Surgery on Patients on Antiplatelet Agents

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Clinical Vignette

A 65-year-old male has recently been evaluated for severe hip pain that has progressively become worse over the past couple of years and was determined that he will need to have the hip replaced. This patient has multiple medical problems including hypertension, hyperlipidemia, and diabetes mellitus. Two months ago he had a non-ST segment elevation myocardial infarction and two drug eluting stents (DES) were placed to the proximal right coronary artery. He was placed on aspirin 81 mg daily and clopidogrel 75 mg daily. The orthopedic surgeon would like to proceed with the hip replacement but is concerned that if he does not stop the dual antiplatelet therapy (DAPT) the bleeding risk will be too high and if he does stop the therapy then the patient is at risk of stent thrombosis. What considerations need to be considered when determining the next course of action?

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Introduction

Antiplatelet drugs are commonly used in the management of thrombotic diseases including transient ischemic attacks (TIA), stroke, acute myocardial infarction (AMI), acute coronary syndrome (ACS), peripheral arterial disease (PAD), percutaneous coronary intervention (PCI), cardiac and vascular surgery, primary and secondary cardiovascular disease prevention, and atrial fibrillation.

Heart disease is the leading cause of death and morbidity in the USA. In 2009 about 1 of every 6 deaths were attributed to coronary artery disease accounting for nearly 400,000 deaths (Go et al. 2013). In 2010 it was estimated that 492,000 patients had percutaneous coronary intervention (PCI) with stents placed in most of the cases (Go et al. 2013). With the advent of stents and the need for dual antiplatelet therapy (DAPT) to prevent stent thrombosis (ST), PCI has become the primary mode of coronary artery revascularization. The obvious advantages of this mode of revascularization are not without its limitations and difficulties. One of the major limitations to PCI with stent placement is the need for long-term DAPT. Early cessation of DAPT can lead to ST, which can cause myocardial infarction and potentially death (Grines et al. 2007). Continuation of these agents in patients undergoing certain invasive procedures can increase the risk of bleeding. The most common reasons for early discontinuation of DAPT include patient

A. Lichtin and J. Bartholomew (eds.), *The Coagulation Consult: A Case-Based Guide*,
DOI 10.1007/978-1-4614-9560-4_15,

noncompliance and the need for noncardiac surgery (van Werkum et al. 2009; Ferreira-Gonzalez et al. 2012; Spertus et al. 2006). It is estimated that between 4 and 8 % of patients undergoing coronary stent placement will undergo some type of noncardiac surgery (NCS) within the first year of stent deployment (Anwaruddin et al. 2009; Cruden et al. 2010; Berger et al. 2010). Thus, the risk of early and late ST can depend on the timing of surgery versus stent deployment. Surgery can produce stress responses including stimulation of the sympathetic nervous system, release of endogenous factors that can cause sheer stress, activate platelets, and cause vascular reactivity potentially increasing the risk of cardiovascular events (Desborough 2000). Also, there is a propensity towards hypercoagulability with increased clotting factors and decreased endogenous fibrinolysis (Bradbury et al. 1997; Mahla et al. 2001; Diamantis et al. 2007; Davenport 2007). All of the above factors may lead to increased risk of ST when DAPT is discontinued. Timing of DAPT discontinuation after stent deployment should be considered to prevent ST or the risks of major bleeding if DAPT were not to be interrupted. A recent review suggests that patients undergoing NCS after bare metal stent (BMS) or DES placement have the highest risk of major adverse clinical events within the first 6 weeks after BMS placement and up to 6 months after DES. This risk decreases over time to rates of 2.8 % in patients where NCS was done between 90 and 360 days after PCI (Singla et al. 2012; Kleinman 2012).

