

Case Report

## Use of Eptifibatide as a Bridge Antiplatelet Agent for Intrathecal Drug Delivery System Placement

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Use of antiplatelet agents is becoming increasingly common, and their management may require new strategies if neuroaxial techniques are to be employed in patients who will not tolerate discontinuation of antiplatelet therapy.

The patient was a 46-year-old man with a past medical history significant for coronary artery disease and who had undergone 14 stents. He developed stent thrombosis (ST) while on clopidogrel. Following the ST, he was subsequently placed on prasugrel. While on prasugrel, the patient presented for an intrathecal drug delivery system (IDDS) trial and placement due to severe peripheral neuropathy unresponsive to several conservative medical treatments. He had previously undergone an unsuccessful spinal cord stimulator trial and received no pain relief. In consultation with his outside cardiologist, the patient received permission to hold his prasugrel for 7 days prior to his intrathecal pump trial. During the trial period's inpatient hospitalization, the patient developed chest pain. In consultation with the cardiology service in our institution, it was decided antiplatelet therapy should be re-instituted. The patient was bridged to his IDDS placement after the trial with intravenous eptifibatide. The eptifibatide drip was administered 6 hours prior to the IDDS implant. Functional platelet count was checked one hour before the IDDS was placed and the pump was placed without incident. The eptifibatide drip was reinstated one hour after the IDDS implantation. The patient was observed for 24 hours on the eptifibatide drip, transitioned to his home dose of prasugrel, and discharged home. At outpatient follow-up one week later, the patient demonstrated no neurologic or hemorrhagic complications and was satisfied with the pain control provided by the IDDS.

Prasugrel is an irreversible platelet inhibitor, which prevents ADP-induced platelet aggregation by binding the P2Y<sub>12</sub> receptor. Patients taking prasugrel will have deficient platelet activity until new platelets have been produced, a span of approximately 7 days. Eptifibatide is an intravenous glycoprotein IIb/IIIa inhibitor with a short half-life of 2½ hours. Inhibition of glycoprotein IIb/IIIa prevents platelet activation and aggregation. The drug effect ceases once it is discontinued and restoration of platelet function is not dependent upon new platelet production.

Patients requiring antiplatelet therapy in need of neuroaxial pain management procedures present challenging problems to pain management physicians. Current guidelines from the American Society of Regional Anesthesia have not identified any bridging agent suitable for patients who may not tolerate prolonged withdrawal from their antiplatelet therapy. In this case, eptifibatide was successfully utilized to bridge a patient whose comorbid conditions necessitated continuous antiplatelet therapy without the prolonged washout common to irreversible antiplatelet agents.

**Key words:** Intrathecal drug delivery system, anticoagulation, pain, eptifibatide, antiplatelet agents.

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Irreversible antiplatelet agents are becoming increasingly common. This provides new challenges to physicians performing neuroaxial pain management procedures. Antiplatelet medications are a therapy cornerstone in percutaneous coronary interventional procedures. They are crucial for periprocedurally avoiding thrombosis.

Stent thrombosis (ST) is a sudden and potentially catastrophic complication of percutaneous coronary interventions. The risk of ST is increased in the perioperative setting and is strongly associated with ceasing antiplatelet therapy. Stent thrombosis is a platelet-mediated process that occurs through progressive platelet activation and aggregation leading to thrombus formation (1,2).

Several risk factors for ST, including stent-related, procedure-related, and patient-related variables, have been described (3-8). However, the single most important predictor of ST is prematurely ceasing dual antiplatelet therapy (9-15). Subsequently, the American Heart Association, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association published an advisory on the risks of prematurely ceasing antiplatelet therapy, its significance in reducing ST risk, and on the hazards of prematurely ceasing this therapy (16).

A patient with significant coronary artery disease was treated with intravenous eptifibatide as a bridge prior to intrathecal pump placement after discontinuing irreversible antiplatelet agents. Using this drug allowed thromboprophylaxis to continue during the posttrial period while avoiding a prolonged drug wash-out common to peroral antiplatelet agents.

