Perioperative Management of Antithrombotic and Antiplatelet Therapy

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Anticoagulant therapy is increasingly used as our population ages. In the United States, it is estimated that 12 million patients with atrial fibrillation will need to be evaluated for long-term anticoagulation. Whereas warfarin has for decades been the mainstay of long-term anticoagulation, a new class of oral anticoagulant—directed at specific targets in the coagulation system—is rapidly expanding in application. The rapidity of therapeutic onset and the ease of administration are positioning these agents to overtake warfarin for long-term anticoagulation. These "Novel Oral Anticoagulants" (also called Target-Specific Oral Anticoagulants, or TSOACs) offer ease of use, decreased dependence on inpatient treatment, and freedom from therapeutic monitoring via laboratory testing.

Historical Anticoagulants

Unfractionated Heparin. Unfractionated heparin was originally isolated from canine liver cells in 1916. It is the highest negatively charged (sulfated) biologic molecule. In today's production, it is usually purified from bovine lung and porcine intestinal sources. Its molecular weight ranges from 12 to 15 kd. Unfractionated heparin acts through accelerating the activity of antithrombin. Therapeutic doses are administered intravenously, which requires hospital care. When so used, it must be monitored with laboratory testing, either for its effect on activated partial thromboplastin time (PTT) or for its anti-Xa activity. Unfractionated heparin is readily reversed with protamine (a highly cationic molecule), which makes it ideally suited for inpatient therapy. Concern regarding adverse allergic reactions and variable responses has led to the growing use of low-molecular-weight preparations. Low-molecular-weight heparin is administered parenterally by the subcutaneous route. It is not desirable for long-term dosing aside from its use in cancer-related thrombosis, where it has been shown to be superior to warfarin.[1]

Warfarin. Warfarin was first discovered by the Wisconsin Research Foundation as an outcome of an epidemiologic analysis of bovine deaths after the ingestion of spoiled sweet clover. Medical use was first applied in the 1950s. The agent reduces posttranslational gamma carboxylation of the vitamin K-dependent proteins (factors II, VII, IX, and X). Dosing is monitored through the international normalized ratio (INR)—a derivative of the prothrombin time (PT) with the sensitivity of the laboratory reagent factored in (PT/PT control)^{ISI}, to reduce the variance of results between testing laboratories. There is a narrow therapeutic window in warfarin dosing. The typical target for antithrombotic therapy (excepting mechanical valve thromboprophylaxis) is an INR of 2 to 3. In that range, the coagulation factor activity is typically at 10% to 20%. Detailed studies recently showed that factor X activity averaged 23% in the INR range of 1.5 to 2.6.[2] In well-designed trials, the time in the therapeutic range (TTR) is approximately 60% at best. The TTR is often worse in a non-study setting.

Pharmacovigilance studies have shown warfarin to be a leading cause for hospital readmission because of bleeding.[3] The long-term bleeding risk is cited as 3% per annum across all subjects, with higher risk in the elderly (age, >80 yr). Warfarin antidotes include vitamin K, prothrombin complex concentrates (PCCs), and plasma. Reversal practices have recently come under review; for example, the American Society

of Hematology's Choosing Wisely® initiative for 2014 warns against overuse of PCCs in the absence of clinical bleeding.[4] Intravenous vitamin K administration, safe when delivered at an appropriate rate, results in quicker reversal when time to a normal INR is crucial. Intravenous vitamin K typically reverses the INR to normal levels in 6 to 8 hours.[5] When immediate reversal is needed, PCCs have been shown to be superior to plasma in time to normal INR, although clinical trials have not shown improved clinical outcomes. The PCCs contain adequate amounts of all 4 vitamin K-dependent factors (II, VII, IX, and X), as well as anticoagulants (proteins C and S).[6,7] Because PCCs contain heparin, their use in patients with heparin-induced thrombocytopenia is proscribed.

Target-Specific Oral Anticoagulants

Target-specific oral anticoagulant agents are small molecules that reversibly bind to the active site of targeted coagulation factors. Current targets include factor IIa and factor Xa. These agents have a fast onset of effect (1–4 hr). The clinical trials for approval were designed to eliminate the need for monitoring. Unlike unfractionated heparin and vitamin K antagonists, specific antidotes were not available at the time of approval by regulatory agencies. Trials of antidotes have begun, but no antidote has yet been approved.

