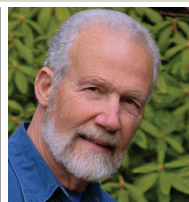


Warfarin and Levothyroxine Revisited

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The interaction between warfarin and thyroid replacement is one of the most frequent alerts provided to pharmacists by computerized drug interaction systems, so it is important to assess any new information on this interaction. Historically, we have held that the interaction between warfarin and thyroid would rarely be clinically important, because the patient is usually taking thyroid first, and is then titrated on warfarin to the appropriate anticoagulation level. New information suggests that even when the patient is on the warfarin first, severe hemorrhage is unlikely.

The Study

Researchers from Toronto performed an epidemiologic study of patients older than 65 years who were taking warfarin and then started on levothyroxine. When they compared study subjects with controls (patients taking warfarin who did not have levothyroxine added), they found no increase in the risk of hospitalization due to hemorrhage.¹ This is good news, because hemorrhage, especially in this population, can be life-threatening.

There are basically 2 possible explanations for these results: 1) in clinically hypothyroid individuals taking warfarin,

adding levothyroxine does not affect the anticoagulant response to warfarin, or 2) initiation of levothyroxine in individuals with hypothyroidism does increase warfarin response, but for 1 or more reasons, it does not result in hemorrhages leading to hospitalization. The current study does not allow us to determine which explanation is more likely for the following reasons.

Severity of Bleeding. The study looked only at hemorrhage leading to hospitalization, and was not designed to detect less severe forms of bleeding. It is possible that levothyroxine increased the relatively common sorts of mild to moderate bleeding without increasing the relatively rare hemorrhages that cannot be handled in the outpatient setting or in the emergency department. Patients who died of bleeding before reaching the hospital would also not be detected in this study.

Dose Adjustments. The study did not collect dosing information, so it was not known if the dosage of warfarin was reduced prophylactically upon initiation of levothyroxine by prescribers who were aware of the potential interaction. The interaction appears on virtually all drug interaction alert systems (including those on handheld devices), so this is a real possibility.

Lab Results. The study did not collect clinical laboratory information on the patients, so researchers did not know if international normalized ratios (INRs) increased after levothyroxine was added. Warfarin dose reductions in response to increased INR may have mitigated the interaction before severe hemorrhage could occur.

Levothyroxine has a long half-life, and it generally takes weeks for the patient to become euthyroid, thus increasing the chance that an increased INR would be detected. Moreover, elderly patients

are often dosed conservatively, which could have prolonged the process even more.

Diagnosis. The study did not determine if the patients started on levothyroxine were actually clinically hypothyroid. Some patients receive levothyroxine for other reasons, and for a patient who is not hypothyroid, feedback mechanisms would reduce endogenous thyroid production to maintain euthyroidism.

Thyroid Status. Clinical evidence indicates that patients with thyrotoxicosis are more sensitive to warfarin, so it appears that thyroid status can affect warfarin response. It is not clear whether going from euthyroid to hyperthyroid would have the same effect on warfarin response as going from hypothyroid to euthyroid, but it cannot be ruled out with current data.

How can this be resolved? In order to determine whether warfarin and levothyroxine interact, one could look at the warfarin dose/INR ratio in patients on warfarin who were started on levothyroxine. Ideally, this would be done prospectively, but a retrospective study could also yield useful information.

Summary

A recent epidemiologic study found that starting levothyroxine therapy in patients on warfarin did not significantly increase hospitalizations for hemorrhage. Although the results are encouraging, it would be premature to ignore the possibility that adding levothyroxine to warfarin therapy can increase warfarin response. Patients should be monitored accordingly until more definitive data are available. ■

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