Case Report

Clinically relevant exaggerated pharmacodynamic response to dual antiplatelet therapy detected by Thromboelastogram® Platelet Mapping™

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Abstract

Dual antiplatelet therapy (DAPT) is the standard of care for primary and secondary prevention strategies in patients with coronary artery disease after stenting. Current guidelines recommend that DAPT be continued for 12 months in patients after receiving drug eluting stents. Approximately 5% of these patients will present within this 12-month period for noncardiac surgery. This case report describes a clinically relevant exaggerated pharmacodynamic response to DAPT detected by preoperative assessment of platelet function. Based on the clinical history and physical exam and subsequent lab results, a general anesthetic was performed rather than a spinal anesthetic and the surgical procedure was changed. An exaggerated pharmacodynamic response to DAPT poses its own set of risks (unexpected uncontrolled bleeding, epidural hematoma following neuraxial block placement) that point-of-care aggregation testing may decrease or mitigate by altering clinical decision making. If the clinical history and physical exam reveal possible platelet dysfunction in patients receiving DAPT, preoperative platelet function testing should be considered.

Key words: Dual antiplatelet therapy, clinical history and physical exam, Platelet Mapping

Introduction

Coronary artery disease (CAD) is the largest cause of mortality in the USA, accounting for 32.8% of deaths.[1] Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is the standard of care for primary and secondary prevention strategies in patients with CAD and peripheral arterial disease after percutaneous intervention and stenting.[2,3] Current American Heart Association and American College of Cardiology guidelines recommend that DAPT be continued for 12 months in patients after receiving drug-eluting stents. Approximately 5% of these patients will present within this 12-month period for noncardiac surgery (NCS). Single antiplatelet therapy increases the risk of urologic surgical hemorrhage by 20%, and DAPT increases the risk by 50%.[1,4] Ultimately, the risk of excessive intraoperative bleeding must be carefully weighed against the increased risk that discontinuing antiplatelet therapy prior to NCS has on myocardial infarction and stroke.[1,5] Current recommendations are to continue acetylsalicylic acid (ASA) and stop clopidogrel 5-7 days prior to NCS. If specifically requested by the surgeon, ASA may be stopped 7-10 days prior to NCS.[1,6,7]

Simple point-of-care devices exist to evaluate platelet function in patients receiving DAPT. One such device is Thromboelastogram® Platelet Mapping™ (TEG® PM™, Haemonetics® Corporation, Braintree, MA, USA). This case report describes a clinically relevant exaggerated pharmacodynamic response to DAPT detected by preoperative assessment of platelet function by TEG® PM™. The anesthetic and surgical management of this patient was amended based on these findings. The perioperative course was otherwise unremarkable with no adverse sequelae.

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Case Report

Written permission was obtained from a family member for this case report describing a patient with CAD on DAPT scheduled for elective transurethral resection of the prostate. This 66-year-old demented male, status-post redo aortobifemoral artery bypass graft 4 months prior, had stable CAD with well-controlled hypertension and normal left ventricular function. Pertinent history included easy bruisability with the presence of petechiae on physical exam. Current medications included clopidogrel 75 mg and ASA 81 mg. Clopidogrel had inadvertently been held for 10 days prior to NCS with low-dose aspirin and statin continued up to the day of surgery. A spinal anesthetic was planned given the large prostate size and extensive predicted surgical resection time. Since the patient was on DAPT and had petechiae, preoperative TEG® PM™ was performed to assess platelet function.

The TEG® PM™ assay quantitatively measures blood viscoelastic properties during clot formation. The maximum amplitude (MA) in the thromboelastographic trace is dependent on platelet function [Figure 1]. Four values that represent clot formation are determined by this test: The *R* value (or reaction time), the *K* value, the angle, and the MA. The *R* value represents the time to initial clot formation. The *K*-time measures the speed to reach a given level of clot strength. The angle is the tangent of the curve made as *K* is reached and provides more comprehensive clot kinetics than *K*. The MA reflects the ultimate strength of the fibrin clot. The percent inhibition of platelet function [Figures 2 and 3] is derived from the following equation:

$$\%\ \text{MA reduction} = 100 - \left| \left\{ \frac{MA_P - MA_{FIBRIN}}{MA_{THROMBIN} - MA_{FIBRIN}} \right\} * 100 \right|.$$

The TEG® PM™ analysis results for arachidonic acid (AA) (AA added to measure MA due to thromboxane A_2 pathway activation of uninhibited platelets, yielding MA_{AA}) are shown in Figure 2. Figure 3 is the TEG® PM™ analysis results for adenosine diphosphate (ADP) (ADP added to measure MA due to ADP receptor uninhibited platelets, yielding MA_{ADP}). The white lines represent the kaolin (soft white clay)-activated TEG® showing maximally stimulated platelets for the whole blood sample. The green lines represent fibrin mesh with no activated platelets. The red lines demonstrate fibrin mesh with platelets stimulated only by thromboxane A_2 [Figure 2] and ADP [Figure 3] respectively.

In Figure 2, the complete overlap of the red and green lines graphically indicates all platelets are inactivated by ASA. The red line in Figure 3 indicates a small fraction of platelets can be activated by ADP while the majority remains inhibited.

