 September	27 September	28 September	29 September	30 September
INR	1.25	1.32	1.46	1.78	2.2	2.59	2.77

Table 2. Liver and kidney values during hospitalization in a 92-year-old female patient treated with phenprocoumon who had experienced an ischaemic stroke.

	Date						
Parameter	29 August	30 August	5 September	8 September	9 September	12 September	16 September
Creatinine, mg/dl	2.63	2.19	1.60	1.67	1.77	1.76	1.76
GFR, ml/min	<20	21	30	29	27	27	27
GGT, U/l	49		64				
GPT, U/l	27		53				
GOT, U/l	22						
AP, U/l	111		121				

GFR, glomerular filtration rate; GGT, γ-glutamyl transferase; GPT, glutamate pyruvate transaminase; GOT, glutamate oxaloacetate transaminase; AP, alkaline phosphatase.

the hospital stay (sodium, 137–145 mmol/l; potassium, 3.92–4.82 mmol/l), and renal parameters were elevated but consistent with her present diagnosis of renal insufficiency. These values improved during hospitalization, and at discharge they matched those recorded at an outpatient appointment prior to the drop in INR and ischaemic stroke. Liver parameters were slightly pathological, but stable during hospitalization and consistent with the patient's previous morbidities (Table 2). Phenprocoumon (Marcumar®) treatment, together with physiotherapy and speech therapy, were maintained during hospital stay and continued following hospital discharge. At the latest follow-up, the patient was able to walk a distance of 80 m, had no further speech or swallowing difficulties, and had no further stroke symptoms.

A retrospective inquiry revealed that the patient received daily personal care from her daughter, and thus had a controlled daily routine, and did not reveal any significant changes in the personal behaviour of the patient or to therapy adherence that may have led to an ischaemic stroke, other than the consumption of 1.5 kg (3.3 lb) of hard-boiled candy liquorice in the days leading up to the stroke. In the present case, the liquorice candy contained liquorice extract, as well as ammonium chloride, sugar, flavouring, and colourant E153. As a result, an intensive literature review was performed to investigate whether the consumption of liquorice candy may explain a sudden fall in INR values prior to the stroke. The PubMed and Ovid Medline databases were searched for articles published between 2001 and 2021 using the terms 'Liquorice' AND/OR 'phenprocoumon' AND/OR 'ischaemic stroke' AND/OR 'herbal substances' AND/OR 'cytochrome P450' AND/OR 'vitamin K antagonists' AND/OR 'PPARα'. Articles that focused on interactions between phenprocoumon and herbal substances in patients and animals were selected from the search

results. Following review, articles that were most relevant in terms of quality and mechanistic insight into the interaction between phenprocoumon and liquorice were selected for discussion. The search was conducted by two independent investigators (HCR and SB).

The University Hospital Essen does not require institutional ethics review board approval for reporting individual cases or case series, thus ethics approval was not obtained. Written informed consent was obtained from the patient for publication of the case report, and the reporting of this study conforms to CARE guidelines.[8]

Discussion

The use of vitamin K antagonists, including phenprocoumon, is complicated by a narrow therapeutic index and an unforeseeable dose-response relationship, giving rise to frequent bleeding complications or insufficient anticoagulation. These large dose response variations are significantly influenced by pharmacokinetic aspects that are defined by genetic, environmental and possibly other unknown factors.[7] Therefore, vitamin K antagonists are well-known for being very prone to interference, particularly by nutrition or metabolic irregularities.[2] This fact may provide initial evidence to suggest that liquorice, as herbal drug, might affect the pharmacokinetics of the vitamin K antagonist phenprocoumon.

When reviewing the literature for comparable interactions between liquorice and medications, members of the cytochrome P450 (CYP) family of enzymes were found to be widely discussed in terms of being affected by a very broad range of orally administered drugs, including warfarin, and several foods and herbs, including liquorice.[9–11] The major biotransformation enzyme, CYP, has over 1000 isoenzymes, of which five (CYP3A4, CYP2D6, CYP2C9, CYP2C19 and CYP1A2) metabolize 90% of all drugs.[10] Among these, CYP1A2, CYP2C9 and CYP3A4 are the most relevant enzymes that interfere with the anticoagulant effect of 4-hydroxycoumarins, such as phenprocoumon and warfarin.[11] This provides further evidence to suggest that liquorice and its principal components may influence the activity of relevant members of the CYP enzyme family, and thus, may influence the efficiency of phenprocoumon.

The enzymes CYP2C9, CYP3A4 and CYP1A2 have been analysed to determine interindividual variation in warfarin dose requirement, as they may contribute to oxidative metabolism of warfarin. The most important of these enzymes is reported to be CYP2C9, as several studies have shown the CYP2C9*2 or CYP2C9*3 variant alleles result in decreased enzyme activity, and this has been associated with a significant decrease in mean warfarin dose requirement.[11] Polymorphisms in the CYP3A4 or CYP1A2 isoenzymes may also affect warfarin dose requirement. The molecular basis of warfarin resistance remains unclear, but may be due to unusually high CYP2C9 activity or to aberrant vitamin K epoxide reductase (pharmacokinetic or pharmacodynamic resistance, respectively). Available information on genetic factors affecting other anticoagulants is scarce, but acenocoumarol dose requirement appears to be affected by the CYP2C9 genotype.[11] Besides the influence of CYP2C9 on warfarin, concomitant oral administration of several foods and herbs is known to affect drug metabolism in humans by inhibiting CYP3A4 activity.[12] For example, liquorice extract has been shown to exert potent CYP3A4 inhibitory activity with a half maximal inhibitory concentration (IC50) value of 0.022 mg/ml *in vitro*.[12] A further *in vitro* study showed the inhibitory effects of licochalcone A, a major bioactive compound in herbal liquorice, on seven CYP isoforms, including

