ACS Case Reviews in Surgery
Vol. 4, No. 7

Clopidogrel and Pharmacogenetics: Rethinking Perioperative Antiplatelet Management

AUTHORS:
Dantu SV; Albright J

CORRESPONDING AUTHOR:
Jeffrey Albright, MD, MBA
750 E. Adams Street
Ste. 8141
Syracuse, NY 13210
Email: albrighj@upstate.edu

AUTHOR AFFILIATION:
Department of Surgery
SUNY Upstate Medical University
Syracuse, NY 13210

Background	Clopidogrel, a prodrug requiring hepatic cytochrome P450 2C19 (CYP2C19) activation to inhibit platelet P2Y12 receptors, can be significantly affected by common genetic variations in CYP2C19, including gain-of-function (GoF) and loss-of-function (LoF) polymorphisms. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, established by the NIH, recommend tailoring clopidogrel prescribing based on a patient's genotype. This case highlights a significant bleeding complication following ligation of the intersphincteric fistula tract (LIFT) attributed to a CYP2C19 GoF variant, resulting in heightened platelet inhibition.
Summary	A 54-year-old male with cardiac stents maintained on clopidogrel presented with a four-month history of purulent drainage from a high transsphincteric anal fistula. He underwent a LIFT procedure and resumed aspirin and clopidogrel on postoperative (POD) 2. On POD 4, he experienced surgical site bleeding controlled with manual pressure. However, bleeding recurred on POD 6 with persistent drainage and orthostasis, estimated at 3 to 4 units of blood loss from a 2.5 cm incision at the skin edge. Sutured closure temporized the bleeding. Notably, a VerifyNow P2Y12 assay revealed persistent platelet inhibition despite clopidogrel discontinuation three days prior. Subsequent CYP2C19 genotyping identified a *17 allele, indicating ultrarapid metabolism likely contributing to the bleeding risk with clopidogrel.
Conclusion	This case highlights the potential for significant postoperative bleeding in patients carrying the CYP2C19*17 gain-of-function allele, which affects clopidogrel metabolism and increases platelet inhibition. Approximately 28% of the population carries this allele, warranting heightened awareness for surgeons. The VerifyNow assay offers a rapid point-of-care method to assess platelet function in these patients. Notably, current surgical guidelines lack recommendations regarding perioperative clopidogrel management based on either platelet function testing or genotyping. Implementing such testing could inform genotype-directed perioperative management of clopidogrel.
Key Words	clopidogrel; Plavix; VerifyNow; hypermetabolizer; surgery

DISCLOSURE STATEMENT:
The authors have no conflicts of interest to disclose.

FUNDING/SUPPORT:
The authors have no relevant financial relationships or in-kind support to disclose.

MEETING PRESENTATION:
Poster presented at 2020 ASCRS Annual Conference, June 2020

RECEIVED: February 7, 2022
REVISION RECEIVED: April 20, 2022
ACCEPTED FOR PUBLICATION: May 12, 2022

To Cite: Dantu SV, Albright J. Clopidogrel and Pharmacogenetics: Rethinking Perioperative Antiplatelet Management. *ACS Case Reviews in Surgery*. 2024;4(7):1–5.

Case Description

A 54-year-old male with a four-month history of a cryptoglandular transsphincteric anal fistula presented for definitive treatment after a prior perianal abscess. He had a history of coronary artery stent placement (more than one year prior) and was maintained on clopidogrel 75 mg daily.

Ligation of the intersphincteric fistula tract (LIFT) was chosen as the surgical approach. Following cardiologist recommendations, clopidogrel was discontinued five days pre-operatively and resumed on postoperative day (POD) 2.

On POD 4, the patient experienced bleeding from the incision site, controlled by local pressure. POD 6 brought renewed concerns as the patient reported excessive bleeding and, upon arrival at the clinic, exhibited significant blood loss on his clothing and person. Examination revealed continuous oozing from the skin edge. Local application of lidocaine with epinephrine achieved hemostasis, followed by reinforcement of the skin closure with chromic sutures; no further bleeding episodes occurred.