## CASE REPORT

The patient is a 46-year-old man with a past medical history significant for coronary artery disease. He had received 14 coronary stents and had a history of ST while he was on clopidogrel. He also had chronic kidney disease and had received 3 renal transplants. When seen, he had Stage 3 chronic kidney disease, and severe bilateral lower extremity peripheral neuropathy after a failed spinal cord stimulator implantation. Following failed pain control with the spinal cord stimulator, the patient agreed to placement of an intrathecal drug delivery system (IDDS). The patient's antiplatelet agents were withheld without incident during spinal cord stimulator implantation and explantation.

The patient had been taking prasugrel, 10 mg

daily, prescribed by his cardiologist after having failed clopidogrel. In consultation with his cardiologist, the patient received permission to hold his prasugrel for 7 days prior to his intrathecal pump trial. The intrathecal pump trial was performed using continuous intrathecal catheter with infusion from an external drug delivery system. The patient was admitted for observation. During his observation period, he experienced crushing sub-sternal chest pain which radiated to his jaw and left arm. Serial cardiac enzymes were within normal limits for the institution and his electrocardiogram was unchanged from previous studies. After consulting in-house cardiologists and noting the patient's previous history of ST, it was decided to reinstitute antiplatelet therapy. At this point, the cardiology team recommended the patient be bridged to his final pump placement on intravenous eptifibatide.

The patient was maintained on an eptifibatide drip during his trial period until his IDDS placement. The eptifibatide drip was discontinued 6 hours prior to the planned incision time, and a test of functional platelets was performed, which determined the patient had 135,000/mm functional platelets at the planned time of surgery. With this information, the patient was taken to surgery. Hemostasis was easily achieved and estimated blood loss was appropriate for the case. The patient tolerated the procedure well and was transferred to the recovery room. He was observed as an inpatient and had no acute events. During this period he was again bridged with eptifibatide one hour after the implant prior to resumption of prasugrel, which was reinstated at his home dose. He returned to the outpatient pain clinic approximately one week later and reported no neurologic or hemorrhagic complications and stated great satisfaction with his pain control.

## DISCUSSION

Coronary stents are high flow areas at risk of platelet-mediated thrombosis. They are not sufficiently protected against thrombosis by agents that target the coagulation pathway. ST is initiated by a platelet plug, which can serve as the foundation for the coagulation cascade, resulting in a cross-linked fibrin clot. Agents like heparin and warfarin will act farther down the cascade, but fail to prevent the platelet plug from forming a thrombus inside the vessel. When these agents are typically used in mono-therapy, it is generally to prevent the coagulation pathway from forming a fibrin clot in areas of blood stasis or in combination with antiplatelet therapy. Disruption of the endothelium, such

as by stents, in areas of high velocity blood flow will be prone to platelet-mediated thrombosis and will require antiplatelet therapy (5).

Prasugrel is a thienopyridine class antiplatelet agent that serves to irreversibly inhibit ADP-induced platelet aggregation by binding the P2Y<sub>12</sub> receptor. The irreversible binding requires new platelet production as a mean of return to platelet activity. Similar to clopidogrel, prasugrel is a pro-drug that requires hepatic bioactivation to its active form (17). In contrast to clopidogrel, CYP2C19 allele variants appear to have less effect on the bioavailability of the active metabolite (18). In this case, it is believed that this patient previously failed clopidogrel in the form of a stent thrombosis secondary to loss of function of the CYP2C19 allele, leading to insufficient bioavailability of the active metabolite.

Given the patient's prior history of ST, his multiple stents, and the need to stop prasugrel to minimize the risk of bleeding associated with the planned procedure, "bridging therapy" with an intravenous glycoprotein (GP) IIb/IIIa inhibitor was planned. GP IIb/IIIa is a platelet integrin. Platelet activation transforms the integrin into a state of high affinity to fibrinogen, which is the final common pathway of platelet aggregation and clot formation. GP IIb/IIIa inhibitors act by blocking fibrinogen-mediated cross-linking between platelets, thereby inhibiting platelet aggregation (19).

Of the available GP IIb/IIIa inhibitors, abciximab causes a prolonged irreversible antagonism of GP IIb/IIIa leading to platelet aggregation inhibition that lasts for at least 48 hours and up to 7 days (20). Given this prolonged inhibition time, abciximab should not be used perioperatively.