The American Heart Association/American College of Cardiology (AHA/ACC) recommendations for ST-segment elevation myocardial infarction undergoing primary PCI recommend a loading dose of aspirin to be continued indefinitely and a loading dose of either clopidogrel or prasugrel or ticagrelor to be continued at their respective maintenance doses for 1 year regardless of the type of stent placed (O'Gara et al. 2013). Similar recommendations are discussed in the non-ST segment elevation myocardial infarction guidelines, PCI guidelines and the American College of Chest Physicians guidelines for antithrombotic therapies (Wright et al. 2011).

However, there are situations in which DAPT may need to discontinued early and the following are issues to be considered: the urgency of the surgery or procedure, the type of stent placed (BMS versus DES), and as mentioned previously, the time from stent placement to the timing of DAPT discontinuation.

Antiplatelet Medications

Aspirin is a nonselective cyclooxygenase (COX) inhibitor that irreversibly binds to the COX enzyme in the platelet inhibiting the conversion of arachidonic acid to thromboxane A_2 (see Table 15.1). Thromboxane A2 is a vasoconstrictor and causes platelet aggregation. The duration of inhibition of aspirin is the life of the platelet, generally considered to be around 6–8 days. Aspirin is absorbed after oral administration with peak levels occurring 30–40 min after ingestion. The

Table 15.1 General information for selected antiplatelet antagonist

Drug	Class	*T½*	Duration of antiplatelet effect	Reversible inhibition
Aspirin	COX-inhibitor	~3 h	Life of platelet	No
Clopidogrel	$P2Y_{12}$ inhibitor	6 h (clopidogrel) 0.6–0.7 h (active metabolite)	Life of platelet	No
Prasugrel	$P2Y_{12}$ inhibitor	7–8 h (active metabolite)	Life of platelet	No
Cangrelor	$P2Y_{12}$ inhibitor	2.5–5.5 min	Reverses quickly	Yes
Ticagrelor	$P2Y_{12}$ inhibitor	7 h (ticagrelor) 9 h (active metabolite)	Reverses within days	Yes
Eptifibatide	Glycoprotein IIb/IIIa	2.5 h	4–9 h	Yes
Tirofiban	Glycoprotein IIb/IIIa	2 h	4–9 h	Yes

major adverse effect of aspirin is bleeding, most commonly from the gastrointestinal tract. This risk can be decreased by the use proton pump inhibitors (PPI's) (Ng et al. 2010).

Commonly used antiplatelet medications work synergistically with aspirin by inhibiting the adenosine diphosphate (ADP) receptor found on the surface of the platelet. The purinergic receptor $P2Y_{12}$ or ADP receptors when stimulated lead to the expression of the glycoprotein IIb/IIIa receptors which are necessary for binding of fibrinogen to cross link platelets during the formation of a stable thrombus. There are two main classes of $P2Y_{12}$ receptors inhibitors the thienopyridines (ticlopidine, clopidogrel, and prasugrel) and the non-thienopyridine (ticagrelor and cangrelor). Both classes bind to the $P2Y_{12}$ receptors to provide potent platelet inhibition but bind at different sites on this receptor.

Thienopyridines

Clopidogrel and prasugrel produce irreversible inhibition of platelet aggregation through binding to the adenosine diphosphate receptors and take approximately 3–7 days after daily administration to reach maximal effects; however, this process is shortened by an initial loading dose. The usual daily dose of clopidogrel is 75 mg given daily. A loading dose of 300–600 mg is commonly used prior to interventional procedures to achieve a therapeutic effect sooner. Both agents are pro-drugs that need to be converted to their active metabolites. Clopidogrel needs to undergo a two step process to become biologically active, whereas prasugrel only needs one metabolic transformation (Abraham et al. 2010). It is eliminated by the feces and urine. Clopidogrel has several adverse effects, mainly bleeding. This is especially of concern around the time of cardiac surgery when an increased need for surgical reexploration and the use of blood products has been reported. Other side effects include diarrhea, rash and rarely neutropenia and thrombotic thrombocytopenia purpura (TTP).

Ticlopidine, a first-generation thienopyridine, is seldom used today because of its neutropenic and TTP potential side effects and slower onset of action compared to clopidogrel and prasugrel.

