

# CASE REPORT

## Probable Warfarin Interaction with Menthol Cough Drops

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Warfarin is a widely used and effective oral anticoagulant; however, the agent has an extensive drug and food interaction profile. We describe a 46-year-old African-American man who was receiving warfarin for a venous thromboembolism and experienced a decrease in his international normalized ratio (INR). No corresponding reduction had been made in his warfarin dosage, and no changes had been made in his concomitant drug therapy or diet. The patient's INR fell from a therapeutic value of 2.6 (target range 2–3) to 1.6 while receiving a weekly warfarin dose of 50 mg. His INR remained stable at 1.6 for 3 weeks despite incremental increases in his warfarin dose. The patient reported that he had been taking 8–10 menthol cough drops/day due to dry conditions at his workplace during the time period that the INR decreased. Five days after discontinuing the cough drops, his INR increased from 1.6 to 2.9. Over the subsequent 5 weeks, his INR was stabilized at a much lower weekly warfarin dose of 40 mg. Use of the Naranjo adverse drug reaction probability scale indicated that the decreased INR was probably related to the concomitant use of menthol cough drops during warfarin therapy. The mechanism for this interaction may be related to the potential for menthol to affect the cytochrome P450 system as an inducer and inhibitor of certain isoenzymes that would potentially interfere with the metabolism of warfarin. To our knowledge, this is the second case report of an interaction between warfarin and menthol. Patients receiving warfarin should be closely monitored, as they may choose to take over-the-counter products without considering the potential implications, and counseled about a possible interaction with menthol cough drops.

**Key Words:** warfarin, menthol, cough drop, interaction.  
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Warfarin is a widely used oral anticoagulant agent that exerts its effects by lowering the amount of active vitamin K available for activation of clotting factors II, VII, IX, and X.<sup>1</sup> Despite its established effectiveness for the prevention of thromboembolic events, continuous monitoring of the international normalized ratio (INR), adverse events, and drug and food interactions influence frequent dosage

adjustments. The extensive interaction profile of warfarin is mainly attributed to its metabolism by the cytochrome P450 (CYP) 2C9, 1A2, and 3A4 isoenzymes.<sup>1</sup> Foods containing vitamin K, such as broccoli, may also affect warfarin dosing by decreasing its therapeutic effects.<sup>1,2</sup>

We describe a patient who experienced an interaction between warfarin and menthol cough drops, which led to a decrease in his INR.

### Case Report

A 46-year-old African-American man was receiving warfarin for a venous thromboembolism and experienced a decrease in his INR. No corresponding reduction had been

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made in his warfarin dosage, and no changes had been made in his concomitant drug therapy or diet. His medical history was significant for hypertension and sleep apnea. His daily drug therapy consisted of fish oil 4 g, enalapril 40 mg, amlodipine 20 mg, fexofenadine 10 mg, omeprazole 20 mg as needed for heartburn, and fluticasone propionate 2 sprays to each nostril as needed for allergic rhinitis. The patient denied drinking alcohol, smoking, or taking recreational drugs.

Two weeks after starting warfarin at a weekly dose of 50 mg, the patient's INR fell from a therapeutic value of 2.6 (target range 2–3) to 1.6. His INR remained at 1.6 for 3 weeks despite incremental increases in his warfarin dose. The patient confirmed that he was taking the correct warfarin dose and remained compliant with all of his concomitant drugs within the past 2 weeks. The patient did report, however, that he had been taking 8–10 menthol cough drops/day due to dry conditions at his workplace during the time period that the INR decreased. Five days after discontinuing the cough drops, his INR increased from 1.6 to 2.9. Over the subsequent 5 weeks, his INR was stabilized at a much lower weekly warfarin dose of 40 mg (Table 1).

## Discussion

Based on the Naranjo adverse drug reaction probability scale,<sup>3</sup> the patient's decreased INR was considered probably related to the interaction between warfarin and the menthol cough drops. The only changes in the patient's lifestyle, diet, or concomitant drugs was the addition of the menthol cough drops. Over the subsequent weeks, after discontinuation of the cough drops, the patient's INR was stabilized with a much lower warfarin dose.

A search of the MEDLINE database was performed to help identify the interaction between warfarin and menthol cough drops. One previously published case report was identified, which documented a possible interaction between warfarin and menthol cough drops in a 57-year-old Caucasian man awaiting cardioversion for atrial fibrillation.<sup>2</sup> The patient's warfarin dosage had been adjusted to 7 mg/day, which resulted in an INR of 2.28–2.68, to be taken for the 4-week period after cardioversion. The INR remained therapeutic for 3 weeks; however, with no changes made in his treatment or lifestyle, the patient's INR fell to 1.45 during week 4. He reported the only change was the

**Table 1. Warfarin Dosing and INR History**

Week	Weekly Warfarin Dose (mg)	INR
1	50	2.6
2	50	1.6 <sup>a</sup>
3	60	1.6 <sup>a</sup>
4	75	1.6 <sup>a</sup>
5	75	2.9 <sup>b</sup>
6	55	1.7
7	55	2.3
9	55	4.3
10	40	2.0
11	40	1.8
13.5	40	1.9
18	40	2.2

INR = international normalized ratio.

<sup>a</sup>Patient was ingesting 8–10 menthol cough drops/day.

<sup>b</sup>Menthol cough drops discontinued.

ingestion of six menthol cough drops/day for 4 days. Subsequently, the dose of warfarin was increased from 49 mg/week to 53 mg/week, and the menthol cough drops were discontinued. During week 5, the patient's INR rose to 2.22, and the dose was then tapered to 49 mg/week over the next few weeks. His INR remained therapeutic (target range 2–3) for the remainder of his warfarin therapy. Based on the Naranjo assessment tool, the patient's decreased INR was considered to be possibly related to the warfarin–menthol cough drop interaction.

A further review of the MEDLINE database was performed to further investigate the potential mechanism of this interaction. It appears that *in vitro* and *in vivo* research in rats has demonstrated the potential for menthol to affect the CYP system as an inducer and inhibitor of certain isoenzymes that would potentially interfere with the metabolism of warfarin.<sup>1, 2, 4, 5</sup> It is also important to note that menthol is derived from the peppermint plant. Peppermint oil has shown to inhibit CYP3A4 activity *in vitro* and *in vivo*, thus potentially having a direct effect on warfarin metabolism.<sup>6</sup> It has not been confirmed if the peppermint plant contains sufficient vitamin K to alter the therapeutic effects of warfarin.<sup>2</sup>

Unfortunately, in this case, the root cause of the interaction between warfarin and menthol cough drops cannot be attributed to one particular mechanism. However, these hypotheses are presented as realistic explanations for causing the interaction.

## Conclusion

To our knowledge, this is the second case

report of an interaction between warfarin and menthol. Based on the Naranjo assessment tool, the patient's decreased INR in the first case report was considered to be possibly related to this interaction,<sup>2</sup> whereas in our patient, the decreased INR was found to be probably related. Patients receiving warfarin should be closely monitored, as they may choose to take over-the-counter products without considering the potential implications, and counseled about a possible interaction with menthol cough drops. Further prospective studies examining the relationship between warfarin and menthol cough drops are warranted.

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