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Oral Platelet Inhibitory Drugs and Bleeding Complications: Implications for Transfusion

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General Background

Drugs that inhibit platelet function may contribute to increased bleeding risk, whether spontaneous or traumatic in nature.¹ The degree of risk and significance of clinical repercussions are determined by the specific medication(s) used, the patient's condition, and the type(s) of interventions applied.

The Medications

The most commonly used anti-platelet drug is aspirin. It irreversibly inhibits platelet cyclooxygenase 1 (COX-1), an effect lasting the lifetime of the platelet. In individuals with typical platelet turnover, the defect reverts to near-normal functionality within 2-3 days after the last dose.² Many procedures, including cardiopulmonary bypass and dental extractions, can be done in non-coagulopathic patients on low-dose aspirin, e.g., 81 mg/day¹, with minimal or no increased bleeding risk.

Other nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen and naproxen, also inhibit COX-1, though not as strongly as aspirin and only while the drug circulates.³ For ibuprofen, with a relatively short half-life ($t_{1/2}$) of ≈ 2 hours, reversal of inhibition is observed after ≈ 24 hours.³ For naproxen ($t_{1/2} \approx 15$ hours), scant data suggest loss of platelet inhibitory effect by 2 days after discontinuation.³

COX-2 specific inhibitors, such as celecoxib, have no significant platelet inhibitory activity.⁴

Drugs inhibiting the platelet ADP P2Y₁₂ receptor, e.g., clopidogrel, prasugrel, and ticagrelor, are in widespread use, often in conjunction with low-dose aspirin. Clopidogrel and prasugrel bind irreversibly to the receptor. The inhibitory

Key Points

- Platelet inhibitory drugs may contribute to spontaneous bleeding and exacerbate bleeding complications during trauma and surgery.
- Many procedures can be performed on patients taking low-dose aspirin without a significant increase in blood loss.
- Platelet transfusions appear to have some efficacy in correcting the platelet inhibitory effect in patients on aspirin and clopidogrel; efficacy in patients on prasugrel, and particularly ticagrelor and vorapaxar, is less clear.
- Scant evidence supports the use of desmopressin in some patients.

effects of these drugs are stronger than those seen with aspirin or other NSAIDs, alone, and can be detected 5-9 days after the last dose; improved platelet function here correlates with new platelet production.^{1,2} Platelet aggregation results for ticagrelor, which binds reversibly to the receptor and has a $t_{1/2}$ (for the active metabolite) of ≈ 9 hours, approach pre-treatment levels by 3 days after discontinuation.^{1,2,5} Both prasugrel and ticagrelor provide stronger platelet inhibition than clopidogrel and are associated with an increased bleeding risk compared to the latter.²

Vorapaxar is a protease-activated receptor-1 (PAR-1) antagonist inhibiting thrombin-induced platelet aggregation.² It is used along with low-dose aspirin and/or clopidogrel in patients who have had myocardial infarction or have peripheral arterial disease.² It is associated with increased bleeding and its anti-platelet effects are still measurable at four weeks after discontinuation.²

Dipyridamole and cilostazol inhibit phosphodiesterase, leading to increased platelet cAMP and decreased platelet response.² Neither, alone, appears to increase the risk of bleeding with surgery.⁶

Implications for Transfusion

The role of platelet transfusions to prevent or treat bleeding with anti-platelet therapy varies by the medication(s) used as well as the severity (and risk of consequences) of the bleeding. For aspirin and other NSAIDs, platelet transfusions are rarely indicated, but may be used in the setting of life-threatening bleeding or for emergent, high risk procedures, such as those involving the



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posterior eye chamber and central nervous system.¹

The APTITUDE studies evaluated: (1) *ex-vivo* addition of non-treated autologous platelets in patients receiving a loading dose of drug prior to percutaneous coronary interventions (APTITUDE-ACS), and also (2) patients on stable drug regimens receiving platelet transfusions for bleeding with CABG (APTITUDE-CABG). These studies found measurable effects of platelet transfusions in both groups receiving clopidogrel, and less for those receiving prasugrel or ticagrelor, although the numbers were small.⁷ Limited data suggest platelet transfusions may be less effective in reversing the platelet inhibitory effect of ticagrelor, consistent with the reversible platelet binding of this drug and its metabolite (both of which would be expected to lead to rapid inhibition of freshly transfused platelets).⁵

In primates, platelet transfusions decreased bleeding times in animals on aspirin, vorapaxar, and clopidogrel (though vorapaxar's FDA-approved prescribing inform-

larger doses may be required for patients on other drugs, e.g., clopidogrel,⁹ known to respond to platelets.

Desmopressin is often administered to patients on aspirin and other platelet inhibitors before surgical procedures. For aspirin, reports document its correction of tests, such as bleeding time or Platelet Function Assay-100 (PFA-100).^{6,10} Prospective, randomized trials to determine if desmopressin-treated patients have better clinical outcomes than those receiving no therapy are lacking.

Can lab tests predict bleeding risk and/or be used to monitor transfusion effects? A number of assays are used to assess the degree of platelet inhibition, e.g., the VerifyNow platelet aggregometry test for aspirin and clopidogrel, the PFA-100, and viscoelastometric testing. A relationship between test results and bleeding is not always clear; caution should be applied when deciding which, if any, to use in guiding transfusion therapy.¹¹

Conclusion

Widely used anti-platelet drugs contribute to bleeding risk; thus, reversal of their platelet inhibitory effects may be required for patients bleeding spontaneously from injuries or from surgery. Refer to the Table for a summary of the means by which bleeding caused by these drugs may be treated.

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Table: Anti-Platelet Drugs – Mechanisms Plus Recommendations for Platelet-Directed Treatment of Bleeding

Drug	Effect on:	R vs. I [†]	Platelet-Directed Treatment of Bleeding
Aspirin	COX-1	I	Desmopressin + Plt tx (severe bleeding)
Other NSAIDS [‡]	COX-1	R	Generally not required
Clopidogrel	P2Y ₁₂	I	Plt tx ± Desmopressin
Prasugrel	P2Y ₁₂	I	Plt tx ± Desmopressin
Ticagrelor	P2Y ₁₂	R	Unclear if Plt tx is helpful
Vorapaxar	PAR-1	R	Unclear if Plt tx is helpful
Dipyridamole	PDE	R	Not indicated
Cilostazol	PDE	R	Not indicated

†Reversible (R) vs. irreversible (I); ‡Includes ibuprofen and naproxen; does not include NSAIDS having only a COX-2-specific effect.
Legend: COX-1 = Cyclooxygenase 1; P2Y₁₂ = A purinergic signaling protein present on the platelet surface; PAR-1 = Protease-activated receptor-1; PDE = Phosphodiesterase; Plt tx = Platelet transfusion.

ation states there is no known treatment to reverse the anti-platelet effect). The recently published PATCH trial strongly suggested that platelet transfusions do not lead to improved—and may even worsen—outcomes in patients with acute hemorrhagic strokes who have been on selected anti-platelet medications (aspirin, clopidogrel, and/or dipyridamole).⁸

When transfusing platelets to treat bleeding, a single dose (e.g., one apheresis unit, or the equivalent, for an adult) usually is sufficient for patients on aspirin alone;