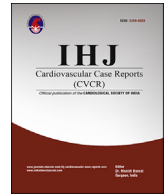




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Case Report

Case report on interaction of warfarin with herbal medicine “kadha”

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ABSTRACT

With the increase in the number of COVID-19 cases worldwide, and a lack of proper preventive and therapeutic treatment, herbal medicine is frequently used by many people to increase the immune status of the body. We describe a case of a 56 year-old-man stabilized on warfarin (7 mg daily) from 12 years, experienced an elevated international normalized ratio (INR) of 5.45 after the consumption of an Indian traditional herbal drink “kadha” as a precautionary measure to prevent COVID-19 infection.

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Introduction

The coronavirus pandemic is one of the foremost global health crisis and the greatest challenge to mankind. It has influenced people more towards complementary and alternative medicine due to the lack of definitive treatment. However, the inclination of patients towards alternative medicine, including herbal or ayurvedic medicine may expose them to harmful herbal-drug interactions by interacting with their existing medications.

The probability of herb-drug interactions is more when compared to drug-drug interactions as the drug may constitute only a single chemical entity whereas herbs may contain a mixture of different pharmacological constituents.¹ Since the start of the COVID 19 pandemic, people are very much acquainted with improving their immune system naturally, which has lead them to the consumption of various herbal products in their diet as a measure of improving their immunity.

Warfarin is one of the commonly used antithrombotic agent for the prevention of cardiovascular events.² It is considered to be one of the most obligatory treatment for patients with valve replacement surgery to prevent the risk of thromboembolic complications.³ However owing to the narrow therapeutic index of warfarin, it has a very high probability of interacting with various other medications including herbal and ayurvedic therapies.

Case report

A 56-year-old man with a history of Acyanotic Congenital Heart

disease had been receiving a daily warfarin dose of 7mg prophylactically, after an aortic valve replacement in 2009. He had no other medical conditions and his other medications included were Metoprolol Succinate 50 mg once/day and Losartan 50 mg once/day. The patient was adherent in taking warfarin regularly and maintained a target INR (2.0–3.0) on a daily maintenance dose of 7 mg (49 mg per week) for 12 years. The patient was compliant regarding the appointment visits and frequent INR monitoring as per the physician's advice.

On the morning of August 25, 2020, the patient developed ecchymosis on his right hand and consequently attended the hospital (Fig. 1). As a part of his regular INR monitoring during his clinic visits, his INR increased to 5.49. He stated that he took only prescribed medications and denied any changes in lifestyle or diet. On being questioned further, the patient admitted consuming “Kadha” – (a traditionally prepared Indian Medicinal drink consisting of a variety of herbs and as a prophylactic measure to prevent the infection of ongoing COVID-19) daily once from August 22 with a time gap of 1–1.5 hours after warfarin administration. As the patient had a target INR range of 1.5–3.0 since 12 years of initiation of warfarin therapy (Fig. 2), the increase in INR was mainly suspected to be due to the consumption of “Kadha”(Table 1). The causality relationship of the event was assessed by the “Naranjo Algorithm”⁴ (score of 5) and Drug Interaction Probability Scale⁵ (score of 6) which indicated a probable relationship between the consumption of “Kadha” and increased INR value.

The patient was advised to discontinue the consumption of Kadha immediately followed by withholding warfarin for 2 days and revisiting the hospital after 2 days with the INR monitoring report. The patient was then advised about an online INR tracker to maintain a daily record of diet intake with warfarin (<http://inrtracker.com>). On 27 August, the patient's INR was 2.45 with no

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Fig. 1. Ecchymosis on right hand.

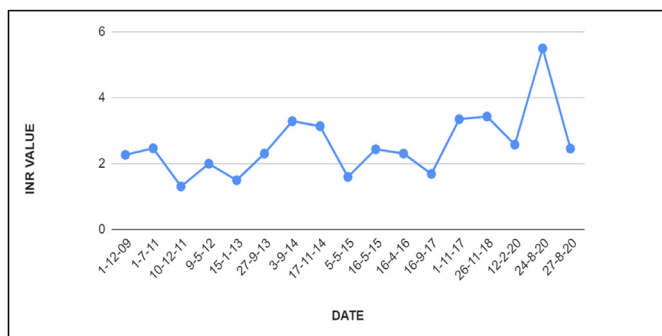


Fig. 2. A brief overview on patient's INR value from the start of warfarin therapy.