Prasugrel, like clopidogrel, is an irreversible inhibitor of the $P2Y_{12}$ ADP receptor. It too is a prodrug that is rapidly absorbed and metabolized. Prasugrel's onset occurs more quickly and to a greater extent when compared with clopidogrel (Payne et al. 2007). Bleeding is the most significant side effect of prasugrel and it is recommended that prasugrel be discontinued 5–7 days prior to high bleeding risk surgical procedures (Antman et al. 2008; Roe et al. 2012).

Reversible $P2Y_{12}$ Receptor Antagonists

Ticagrelor is an orally administered, reversible inhibitor of the $P2Y_{12}$ receptor. Absorption is rapid and does not require biotransformation to an active compound unlike clopidogrel and prasugrel. Ticagrelor is metabolized into an equally potent active metabolite (AR-C124910XX) by the cytochrome P450 3A4 enzymes, however only achieves levels of one-third that of the parent compound (van Giezen and Humphries 2005; Storey et al. 2007). The half-lives of ticagrelor and AR-C124910XX are similar ranging from 7 to 12 h. A single loading dose of ticagrelor produces peak inhibition of platelet aggregation within 2 h. The offset of ticagrelor is between 72 and 120 h depending on the type of platelet inhibition assay employed, suggesting that this time period is required to decrease the risk of bleeding complications in patients undergoing noncardiac surgery. In the PLATO trial (Wallentin et al. 2009), patients who were to undergo cardiothoracic surgery had ticagrelor discontinued for at least 5 days prior to surgery.

Cangrelor is a reversible inhibitor of platelet function. It is given intravenously. Cangrelor reaches a steady state within 30 min without a loading dose. It has an elimination half-time of less than 9 min. Platelet function returns to normal within 60 min (Angiolillo et al. 2012). It is not currently available in the USA.

Glycoprotein IIb/IIIa Inhibitors

Abciximab is a monoclonal chimeric antibody that essentially irreversibly binds to the glycoprotein

IIb/IIIa receptor. It has a short half-life, however a long duration of effect secondary to its high binding affinity to the receptor. Platelet function returns to normal within 48–72 h of discontinuing therapy without platelet transfusion. Platelet transfusion can reverse the effects of abciximab due to its irreversible nature and no active metabolites. Eptifibatide and tirofiban reversibly bind to the glycoprotein IIb/IIIa receptors. Their half-lives are relatively short (2–2.5 h) in patients with normal renal function and prolongs in patients with renal insufficiency. These agents are dosed based on weight, and are continuous infusions. Once the drugs are discontinued, platelet function returns to normal within 6–12 h in patients with normal renal function, however may be prolonged in patients with severe renal insufficiency. The most common side effect of these agents is bleeding. The most common bleeding complaints include epistaxis, genitourinary and gingival bleeding. Other more serious but rare bleeding complication includes alveolar/pulmonary hemorrhages. Infusion durations of these agents have been limited to 96 h; however, there are occasions where longer infusions have been use.

Strategies for Patients Requiring Discontinuation of DAPT for Noncardiac Surgery

The most practical approach to patients requiring noncardiac surgery and disruption of DAPT would be to delay, if possible, the surgery until after 1 month for BMS and 12 months for DES. Patients should have their $P2Y_{12}$ therapy discontinued for 5–7 days before surgery and maintain aspirin if possible. Of the $P2Y_{12}$ inhibitors, prasugrel should be discontinued 7 days prior to surgery; however, clopidogrel and ticagrelor may be discontinued for 5 days as their effects dissipate more quickly. Ticagrelor's effects on platelets reverse more quickly in less than 5 days. However in the PLATO trial, which compared ticagrelor to clopidogrel in patients with ACS, the study design recommended to discontinue therapy 5 days before cardiovascular surgery (Wallentin et al. 2009).

If surgery cannot be delayed then the type of stent needs to be taken into consideration prior to discontinuation of DAPT. Patients who have received a BMS may have DAPT interrupted while continuing aspirin after 4–6 weeks and reinitiated once hemostasis is achieved (Grines et al. 2007). In contrast, patients who had a DES placed should wait, if possible, for 12 months (Grines et al. 2007).

