Novel oral anticoagulants: What dermatologists need to know

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The development of novel oral anticoagulants provides clinicians and patients a welcome alternative to the challenges of warfarin therapy. Dermatologists must be aware of the potential impact of novel oral anticoagulants on their surgical and medical practice. This review provides a concise summary of the novel oral anticoagulants for dermatologists with particular emphasis on: (1) the pharmacokinetic properties of these drugs and how they differ from warfarin, (2) suggested management during cutaneous surgery, (3) adverse drug interactions with commonly prescribed medications in dermatology, and (4) potential use within dermatology for treatment of disorders of cutaneous thrombosis. (J Am Acad Dermatol 2015;72:535-40.)

Key words: anticoagulation; apixaban; cutaneous surgery; dabigatran; novel drugs; rivaroxaban; warfarin.

Warfarin's reign as the sole oral anticoagulant medication began with its approval in 1954 and ended with the approval of dabigatran in 2010.[1,2] Warfarin blocks the activation of vitamin K, thereby preventing the formation of a necessary cofactor for the synthesis of calcium-dependent clotting factors, which include factors II, VII, IX, and X. Despite the efficacy of warfarin for numerous indications, its use in the clinical setting has been complicated by a narrow therapeutic index, abundant drug and dietary interactions,[3,4] and genetic polymorphisms that impact warfarin and vitamin K metabolism.[5,6]

As a result, patients on warfarin are within their therapeutic international normalized ratio goal only about 50% of the time.[7] Unfortunately, time spent outside of the international normalized ratio goal may lead to devastating consequences for patients including thromboembolic events and hemorrhage.[8] The introduction of novel oral anticoagulants (NOACs) with mechanisms outside of the vitamin K pathway provides patients and providers with alternative options that may provide safer, more efficacious treatment. The first 3 NOACs to be approved in the United States are dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis).

Abbreviations used:

CYP3A4:	cytochrome P450 3A4
NOAC:	novel oral anticoagulant
P-gp:	permeability glycoprotein

Dermatologists treating patients using NOACs must be aware of their use. If not treated correctly in the perioperative setting, patients may face complications ranging from increased intraoperative bleeding to postoperative hematoma formation or skin graft compromise.[9,10] NOACs may also adversely interact with common dermatologic drugs,[11] placing patients at increased risk for bleeding or thrombosis.[12]

The purpose of this review is to: (1) discuss the general advantages and drawbacks of NOACs, (2) provide an overview of NOACs currently approved for use in the United Sates, (3) outline recommendations for management within the cutaneous surgical setting, (4) discuss potential interactions of these drugs with drugs commonly prescribed by dermatologists, and (5) examine potential uses for these agents in treatment of disorders of cutaneous thrombosis.

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SUMMARY OF NEW AGENTS

Mechanism and pharmacokinetics

Although warfarin inhibits synthesis of activated vitamin K, the NOACs directly inhibit activated coagulation factors. Dabigatran inhibits thrombin (factor IIa) whereas rivaroxaban and apixaban inhibit factor Xa (Fig 1). Unlike warfarin, these drugs act independently of the vitamin K pathway and are advantageous in that they have predictable pharmacokinetics between individuals and do not require therapeutic monitoring.[13] Compared with warfarin, which has a prolonged half-life and delayed peak effect, the NOACs have shorter half-lives and time to peak effect, which enables the drugs to be rapidly adjusted to achieve a desired clinical effect, including anticoagulation or normalization of the coagulation pathway (Table I). In addition, given that the NOACs act quickly and independently of protein C and S, there is no need to institute heparin or low-molecular-weight heparin as a bridge to therapy.

CAPSULE SUMMARY

- Novel oral anticoagulants include dabigatran, rivaroxaban, and apixaban. They offer several advantages over warfarin.
- If the decision to interrupt therapy for surgery is made, renal function and surgical risk should guide the time frame of cessation.
- These drugs adversely interact with several commonly prescribed drugs in dermatology.

All of these drugs are excreted renally and must be dosed based on glomerular filtration rate to avoid excessive anticoagulation (Table I). The NOACs are metabolized by the liver. At present, their use in moderate liver dysfunction has not been evaluated and thus, the NOACs are generally avoided in this population.

Clinical indications

Head-to-head clinical trials have demonstrated that NOACs have equal or superior efficacy to warfarin for a number of common indications. As such, dabigatran, rivaroxaban, and apixaban have each been granted Food and Drug Administration approval for at least 2 of 3 indications, including stroke prevention in nonvalvular atrial fibrillation,[14-16] venous thromboembolism treatment,[17-19] and prophylaxis of deep venous thrombosis (DVT) after surgery[20-22] (Table I). The use of NOACs has also been expanded to include novel indications for anticoagulation, such as extended DVT prophylaxis after treatment for an acute DVT.[18,23,24] Despite the clinical success of NOACs for most indications, it is important to remember that these agents have not matched warfarin's efficacy for all indications. For example, in patients with prosthetic heart valves, dabigatran was associated with higher rates of stroke.[25]

Monitoring

As mentioned above, coagulation monitoring for patients taking these drugs is not required given their predictable pharmacokinetics. However, in the setting of emergent operation or hemorrhage, it may be helpful to determine whether a patient is excessively anticoagulated. Even though these agents inhibit the activity of activated coagulation factors in the final pathway of the coagulation cascade, data suggest that the new oral anticoagulants have variable and inconsistent effects on international normalized ratio and partial thromboplastin time, making these tests unreliable.[26,27]

Alternative monitoring tests are currently in development for all 3 agents. In patients taking dabigatran, the thrombin clotting time (thrombin time) exhibits a dose-dependent increase across a wide range of dabigatran concentrations and may be a suitable monitoring test.[28] This test is not widely available at this time, prohibiting its use as a practical option for routine clinical monitoring for most physicians.

Rivaroxaban and apixaban may be evaluated through chromogenic anti-Xa assays.[27,29-31] Again, although these tests are promising for monitoring coagulation status in the setting of Xa inhibitors, they are not routinely available at this time. A potential limitation of anti-Xa testing is that the quantitative result needs to be compared with a standard pharmacokinetic profile, which requires knowing when the patient ingested the medication. This information may be incorrect or unknown, depending on the clinical setting.

Reversal

Unlike warfarin, which can be readily reversed with fresh frozen plasma and vitamin K, the new oral anticoagulants lack "antidotes" that can be used in the event of hemorrhage or overdose. The first step in any reversal is discontinuation of the drug. Fortunately, these agents have a short half-life, so withdrawal of the drug is often an effective intervention to correct a bleeding