

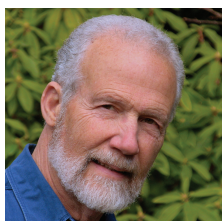
Warfarin and Levothyroxine

No Interaction

BY JOHN R. HORN, PHARM.D, FCCP, AND PHILIP D. HANSTEN, PHARM.D



JOHN R. HORN, PHARM.D, FCCP



PHILIP D. HANSTEN, PHARM.D

AUTHOR BIO

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

THE POTENTIAL INTERACTION BETWEEN LEVOTHYROXINE AND WARFARIN IS responsible for many alerts in computerized drug interaction screening programs.¹ Knowledge of this interaction is based on a number of case reports of patients (1) experiencing increased warfarin response (international normalized ratio [INR] or prothrombin time) when administered levothyroxine or (2) developing thyrotoxicosis. The mechanism of this interaction is unknown; however, it has been theorized that thyroid hormone increases the rate of clotting factor catabolism. This would increase both the INR and the response to warfarin. The lack of a biologically plausible mechanism and scarcity of controlled trials evaluating the potential interaction have led us to believe that this drug combination would rarely result in patient harm.

PREVIOUS STUDIES

Several years ago, this column noted the results of a large, nested, case-controlled epidemiologic trial that examined elderly patients (older than 65 years) who were stabilized on warfarin and then prescribed levothyroxine.² This study examined the risk of hospitalization for hemorrhage as its end point.³ The study found no association between hospitalization and the initiation of levothyroxine in the preceding 30 days in patients stabilized on warfarin. The results failed to show a relationship between levothyroxine administration and bleeding events; however, the study did not identify the thyroid status of the patients or the effect of levothyroxine on INR values.

NEW EVIDENCE

A recent retrospective, self-controlled study evaluated the effect of adding levothyroxine to patients stabilized on warfarin.⁴ Patients older than 18 years (n = 119) who had been taking warfarin for at least 100 days prior to the start of levothyroxine were included. All study patients had elevated thyroid-stimulating hormone values, at least 1 INR in the 90 days prior to starting levothyroxine therapy, and 2 consecutive INRs in the 90 days following levothyroxine administration without warfarin dose adjustment. Patients were excluded if they took any drugs reported to interact with warfarin or had a diagnosis of heart failure, liver or kidney disease, or a bleeding or thromboembolic event.

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To evaluate the possible effect of levothyroxine on the INR response to warfarin, the warfarin dose:INR ratio was calculated. This ratio accounts for variation in the dose of warfarin, intake of vitamin K, formation and catabolism of clotting factors, and warfarin metabolism. In the patients studied, the mean warfarin dose:INR ratios before and following the addition of levothyroxine did not differ. When the warfarin dose:INR ratio was compared in patients who became euthyroid during levothyroxine therapy, again, no difference was observed. No difference in warfarin dose:INR ratio was observed in patients who were initiated on daily levothyroxine doses greater than 50 mcg compared with those started on lower doses.

SUMMARY

When considered together, these 2 controlled patient studies demonstrate little evidence of a potential interaction between warfarin and levothyroxine. The lack of change in the warfarin dose:INR ratio would explain the absence of increased bleeding risk previously reported. Certainly, there does not appear to be evidence to support the labeling of this drug pair as likely to cause patient harm. The warfarin-levothyroxine interaction has been noted to produce 2% to 5% of drug interaction alerts considered clinically important by clinical decision support software.

An important step to reduce alert fatigue is the reassessment of alert seriousness as new data become available. We propose that this interaction should be removed from lists of clinically important drug interactions. The lack of an interaction between levothyroxine and warfarin does not mean that patients receiving both drugs will not experience a change in their response to warfarin. Many factors are known to alter warfarin response; however, it would appear that the administration of levothyroxine is not one of them. ♦

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