Following hospital admission and resuscitation, the patient experienced significant blood loss of 3-4 units following LIFT surgery raised concerns, exceeding the expected bleeding typically associated with sphincter muscle injury or missed terminal branches in the intersphincteric space. The unusual bleeding source and severity prompted an investigation into the patient's ongoing clopidogrel use as a potential contributing factor. A point-of-care (PoC) VerifyNow P2Y12 (Accriva Diagnostics, San Diego, CA, USA) test assessing platelet inhibition was utilized.[1] The VerifyNow P2Y12 cartridge measures the effect of P2Y12 adenosine diphosphate (ADP)-receptor inhibitors (such as clopidogrel and ticagrelor) on platelet aggregation. Despite discontinuing clopidogrel three days prior to surgery, the patient's P2Y12 reaction units (PRU) measured 110.[2] This finding, along with the established therapeutic range (85-208 PRU, with lower values indicating greater inhibition[3]), suggested a potential underlying CYP2C1917 gain-of-function (GoF) allele[2] leading to abnormally rapid clopidogrel metabolism. Genetic testing subsequently confirmed a heterozygous CYP2C19*17 and a corresponding *1/*17 genotype, indicating a CYP2C19 rapid metabolizer phenotype.[4]

Discussion

Bleeding is a recognized complication across all surgical procedures, from minor outpatient surgeries to major interventions. Surgeons often encounter patients on antiplatelet and anticoagulant medications, a necessity considering up to 20% of patients with coronary stents require noncardiac surgery within a year while still on these medications.[5] Despite this overlap, bleeding complications following minor outpatient surgery in such patients are relatively uncommon.

Clopidogrel, a thienopyridine prodrug, is a mainstay antiplatelet medication for various vascular diseases like coronary artery disease, peripheral vascular disease, and stroke. It acts by irreversibly inhibiting the P2Y12 ADP receptor on platelets,[6] effectively preventing its noncompetitive antagonism by ADP. The normal activation of the P2Y12 receptor by ADP potentiates platelet aggregation.[6] Notably, platelet activity contributes to roughly 80% of clot strength, with fibrin playing a secondary role (20%).

The primary pathway for the activation of clopidogrel into its active form is through the cytochrome P450 CYP2C19. People who are homozygous wild-type *1/*1 will typically activate approximately 15% of the clopidogrel, thus resulting in the desired level of platelet inhibition.[8] The median level of platelet inhibition on maintenance clopidogrel dosing is estimated to be 40-60%.[6,8]

However, significant inter-individual variability exists. Platelet inhibition levels can vary widely in the American population, with a median of only 12% remaining five days after stopping clopidogrel and only 5% retaining greater than 40% inhibition.[6]

It is estimated that CYP2C19 genetic variations further influence clopidogrel's effectiveness. The CYP2C19 17 allele, a gain-of-function variant (*17), is present in approximately 21% of Blacks (African-American/Afro-Caribbean) and 11% of Whites (Caucasian-Americans), compared to only 2% in East Asians.[4] This allele (C to T promoter transition) increases , leading to higher active metabolite levels and a potential bleeding risk in carriers taking clopidogrel. This C>T transition in the promoter results in increased CYP2C19 expression and activity.[9] Higher concentrations of clopidogrel's active metabolite increase bleeding risk in patients with CYP2C19 *17 allele who are taking clopidogrel.

Platelet function following clopidogrel therapy exhibits significant variability, prompting the development of various tests to assess and manage post-treatment activity. Light transmission aggregometry (LTA) remains the gold standard due to its comprehensive evaluation. LTA measures platelet function in platelet-rich plasma stimulated by an agonist. As aggregation proceeds, the solution clears, allowing for increased light transmissionGiven the inherent unpredictability of platelet function after clopidogrel dosing, a number of tests have been utilized to detect and control for platelet activity in patients after administration. The gold standard test for platelet function is light transmission aggregometry (LTA). This method measures platelet function by using a sample of platelet-rich-plasma accompanied by an agonist. Platelet aggregation effectivity decreases the turbidity of the solution and allows for increased light transmission.[13] However, LTA's technical complexity and time constraints limit its use in acute settings. To address these limitations, several point-of-care (PoC) tests have emerged, including thromboelastometry (ROTEM), platelet function assay-100 (PFA-100), Multiplate® analyzer, Plateletworks®, and VerifyNow P2Y12 assay. These PoC tests offer faster turnaround times and improved feasibility in clinical settings.

The VerifyNow P2Y12 assay stands out among PoC tests due to its extensive clinical validation and close correlation with LTA. This rapid assay utilizes a turbidometric detection system. Fibrinogen-coated microbeads within the cartridge bind to activated platelets following ADP stimulation.[1] The degree of aggregation directly reflects the availability of functional P2Y12 receptors on platelets, translating into a proprietary unit called the PRU value.[10] This PoC test offers a significant advantage by enabling rapid assessment of platelet inhibition status.