Dabigatran. Dabigatran etexilate was the first TSOAC approved for use in the United States. It targets factor IIa and causes dose-dependent thrombin inhibition (Table I). The drug's peak effect occurs at 1.5 hr, with a trough at 12 hr. Dosing is twice daily. The steady state is achieved in 3 d. The half-life is 12 to 15 hr. The agent is largely cleared (80%) by renal mechanisms. If the creatinine clearance is <30 mL/min, the half-life is >24 hr. The RE-LY trial[8] revealed safety superior to warfarin for intracranial hemorrhage and life-threatening bleeds; however, gastrointestinal (GI) bleeding occurred more often in patients treated with dabigatran. Although the clinical trials did not specify a therapeutic range, the effect of dabigatran on coagulation has been tested and analyzed.[9] In routinely available tests (PT and PTT), dabigatran has more effect on PTT, although PT and PTT are nonlinear and therefore cannot be used for drug monitoring. The onset of drug effect can be gauged roughly by an elevated PTT. Dabigatran has a strong effect on the thrombin time, but the thrombin time is too sensitive in its typical setup to monitor for dabigatran effect. A modified (that is, dilute) thrombin time assay can give linear effect but requires in-laboratory validation.[10] If a routine thrombin time is negative, one can be assured for purposes of surgical clearance or bleeding management that clinically significant levels of dabigatran are not present in the tested blood.

Rivaroxaban. Rivaroxaban targets factor Xa. It is rapidly absorbed, and the onset of activity occurs in 1 to 4 hr. Dosing is once daily. Modification to an active form is not required; excretion is 2/3 by renal mechanisms and 1/3 by the hepatobiliary system. Drug half-life is 6 to 9 hr. It affects PT more than PTT. Given its effect on factor X activity, its concentration can be measured by specific calibrators designed for use in assays for factor

TABLE I. Anticoagulant Properties

Variable	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Onset of action	2–5 d	0.5–2 hr	1–4 hr	3–4 hr
Dosing	Once/d	Twice/d	Once/d	Twice/d
Bioavailability (%)	90	4–10	60–80	50
Prodrug	No	Yes	No	No
Variability	Common	Uncommon	Uncommon	Unknown
Therapeutic index	Narrow	Unknown	Unknown	Unknown
Diet/medications	++++	+	Unknown	+
Monitoring needed	Yes	No	No	No
Test to monitor	INR	Thrombin time	Anti-Xa assay	Anti-Xa assay
Elimination half-life (hr)	20–60	12–17	6–9	12
Excretion	Liver	85% Kidney	66% Kidney	27% Kidney
Antidote	PCC/FFP/vitamin K	None	None	None

FFP = fresh frozen plasma; INR = international normalized ratio; PCC = prothrombin complex concentrate

+ = Semiquantitative estimate of the degree to which drug pharmacokinetics is affected by diet or medications. The lower the number, the easier the drug is to manage.

X activity. Many laboratories have set up anti-Xa activity assays for monitoring heparin effect and, therefore, have the infrastructure needed to provide this test. In general terms, the absence of anti-Xa activity, even with a non-rivaroxaban-calibrated curve, serves as a reasonable indicator of the absence of drug effect, for the purposes of surgical clearance or bleeding management. In comparison with warfarin, rivaroxaban also has a superior safety profile in regard to critical bleeding and fatal bleeding; however, in the Rocket-AF trial,[11] rivaroxaban was inferior to warfarin in its higher rates of GI bleeding, hemoglobin decline (>2 points), and red blood cell transfusion requirements.

