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Better Oral Anticoagulation: New agent or better management method?

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Background and Introduction

Some time ago a senior member of the pharmaceutical industry told me: "Henry, we want to compare [the company's new oral anticoagulant] to well-managed warfarin; we are not interested in comparing it to optimally managed warfarin." That view caused me to consider in more detail the relative merits of the new oral anticoagulants currently in development and what should be possible if vitamin K antagonist (VKA) therapy could be easily optimized. Reviewing the characteristics and clinical data for each of the new agents in development is beyond the scope of this review. Rather, the new agents will be considered as a group as "non-inferior" to conventional VKA therapy and compared to what the available data suggest might reasonably be accomplished with better VKA management.

If one considers what is known currently about VKA therapy and the new direct thrombin inhibitors (DTI) and anti-factor Xa inhibitors (anti-Xa), it appears that VKA therapy offers several advantages while therapy with the new agents presents several potential pitfalls (**Table 1**). Clearly, with VKA therapy the major problem is the difficulty of monitoring and managing such therapy. If we set aside the management problem for the moment and consider other aspects of VKA therapy (as will be presented in more detail later), it is clear that VKA therapy could be very effective and very safe if only it were managed optimally. By contrast, the new agents are, for the most part, simply trying to show that they are "non-inferior" to VKA therapy as it currently is managed.

Selected potential problems with the new agents

Potential, not-yet-recognized adverse effects: Although the increase in liver toxicity and myocardial infarction seen with ximelagatran have not been seen with the new agents, we must be aware of the potential for these and other adverse effects.

No antidote: At present, none of the new oral anticoagulants can be readily reversed. This may be of limited significance if toxicity and/or bleeding is limited and/or if the agent has a short duration of action. But it is my understanding that one lawsuit has already been filed



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claiming that the consent form signed by a study patient did not adequately inform the patient that there was no specific way to reverse the effect of the new anticoagulant if bleeding should occur. Also, at least one attorney's website already has questioned the safety of one new agent and posted an invitation for harmed patients to contact his office (see <http://seelielaw.com/blog/?p=74>).

No test for dosage adjustment, assessing adherence, or evaluating interactions: Although the lack of need to monitor the INR often is heralded as an advantage of the new agents, the lack of such monitoring also presents several problems. There is no way to assess whether a dosage adjustment may be warranted, there is no way to confirm that the patient is actually taking an adequate dose (or is adhering to the regimen), and there is no way to monitor the patient (other than the development of bleeding or clotting events) for potentially interacting drugs or other factors. Although the number of factors that may interact with the new agents may be limited, the absence of a monitoring test will make it difficult (if not impossible) to identify such interactions in routine clinical practice. Prospective pharmacokinetic drug interaction studies can confirm that a given interaction does not occur predictably in all patients but, unfortunately, such studies can not exclude the possibility that certain patients or sub-groups of patients will exhibit a dangerous interaction. For example, our group conducted a randomized, double-blind, placebo-controlled trial to evaluate the effect of ciprofloxacin on the INR in warfarin-treated patients. That small trial failed to show any interaction at all between the two medications.¹ Even so, clinical experience and other data suggest that such an interaction does occur in some patients. Whether the interaction is related to the patient having an infection, being febrile, having a particular genetic polymorphism, or some other factor is not certain; but even the investigators of our negative study are convinced that such an interaction does occur from time to time.

Pharmacokinetic considerations: Several of the new agents have a relatively short half-life, exhibit limited oral bioavailability, and rely on hepatic and/or renal elimination. The short half-life may jeopardize the safety and efficacy of the agent in clinical practice because of limited or sporadic patient adherence to the regimen. In general, agents that are not well absorbed following oral administration carry the potential for other factors to substantially increase or decrease the extent of absorption which could result in excessive or inadequate anticoagulation, respectively. Those agents that depend on renal and/or hepatic elimination, of course, are subject to requiring dosage adjustments in the face of renal or hepatic disease, or when other medications are administered that may alter the renal or hepatic clearance of the anticoagulant. Unfortunately, there is no "INR –equivalent" method to assess either the need for - or the appropriateness of - dosage changes in such situations.