Clopidogrel therapy is associated with a significant increase in perioperative bleeding risk. A study analyzing Texas administrative data for emergency gastrointestinal surgery demonstrated a 60% higher risk of postoperative bleeding events within 30 days in patients taking clopidogrel than those not (OR 1.60, 95% CI 1.08-2.38).[12] Furthermore, the BIANCA Observational Study demonstrated a positive correlation between platelet reactivity, measured via LTA, and postoperative bleeding in noncardiac surgery patients on clopidogrel.[5]

Beyond the well-known variability in bleeding risk with clopidogrel, a significant concern lies in clopidogrel "resistance," affecting up to 40% of patients.[15] Several factors are believed to contribute to this resistance, including drug interactions and genetic polymorphisms like CYP2C19 loss-of-function alleles (*2, *3).[4] Currently, research is actively exploring the potential of platelet function tests to guide personalized clopidogrel dosing strategies.

While numerous randomized controlled trials have investigated the use of platelet function tests to guide tailored antiplatelet therapy after coronary stenting, these trials have not shown clear clinical benefit. Consequently, current guidelines advise against routinely using such tests in this context.[15] However, some practitioners may still employ them to identify patients exhibiting clopidogrel resistance, potentially leading to a switch to alternative antiplatelet agents like ticagrelor.

Preoperative assessment for patients on antiplatelet and anticoagulant medications requires a detailed history and physical examination. While medication discontinuation (e.g., clopidogrel) is common before surgery, a history of significant bleeding or bruising during use may indicate a genetic predisposition due to individual metabolic factors. A heightened suspicion based on such a history can guide further evaluation. In the setting of unexpected or excessive bleeding following surgery, as seen in this scenario, utilizing the VerifyNow P2Y12 testing can help to determine if patients are potential hypermetabolizers. In cases of unexpected or excessive postoperative bleeding, as illustrated in this scenario, the VerifyNow P2Y12 test can be instrumental in identifying potential hypermetabolizers. If excessive platelet inhibition is detected, genetic testing for the CYP2C19 *17 variant is recommended. This information is crucial for optimal medication management, as these medications play a vital role in reducing cardiovascular risk. Identifying excessive platelet inhibition allows for the selection of alternative antiplatelet agents with lower bleeding risk.

This case underscores the value of PoC platelet function testing in identifying patients with higher-than-expected platelet inhibition on clopidogrel therapy. This information can then guide decisions about who might benefit from pharmacogenomic testing. CYP2C19 is of over 50 genes included in the Clinical Pharmacogenetics Implementation Consortium's (CPIC's) guidelines, which offer prescribing recommendations based on genetic variations.[4]

As both pharmacogenomic testing and direct-to-consumer options like 23andMe become more affordable and accessible, healthcare providers will increasingly need to consider

individualized patient factors related to drug metabolism (pharmacokinetics) and response (pharmacodynamics) to optimize care.

Surgeons and clinicians should anticipate the rising use of pharmacogenomic testing and integrate this information into patient management. This case highlights the significant interindividual variability in drug response driven by genetics. Traditionally considered factors like age, organ function, and drug interactions, while important, should be viewed alongside a patient's genetic makeup to predict potential complications. Here, a patient with a rapid metabolizer genotype for clopidogrel, a medication taken at home, experienced a substantial postoperative hemorrhage from a minor skin incision due to significantly increased bleeding risk.

The authors propose a dual role for VerifyNow P2Y12 testing. First, it can be used as a screening tool to identify patients with abnormal platelet inhibition at baseline. This information can guide further genetic testing to determine if a different antiplatelet medication or adjustments to the standard "start" and "stop" times of perioperative antiplatelet administration.

Secondly, this assay's utility extends to the immediate preoperative and postoperative settings, serving as a point-of-care tool. Real-time information on a patient's platelet inhibition status can be obtained, which can benefit patient care in two ways:

- **Preoperative Risk Stratification.** Guidance on potential bleeding risks before surgery, facilitating informed decision-making.
- **Postoperative Bleeding Management.** Identification of the pharmacological cause of bleeding postoperatively. This can expedite crucial clinical decisions, such as platelet transfusion or the need to return to the operating room.

Conclusion

Established POC platelet function assays offer a feasible and rapid approach to assess bleeding risk in surgical patients on antiplatelet medications. This technology provides valuable real-time data to guide surgical decision-making and potentially improve patient safety. In select cases, POC assays may also serve as a stepping stone for further pharmacogenomic testing to optimize future antiplatelet therapy.

Lessons Learned

Interindividual variability in antiplatelet medication metabolism presents a challenge for optimal perioperative management. The emergence of readily available point-of-care testing offers surgeons a valuable tool to personalize treatment decisions and guide critical perioperative choices.

Acknowledgment

We thank Karen Albright, DO, PhD, MPH, for her support.

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