Apixaban. Apixaban is directed against factor X. It is rapidly absorbed, and peak onset of activity occurs at 3 to 4 hr. Dosing is twice daily. Like rivaroxaban, it has the greatest effect on the PT and it also has calibrators available for anti-Xa monitoring. This drug differs in elimination methods: only 25% is cleared by renal mechanisms and the remaining 75% by the fecal route. Patients with renal impairment better tolerate it, although the clinical trials used for approval excluded patients with renal deficiency. In ARISTOTLE,[12] patients treated with apixaban or with warfarin had similar rates for GI bleeding, but apixaban had a significantly lower rate of bleeding for intracranial hemorrhage and a lower

TABLE II. Drug Half-Lives and Recommendations for Periprocedural Hold

Drug	Creatinine Clearance (mL/min)	Low-Bleeding-Risk Surgery* (2 or 3 drug half-lives between last dose & surgery, d)	High-Bleeding-Risk Surgery** (4 or 5 drug half-lives between last dose & surgery, d)
Dabigatran			
$t_{1/2}$ = 14–17 hr	>50	2 (skip 2 doses)	3 (skip 4 doses)
$t_{1/2}$ = 16–18 hr	30–50	3 (skip 4 doses)	4–5 (skip 6–8 doses)
Rivaroxaban			
$t_{1/2}$ = 8–9 hr	>50	2 (skip 1 dose)	3 (skip 2 doses)
$t_{1/2}$ = 9 hr	30–50	2 (skip 1 dose)	3 (skip 2 doses)
$t_{1/2}$ = 9–10 hr	15–29.9	3 (skip 2 doses)	4 (skip 3 doses)
Apixaban			
$t_{1/2}$ = 7–8 hr	>50	2 (skip 2 doses)	3 (skip 4 doses)
$t_{1/2}$ = 17–18 hr	30–50	3 (skip 4 doses)	4 (skip 6 doses)

*Aiming for mild-to-moderate anticoagulant effect at surgery (<12%–25%)

**Aiming for no or minimal anticoagulant effect at surgery (<3%–6%)

$t_{1/2}$ = half-life

Adapted with permission from: Spyropoulos AC, Douketis JD. Blood 2012;120(15):2954-62.[13]

TABLE III. Postoperative Resumption of Target-Specific Oral Anticoagulants: A Suggested Management Approach

Drug	Low-Bleeding-Risk Surgery	High-Bleeding-Risk Surgery
Dabigatran	Resume on day after surgery (24 hr postoperatively), 150 mg twice/d	Resume 2–3 d after surgery (48–72 hr postoperatively), 150 mg twice/d*
Rivaroxaban	Resume on day after surgery (24 hr postoperatively), 20 mg once/d	Resume 2–3 d after surgery (48–72 hr postoperatively), 20 mg once/d**
Apixaban	Resume on day after surgery (24 hr postoperatively), 5 mg twice/d	Resume 2–3 d after surgery (48–72 hr postoperatively), 5 mg twice/d**

*For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran (for example, 110–150 mg once/d) on the evening after surgery and on the next day after surgery (first postoperative day).

**Consider a reduced dose (such as rivaroxaban 10 mg once/d or apixaban 2.5 mg twice/d) in patients at high risk for thromboembolism.

Adapted with permission from: Spyropoulos AC, Douketis JD. Blood 2012;120(15):2954-62.[13]

rate of major or clinically relevant non-major bleeding, in comparison with warfarin.

Periprocedural Management

The relatively fast onset and offset of activity enables relatively simple management of most TSOACs. Crucial factors in management include understanding the drug half-life and the impact of renal function on half-life. Spyropoulos and Douketis[13] (Table II) proposed a strategy for drug withdrawal that aims for a 12% to 25% reduction (2–3 half-lives) in patients undergoing surgery with low bleeding risk, and for 3% to 6% residual activity (4–5 half-lives) in patients undergoing surgery with high bleeding risk. Anyone who wishes to be absolutely certain of drug clearance can use anti-Xa (rivaroxaban or apixaban) or thrombin (dabigatran) time assays to establish drug clearance. For patients receiving apixaban, bridging with a parenteral agent (for example, low-molecular-weight heparin) is required, because the study cohort that underwent drug interruption experienced an increased rate of thrombosis upon reversion to warfarin.

The time for resumption of anticoagulant therapy depends on the bleeding risk associated with the surgical procedure and needs to be established with the help of the surgical team. Recommendations are provided in Table III.[13]

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