

42. Sensitivity to warfarin - Genetic predisposition

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Q: "I heard that some people have a genetic mutation that results in these people having little or none of a drug metabolizing enzyme that gets rid of warfarin (coumadin®). They said these people were in serious danger of bleeding since the warfarin (coumadin) stayed in their blood longer and could build up. Variations in the concentration of this enzyme could be one reason some of us take low doses of warfarin (coumadin) to maintain therapeutic levels and others need higher doses. Would it be worth testing people on warfarin (coumadin) for this enzyme? Also, I am thinking, if there were another mutation that resulted in extra high levels of the enzyme that could explain why some folks take huge doses and can't get INR's above 1.5 or so."

A: Firstly, some enzyme variants indeed predispose to warfarin sensitivity. Patients with these variants may be at increased risk of bleeding at the time of initiation of warfarin therapy, but not once a stable dose of warfarin has been determined. It would not be worth testing everybody who is already on warfarin for these enzyme variants, but it might be worthwhile to test patients who will be started newly on warfarin.

Secondly, it is known that mutations exist in one of the genes dealing with vitamin K metabolism which makes patients with these mutations require high doses of warfarin, i.e. cause "warfarin-resistant" (see [Q/A 28](#)).

The enzyme that metabolizes and inactivates warfarin (coumadin) is called cytochrome P-450. It exists in 3 variants: (1) one that is normally active, i.e. 100 % active (called CYP2C9*1), (2) one that has only 12 % enzymatic activity (called CYP2C9*2), and (3) one that has only 5 % activity (called CYP2C9*3). 80 % of people have the variant number 1, but 20 % of the general population have one of the two variants with decreased enzyme activity. If the later people are started on regular doses of warfarin, they may not metabolize the drug well. Higher than desirable warfarin levels and INRs may result, and bleeding may occur. Because of the decreased enzyme activity some of these patients need only low doses of warfarin. However, most patients with these variants need normal doses of warfarin, indicating that presence of these enzyme variants alone is not enough to make a patient warfarin-sensitive.

To illustrate: approximately 2.3% of all patients on warfarin need low doses of warfarin (1.5 mg of warfarin per day or less) to maintain their INRs in the therapeutic range. Of the patients who have the variants 2 and 3, the majority (95 %) are not extremely warfarin-sensitive; only 5 % are very warfarin-sensitive and need warfarin doses of 1.5 mg per day or less. Furthermore, even if a patient has normal enzyme activity (i.e. variant 1), 1.3 % will be very warfarin-sensitive and will still need low doses of warfarin.

Knowledge of what type of enzyme variant a patient has might help reduce some bleeding complications in the initiation phase of warfarin therapy. Since patients who start warfarin are often given a standard dose of 5 mg per day as initial doses, there is a risk that patients with variants 2 and 3 will be over-anticoagulated during warfarin initiation. This may result in an increased risk of bleeding, delayed hospital discharges, and multiple visits to clinics for INR determination during warfarin initiation. And indeed, it has been shown that patients with variants 2 and 3 have more bleeding complications during the initiation of warfarin therapy (Lancet 1999;353:717-719). However, once a stable dose of warfarin has been determined for a patient, there is no advantage of knowing the patient's enzyme variants. Possession of variants 2 or 3 does not increase the likelihood of severe over-anticoagulation (Blood 2000;96:1816-1819).

I am not aware of any anticoagulation clinic that routinely determines the cytochrome P-450 mutations before starting a patient on warfarin. One of the reasons for this is certainly the long time it takes to get the genetic test results back (which is often a week after the blood was drawn). This unfortunately limits the usefulness of this genetic test. Development and availability of a rapid genetic test might be useful, since it might allow better and safer dosing.