Reversal of Systemic Anticoagulants and Antiplatelet Therapeutics

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KEYWORDS

• Anti-platelet • Anticoagulation • Stroke • Intracranial hemorrhage

KEY POINTS

- No reversal agents exist for antiplatelet medications, although platelet transfusion and desmopressin administration may partially restore appropriate thrombogenesis.
- Anticoagulation with warfarin is frequently encountered in neurosurgery patients but can be quickly reversed with prothrombin complex concentrate, fresh frozen plasma, or and vitamin K.
- New agents like andexanet alfa and idarucizumab provide reversal strategies for factor Xa inhibitors and direct thrombin inhibitors, respectively.

INTRODUCTION

Coagulopathy secondary to antiplatelet medications and anticoagulation is a frequently encountered source of morbidity in neurosurgical patients. Reversal of these agents plays an important role, whether preparing for elective surgery or in an emergent fashion after trauma or spontaneous intracranial hemorrhage (ICH). Patients treated with anticoagulation carry an annual systemic bleeding incidence of 15% to 20%, with a 2% risk of ICH.[1] Furthermore, 15% of all ICH occurs secondary to anticoagulation treatment[2] and is associated with a substantial mortality of 70%.[3] Despite the utilization of reversal agents or protocols for the majority of current anticoagulants, potential delays in medication reversal can have significant consequences secondary to hematoma expansion.

The advent of newer-generation anticoagulants and antiplatelet agents presents unique challenges. The introduction of new reversal agents for factor Xa inhibitors and direct thrombin inhibitors (DTIs) over the past few years has had a profound effect, showing significant benefit compared with prior reversal protocols. Furthermore, continued development of new antiplatelet agents has presented challenges to limit hemorrhage propagation when a true reversal agent does not exist.

Hemostasis is a dynamic process involving platelet adhesion and aggregation, in addition to the interactions of numerous factors within the coagulation cascade. The intrinsic and extrinsic pathways provide a target for the majority of anticoagulant therapeutics. Contained entirely within the intravascular space, the intrinsic pathway involves the activation of factors XII, XI, and IX in succession, ultimately activating factor Xa with the cofactor XIIIa.[4] The extrinsic pathway, initiated outside of the intravascular space, is initiated by the activation and coassociation of factor VII and tissue factor. The tissue factor VIIa complex with cofactor VIIIa is able to activate factor Xa as the 2 pathways converge. Once activated, factor Xa and cofactor Va convert prothrombin (factor II) to

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thrombin (factor IIa), which then converts fibrinogen to fibrin.[4]

Although the activation of thrombin and fibrin is essential to hemostasis, platelet activation and aggregation are critical to thrombus plug formation. Inactivated platelets contact and bind von Willebrand factor (vWF) at a site of vascular injury via the platelet surface glycoprotein (GP) Ib-IX-V.[5] The small amount of thrombin, generated through the extrinsic pathway at the site of vascular injury, then plays a major role in further thrombus propagation. First, thrombin converts GP IIb/IIIa from a quiescent protein to an active platelet-surface molecule. GP IIb/IIIa then is able to bind fibrin and assist in platelet cross-linking, and it triggers more GP IIb/IIIa molecules to be expressed at the cell surface. Second, thrombin further activates factor VIIIa and Va on the platelet surface, substantially increasing thrombin generation via the coagulation cascades. Finally, thrombin activates factor XIIIa, which is responsible for stabilizing platelet-platelet interactions by cross-linking fibrin monomers.

A thorough understanding of the platelet biology and coagulation underlying hemostasis is vital to the reversal strategies designed to combat coagulation and platelet inhibition in clinical practice. Although many antiplatelet and anticoagulant agents have existed for years, newer agents have posed new challenges. Appropriate reversal strategies for these medications are a vital resource to the neurosurgical armamentarium in combatting medication-induced coagulopathy. This review highlights recent data to provide a comprehensive summary of the latest antiplatelet and anticoagulant therapies and the role of emergency reversal in the setting of ICH or emergent neurosurgical procedures.

ANTIPLATELET AGENTS

Cyclooxygenase Inhibitors

Acetylsalicylic acid (aspirin), with a half-life 30 minutes, is a cyclooxygenase (COX)-1 inhibitor, preventing the metabolism of arachidonic acid and the generation of prostaglandin H2, a precursor to thromboxane A2. Thromboxane A2, after binding to its receptor, induces a significant increase in intracellular calcium, promoting platelet activation and aggregation and creating a substantially prothrombotic environment. Aspirin irreversibly binds to COX-1, effectively inhibiting thromboxane A2 production for the life of the platelet. Additionally, inhibition of COX-1 and COX-2 blocks prostaglandin production, resulting in analgesic and antipyretic effects as well.

Aspirin is an oral medication and is prescribed at a dosage of 81 mg to 325 mg daily. Aspirin is widely used in primary and secondary prevention of ischemic stroke and cardiovascular events, providing a 22% reduction in nonfatal myocardial infarction (MI) and a 6% to 8% decrease in all-cause mortality over 10 years.[6,7] Major bleeding is the primary adverse effect of aspirin, which is most often observed in the gastrointestinal tract (rarely fatal). The risk of ICH associated with aspirin use is dose dependent. Unsurprisingly, the use of aspirin increases the potential need for surgery, morbidity, and mortality after spontaneous ICH.[8,9]

Prior to elective surgery, aspirin should be held for 7 days to 10 days prior to surgical intervention, given that aspirin provides irreversible platelet inhibition for the life span of the platelet. For patients on antiplatelet agents presenting with spontaneous or traumatic ICH, there is no reversal agent available, and some studies suggest that platelet transfusions may not improve outcomes.[10,11] Nonetheless, platelet transfusion (1 pool, $>3 \times 10^9$ platelets/L) with desmopressin (0.3 μg/kg) may be used to provide patients with uninhibited platelets (**Table 1**). Up to 5 U of platelets often are needed for sufficient clot formation, and desmopressin can be administered every 12 hours, with a maximum of 6 doses.

Although several studies have revealed no significant difference in hematoma growth or outcome after platelet transfusion,[12,13] these results are counterbalanced by numerous studies revealing a benefit. A transfusion of 10 U to 12.5 U of platelets has been shown to restore normal platelet function in patients on dual-antiplatelet regimens of aspirin and clopidogrel.[14] The administration of platelets to patients suffering from an aspirin-associated ICH has further been shown to reduce hematoma growth and mortality in several other studies as well.[15,16] The utilization of desmopressin carries some risk, particularly for patients with significant cardiac histories, but has been shown to increase platelet reactivity through the release of vWF multimers from platelet alpha-granules and Weibel-Palade bodies of endothelial cells.[17] Although the results of studies assessing the utility of these treatments remains mixed, the use of both platelet transfusion and desmopressin is recommended for severe and life-threatening ICH.

P2Y12 Inhibitors

Clopidogrel (half-life 6 hours) is a thienopyridine that irreversibly blocks the P2Y12 component of

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