Finally, if surgery cannot be delayed until the recommended duration of DAPT therapy is complete, the risks of bleeding versus the risk of ST needs to be considered. There are little data available to make general recommendations for urgent/emergent scenarios. Some institutions utilize glycoprotein IIb/IIIa inhibitors as a bridge prior to the surgery. Heparin and low-molecular-weight heparin have also been used; however, formal recommendations are lacking. Initiating either tirofiban or eptifibatide after DAPT has been discontinued and stopping the GP IIb/IIIa inhibitor 4–6 h prior to surgery has also been recommended. Currently, there have been no prospective randomized trials evaluating the use of GP IIb/IIIa inhibitors for bridging therapy. An initial case series of three patients with DES bridged with tirofiban demonstrated no cases of ST or major bleeding events (Broad et al. 2007). Ben Morrison (Ben Morrison et al. 2012) reviewed the use of GP IIb/IIIa inhibitors as a bridge for patients with DES undergoing either cardiac or noncardiac surgery. The primary endpoint of this study was the development of ST. Other endpoints included major and minor bleeding, the occurrence of ACS and death. Of the 19 patients included in this study, 6 patients underwent noncardiac surgery and 13 patients had cardiac surgery. No patients in the noncardiac surgery arm had an occurrence of ST or major bleeding; however in the cardiac surgery patients, there were seven episodes of major bleeding and one episode of minor bleeding without any occurrences of ST. Rassi et al. (2012), reviewed 100 consecutive patients receiving eptifibatide as a bridge to both noncardiac and cardiac surgery matched with historical controls. This study was primarily a safety study with the main endpoint being the number of units of blood received dur-

ing the hospital admission. Other endpoints included transfusion of platelets or fresh frozen plasma, major adverse cardiovascular events, intracranial and intraocular hemorrhage, gastrointestinal bleeding, severe epistaxis, surgical wound bleeding, and the need for return to the operating room. In this study, there were no significant differences between the groups in terms of the primary endpoint and secondary endpoints. This trial may not have had a sample size large enough to determine a difference. There were no events of ST in the groups. These studies suggest that bridging with a glycoprotein IIb/IIIa inhibitor does not increase the risk of major bleeding and may protect against ST in patients needing discontinuation from DAPT within the first year of stent implantation. However, there are a number of limitations to these trials including the retrospective nature of the trials, with limited comparisons to other therapies. There is one small prospective phase II trial evaluating tirofiban as a bridge in patients who had received a DES within the previous 1–12 months that required discontinuation of DAPT. Savonitto (Savonitto et al. 2010) systematically evaluated patients requiring discontinuation of oral therapy. They discontinued clopidogrel 5 days prior to surgery and initiated tirofiban on preoperative day minus 4. They also evaluated perioperative bridging with initiation of either clopidogrel or tirofiban postoperatively. The primary endpoint was the composite of cardiovascular death, MI, ST, or the need for surgical reexploration because of bleeding. No patients met the primary endpoint in this trial and there was one patient who developed major bleeding. However, 20 % ($n=6$) of the study subjects required either preoperative or postoperative blood transfusions.

The two greatest considerations in discontinuing a patient's DAPT are ST and risk of perioperative and postoperative bleeding. The risks of each need are to be considered in making the decision to interrupt DAPT. Procedures that are considered low risk of bleeding, such as endoscopy, dental extraction and surgery, minor orthopedic surgery, and cutaneous surgery may not necessitate the discontinuation of DAPT. However, surgery and procedures with intermediate and high risk of bleeding will need consideration of discontinuing DAPT and maintaining aspirin if possible through the perioperative course.

Case Conclusion

In this situation it would be best to post pone surgery until one year after the sent had been placed. If surgery was required sooner then waiting as long as possible and consulting with the provider that placed the stent would be most appropriate.

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