Table 1
Composition of kadha.

COMMON NAME	SCIENTIFIC NAME	FAMILY
Ashwagandha	Withania Somnifera	Solanaceae
Holy Basil	Ocimum sanctum	Lamiaceae
Ganthoda	Valeriana Wallichii	Valerianaceae
Black pepper	Piper nigrum	Piperaceae
Nutmeg	Myristica fragrans	Myristicaceae
Ginger	Zingiber officinale	Zingiberaceae
Coriander seeds	Coriandrum sativum	Apiaceae
Cardamom	Elettaria cardamomum	Zingiberaceae
Red Clove	Trifolium pratense	Fabaceae
Cinnamon	Cinnamomum verum	Lauraceae
Bura Sugar	Demerara sugar	Poaceae

changes in diet or lifestyle. He was resumed with warfarin at a daily dose of 7 mg. The patient was explained about the risk of taking herbal medications along with warfarin, as how it may lead to improper anticoagulation control.

Discussion

Our case report mainly concluded that the intake of kadha concomitantly with warfarin played a dominant role in a significant increase in the INR of the patient. All the other possible etiologies and precipitating factors that would have lead to an increase in INR

were sufficiently ruled out. The absolute causality was mainly estimated to be due to herb-drug interaction, herb-herb interactions, or independent action of different herbs on anti-coagulation control of the patient. The patient never had any bleeding complication or greater INR value (>5) from the initiation of warfarin therapy until the consumption of the “kadha”. The causality relationship was assessed by Naranjo Algorithm⁴ (score 5) and Drug interaction Probability scale⁵ (DIPS) (score 6) which indicated that the elevation of INR value may be due to an interaction between warfarin and Kadha.

Kadha is a traditionally prepared drink in India containing a mixture of herbal products with a lot of healthy benefits. The Ministry of Ayurveda, Yoga, and Naturopathy, Unni, Siddha, and Homeopathy (AYUSH) recommends the consumption of this drink twice a day during the pandemic for boosting immunity.⁶

The interaction of warfarin with herbal products has been suspected in the literature through a variety of case reports.^{7–9} In our case report, after a comprehensive literature review, we found that a total of 3–4 herbs were interacting with warfarin (herb-drug interaction) and 2 herbs were reacting concomitantly with each other (herb-herb interactions) resulting in improper anti-coagulation. They mainly included black pepper, ginger, clove, cinnamon, and cardamom interacting with warfarin followed by estimated herb-herb interaction between cinnamon and dry ginger.

Aref Zayed et al.⁷ conducted a study in rats that concluded that piperine, an active compound present in black pepper is a potent inhibitor of cytochrome 450 for warfarin metabolism, thereby reducing the plasma concentration of warfarin. In another case report by Rubin et al.⁸ in 2019 a 70 year old female prescribed with warfarin 7.5 mg daily except 10 mg on Wednesdays, found an elevated INR of 8.0. On being questioned further the patient revealed taking a chewable ginger supplement of 48 mg which may be one of the reasons for the increased INR value. Although there was not much evidence on the interaction of warfarin with red clove, we found a case report of 53-year-old women who developed subarachnoid hemorrhage after taking a herbal supplement containing red clove for premenstrual syndrome along with warfarin for 4 months.⁹ Although there is not much information on the definite mechanism of interaction of warfarin with all the following herbs, we believe that the herbs may have interfered with the pharmacokinetic or pharmacodynamic properties of warfarin.

Conclusion

With the increased use of herbal medicine by the people, it is important to educate them on the effect of herbal products with their concurrent pharmacotherapy. Our report also explains the importance of taking detailed medical history with equal importance in enquiring about self-medication, dietary changes, and alternative therapies taken by the patients who are on warfarin.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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