

Does Menthol Affect Warfarin Response?

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, visit www.hanstenandhorn.com.

A case was recently reported of a patient on warfarin who developed a substantial decrease in his international normalized ratio (INR) after taking 8 to 10 menthol cough drops daily for 3 weeks to counteract dry air at his workplace.¹ When the cough drops were stopped, his INR returned to the values observed before the menthol.

The fact that the reduced warfarin effect resolved after the menthol cough drops were stopped supports the author's contention that a drug interaction occurred. The case is also supported by the fact that no other cause for the reduced warfarin response could be found. The patient denied any change in drug doses or diet and denied consuming alcohol or taking recreational drugs.

Evidence suggests that peppermint oil (which contains menthol) inhibits CYP2C9.

Does Other Supporting Evidence Exist?

Another case of menthol cough drops possibly inhibiting warfarin effect was published several years ago.² In that case, the patient took about 6 menthol cough drops per day for 4 days, and his INR fell to about half the previous value. As with the patient described above, he denied any changes in his

medications or diet and denied missing any warfarin doses.

Unlike the recent case, however, this patient took the cough drops for a flu-like illness. Acute illness by itself can affect warfarin, but the effect is usually an increase in warfarin response. In any case, the illness complicates evaluation of the interaction in this patient.

The mechanism for this possible interaction is unknown, but in vitro evidence suggests that peppermint oil (which contains menthol) inhibits CYP2C9, the most important enzyme in the metabolism of warfarin.³

Does Menthol Interact with Other Drugs?

Clinical evidence suggests that individuals who smoke mentholated cigarettes have more difficulty stopping smoking.⁴ One possible explanation is that menthol inhibits nicotine metabolism, thus increasing the addictiveness of smoking. In a randomized crossover study of 14 healthy smokers, mentholated cigarettes resulted in higher nicotine plasma concentrations, probably through inhibition of both CYP2A6 and glucuronide conjugation.⁵

The effect of menthol on CYP3A4 has also been studied by assessing felodipine metabolism in healthy subjects with and without menthol or peppermint oil. One study found no effect of menthol 200 mg in divided doses,⁶ while another study using larger amounts of menthol (as peppermint oil) found modest increases in felodipine concentrations.⁷ More study is needed, but assume that large amounts of menthol may modestly inhibit CYP3A4.

The effect of menthol on caffeine pharmacokinetics has also been studied in healthy subjects given a single oral 200-mg dose of caffeine with and

without a single oral dose of 100 mg of menthol.⁸ Menthol did not affect caffeine half-life, area under the plasma concentration-time curve, or clearance, suggesting that menthol does not affect CYP1A2, the primary isozyme for the metabolism of caffeine. Menthol did approximately double the time to maximal caffeine serum concentrations, however, suggesting that menthol delays the absorption of caffeine. Theoretically, if you are gobbling menthol cough drops or ingesting peppermint oil, you will not get that caffeine jolt in the morning as quickly as you expect.

Summary

Two case reports suggest that menthol cough drops can reduce warfarin response, but—given that so many factors are known to affect the response to warfarin—controlled studies are needed to confirm that menthol and warfarin interact. Until this interaction is confirmed, it would be prudent to advise patients on warfarin to limit their use of menthol cough drops or peppermint oil.

Menthol does not appear to affect CYP3A4 or CYP1A2, but study with nicotine suggests that menthol may inhibit CYP2A6 and glucuronidation. Because some other drugs undergo metabolism by these 2 pathways, one should be alert for evidence of altered drug response due to menthol. Nonetheless, the evidence for drug interactions with menthol is still meager, so there is no reason at this point to discourage people from using menthol cough drops. ■



For a list of references, go to www.PharmacyTimes.com/issue/pharmacy/2010/May2010.