CYP1A2, CYP2C9 and CYP3A4, in human liver microsomes.[13] Both *in vitro* experiments showed an inhibition of CYP activity, whereas an *in vivo* study showed that the oral bioavailability of Ciclosporin A (CsA) was drastically reduced in rats in response to liquorice extract and glycyrrhizin, because glycyrrhetic acid activated the functions of P-glycoprotein and CYP3A4 enzymes, resulting in faster inactivation of CsA.[9] These enzymes, and particularly CYP3A4, play a crucial role in the metabolism of phenprocoumon, which is mainly metabolized by CYP3A4.[14] Therefore, in the present patient, liquorice may have stimulated the function of CYP3A4, or other enzymes of the CYP family, leading to reduced bioavailability of phenprocoumon through increased phenprocoumon metabolism, which may explain the sudden fall of INR values in the patient.

Interaction between phenprocoumon, CYP3A4 and the nuclear receptor peroxisome proliferator-activated receptor alpha (PPARα), which influences expression of the *CYP3A4* gene, may also be affected by liquorice and therefore might have played a role in the present case. One study investigating whether PPARα gene polymorphisms and the CYP3A4*22 allele are associated with phenprocoumon dose variability found a relationship between variations of PPARα and the required dose of phenprocoumon.[14] A further study investigating PPARα activation by culinary herbs and spices *in vitro* showed that nine of 34 tested plant extracts, including liquorice, exhibited low to moderate PPARα transactivation.[15] Therefore, it appears that liquorice may also affect PPARα transactivation, which may lead to a required adjustment of the phenprocoumon dose.

In conclusion, the interactions between herbal substances and medications in humans have been extensively studied. In the context of the present case, the sudden fall of INR values may be explained by the influence of liquorice and its compounds on the pharmacokinetics of phenprocoumon (Marcumar®), particularly as no significant changes in the personal behaviour or therapy adherence were identified in this patient prior to the ischaemic stroke, and as she received daily personal care from her daughter and had a controlled daily routine. The most important factors in this case are the susceptibility of vitamin K antagonists to nutritional or metabolic changes, and the influence of liquorice on the function of isoenzymes of the CYP family and on PPARα transactivation. The present case highlights the need to monitor herbal intake in the medical record in order to document potential drug interactions and to avoid potential medical emergencies.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: Funding to publish this research was received from the Open Access Publication Fund of the University of Duisburg-Essen.

ORCID iD

Suzan Botzenhardt https://orcid.org/0000-0002-7648-086X

References

1. Li JY, Cao HY, Liu P, et al. Glycyrrhizic acid in the treatment of liver diseases: literature review. *Biomed Res Int* 2014; 2014: 872139.
2. Zineh I, Pacanowski M and Woodcock J. Pharmacogenetics and coumarin dosing – recalibrating expectations. *N Engl J Med* 2013; 369: 2273–2275.
3. Hosseinzadeh H and Nassiri-Asl M. Pharmacological effects of *Glycyrrhiza* spp.

and its bioactive constituents: update and review. *Phytother Res* 2015; 29: 1868–1886.
4. Nazari S, Rameshrad M and Hosseinzadeh H. Toxicological effects of *Glycyrrhiza glabra* (licorice): a review. *Phytother Res* 2017; 31: 1635–1650.
5. Isbrucker RA and Burdock GA. Risk and safety assessment on the consumption of licorice root (*Glycyrrhiza* sp.), its extract and powder as a food ingredient, with emphasis on the pharmacology and toxicology of glycyrrhizin. *Regul Toxicol Pharmacol* 2006; 46: 167–192.
6. Verhoef TI, Redekop WK, Daly AK, et al. Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. *Br J Clin Pharmacol* 2014; 77: 626–641.
7. Ufer M. Comparative pharmacokinetics of vitamin K antagonists. *Clin Pharmacokinet* 2005; 44: 1227–1246.
8. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Glob Adv Health Med* 2013; 2: 38–43.
9. Hou YC, Lin SP and Chao PDL. Liquorice reduced cyclosporine bioavailability by activating P-glycoprotein and CYP 3A. *Food Chem* 2012; 135: 2307–2312.
10. Sychev DA, Ashraf GM, Svistunov AA, et al. The cytochrome P450 isoenzyme and some new opportunities for the prediction of negative drug interaction in vivo. *Drug Des Devel Ther* 2018; 12: 1147–1156.
11. Daly AK and Aithal GP. Genetic regulation of warfarin metabolism and response. *Semin Vasc Med* 2003; 3: 231–238.
12. Tsukamoto S, Aburatani M, Yoshida T, et al. CYP3A4 inhibitors isolated from licorice. *Biol Pharm Bull* 2005; 28: 2000–2002.
13. He W, Wu JJ, Ning J, et al. Inhibition of human cytochrome P450 enzymes by licochalcone A, a naturally occurring constituent of licorice. *Toxicol In Vitro* 2015; 29: 1569–1576.
14. Botton MR, Bandinelli E, Leiria TLL, et al. PPARA gene and phenprocoumon. *Pharmacogenet Genomics* 2015; 25: 93–95.
15. Mueller M, Beck V and Jungbauer A. PPARα activation by culinary herbs and spices. *Planta Med* 2011; 77: 497–504.

DOI: 10.1177/03000605211049649
URN: urn:nbn:de:hbz:465-20220722-142110-8