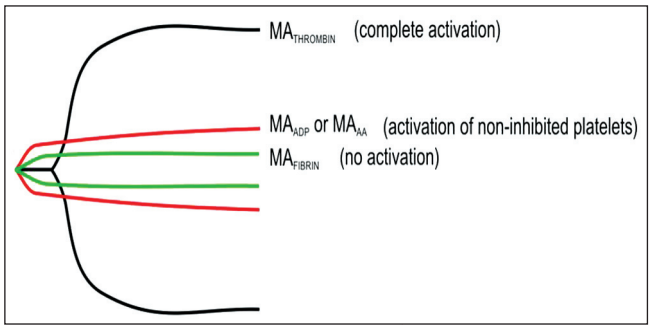
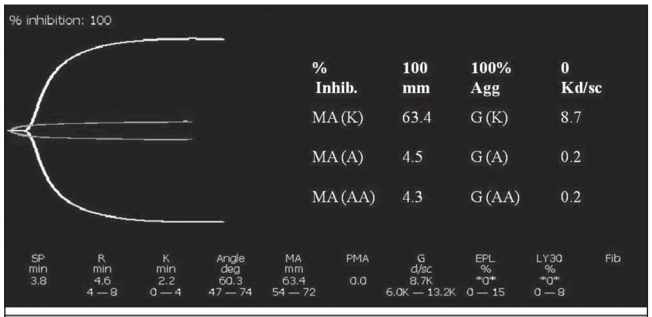
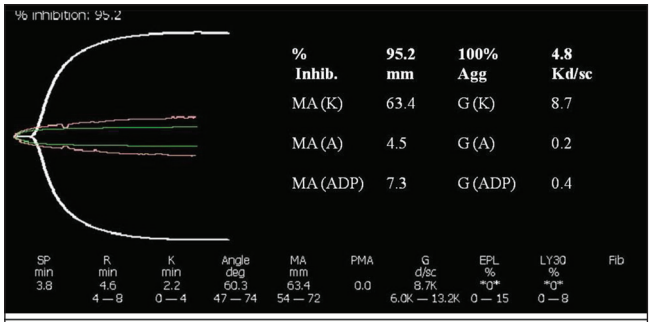


Figure 1: Schematic Thromboelastogram® Platelet Mapping™ tracings



Line Color	Seq	Channel	SP min	R min	K min	Angle deg	MA mm	PMA	G kd/sc	EPL %	LY30 %
White	1	1	3.8	4.6	2.2	60.3	63.4	0.0	8.7	*0.0*	*0.0*
Green	2	2	0.7	1.6	N/A	21.6	4.5		.2	0.0	0.0
Red	3	4	0.8	2.1	N/A	16.5	4.3		.2	0.0	0.0

Figure 2: Thromboelastogram® Platelet Mapping™ analysis results for arachidonic acid (AA) added to measure MA due to thromboxane A_2 pathway activation of non-inhibited platelets, yielding MA_{AA}. Note that percent inhibition is 100



Line Color	Seq	Channel	SP min	R min	K min	Angle deg	MA mm	PMA	G kd/sc	EPL %	LY30 %
White	1	1	3.8	4.6	2.2	60.3	63.4	0.0	8.7	*0.0*	*0.0*
Green	2	2	0.7	1.6	N/A	21.6	4.5		.2	0.0	0.0
Red	3	4	0.2	1.0	N/A	27.8	7.3		.4	0.9	0.9

Figure 3: Thromboelastogram® Platelet Mapping™ analysis results for adenosine diphosphate (ADP) added to measure MA due to ADP receptor uninhibited platelets, yielding MA_{ADP}. Note that percent inhibition is 95.2

Note that the percent inhibition of platelets by both ASA [Figure 2 with 100% inhibition] and clopidogrel [Figure 3 with 95.2% inhibition] is near complete.

Given these TEG® PM™ results, a general anesthetic was performed to avoid risking an epidural hematoma from a spinal anesthetic. In addition, the surgeon amended the procedure to a photoselective laser vaporization of the prostate to minimize

blood loss.[8] The procedure and postoperative course for the patient were uneventful.

Discussion

Studies of DAPT have noted individual response variability to clopidogrel and aspirin, highlighting various degrees of resistance.[9-11] This case report documents the other extreme of a resistance-sensitivity continuum: Exaggerated pharmacodynamic response to DAPT. Aspirin sensitivity, in terms of salicylate intolerance, has been documented but not in terms of greater-than-expected, clinically relevant platelet inhibition. Performing spinal anesthesia given the preoperative DAPT management in this case adheres to the American Society of Regional Anesthesia guidelines.[12] Assessment of platelet function was performed based on the history of easy bruisability and the presence of petechiae.

This case report is unusual since clopidogrel (held for 10 days) and low-dose aspirin taken up to the day of surgery resulted in near total platelet inhibition. A recent study at our institution documented a similar occurrence by aspirin but not by clopidogrel.[1] Notably, studies have demonstrated variable ADP and thromboxane A_2 receptor inhibition in patients not receiving antiplatelet medication.[13,14] Possibly less common than resistance, exaggerated pharmacodynamic response to DAPT poses its own set of risks (unexpected uncontrolled bleeding, epidural hematoma following neuraxial block placement) that point-of-care platelet aggregation testing may decrease or mitigate.

Conclusion

The clinical implications of this case report may be significant for both perioperative anesthetic management of individuals as well as DAPT management for primary and secondary prevention strategies in patients with CAD. If the clinical history and physical exam reveal easy bruisability, gingival bleeding, ecchymoses, petechiae, or hemarthroses in patients receiving DAPT, then platelet function testing should be considered prior to neuraxial blocks. Current recommendations for perioperative DAPT management in CAD patients undergoing NCS may require modification in this small subset of patients.

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