The synthetic peptides eptifibatide and tirofiban are competitive reversible binders to GP IIb/IIIa receptors and dissociate rapidly with less affinity than abciximab (21). Their half-life is quite short, and platelet function is completely restored 2-4 hours after stopping the infusion, making them potentially suitable for perioperative use. In essence, when the drug is discontinued, platelet activity returns quickly, and is not dependent on production of new platelets (11).

A review of the current literature failed to demonstrate any uses of eptifibatide as a bridging agent for interventional pain procedures. Morrison et al (22) performed a retrospective review of 19 patients (6 noncardiac and 13 cardiac) at their institution who received eptifibatide bridging therapy following discontinuation of their antiplatelet therapy. Major bleeding was recorded in seven (53.9%) cardiac patients and no noncardiac

patients. Minor bleeding was recorded in one (7.7%) cardiac and one noncardiac patient (16.6%). Rassi et al (23) performed a case-controlled retrospective review of 100 patients with coronary artery stents that were bridged to surgery following discontinuation of antiplatelet therapy. Seventy-one of those patients underwent cardiac surgery. Blood transfusion rates were observed and were not statistically different. The quantity of units transfused was also observed and was not statistically different. Finally, the rates of return to the operating room for bleeding and tamponade were observed, and while slightly higher in the bridged group (10% compared to 2.9%), this failed to achieve statistical significance. The authors concluded that there was not an increase in bleeding or transfusion requirement in the eptifibatide group; however, they do cite the sample size and power of the study as significant limitations.

Wessler et al (24) described a case of a patient who received 2 drug-eluting stents and one non-drug-eluting stent and subsequently required bronchoscopy and cervical mediastinoscopy for evaluation of possible lung cancer. The patient's clopidogrel was discontinued 5 days prior to the procedure and the patient was bridged on intravenous eptifibatide. On postoperative day one, the patient received a loading dose of 300 mg clopidogrel and was then maintained on 75 mg daily. He was discharged home on postoperative day 2. On postoperative day 7, the patient presented to the emergency department complaining of chest pain that had persisted for several days. A cardiac work-up was negative; however, computed tomography of the chest demonstrated a hematoma measuring 5 x 5 x 4 cm. The hematoma was treated conservatively and resolved without complication.

Roth et al (25) described a case of a patient who required an L4-L5 discectomy and decompression of the L4-L5 nerve root 3 months following placement of 2 drug-eluting stents. This patient had been maintained on aspirin and clopidogrel. The patient's clopidogrel was held 5 days prior to surgery and an eptifibatide bridge was instituted until 8½ hours prior to surgery. The patient then resumed her daily aspirin dose of 81 mg 6 hours after surgery and received a loading dose of 300 mg of clopidogrel 15 hours after surgery, followed by her daily dose of 75 mg. The patient tolerated the procedure well without hemorrhagic or thrombotic complications.

The available data do not support the conclusion that eptifibatide bridging increases bleeding risk over traditional antiplatelet therapy; however these data

come from limited studies and further evaluation is warranted. Given the increased bleeding risk inherent to antiplatelet therapy, all patients receiving antiplatelet therapy should be observed for bleeding complications.

The American Society of Regional Anesthesia currently has no formal recommendations for patients taking prasugrel, but recommends that patients taking clopidogrel at risk for ST have elective surgeries postponed or hold their clopidogrel for 7 to 10 days if surgery is necessary (26-27). No recommendations for bridging therapy are rendered for patients that will not tolerate withdrawal of their antiplatelet therapy (26). The *British Journal of Haematology* offers similar guidelines, with no specific recommendations for prasugrel, but a 7 day washout period for clopidogrel and a 4-8 hour washout period for eptifibatide. The *British Journal of Haematology* does recommend checking the platelet count for patients taking eptifibatide as this agent can cause profound thrombocytopenia (28).

## CONCLUSION

Patients requiring antiplatelet therapy in need of neuroaxial pain management procedures present challenging problems for pain management physicians. Current guidelines from the American Society of Regional Anesthesia have not identified any bridging agent suitable for patients who may not tolerate prolonged withdrawal from their antiplatelet therapy. After a review of the literature, we have not identified an increased bleeding risk related to the use of eptifibatide as a bridging agent, however we note that all patients receiving antiplatelet therapy are at a higher risk for hemorrhage and should be observed for such a complication in the perioperative period. In this case, eptifibatide was successfully utilized to bridge a patient whose comorbid conditions necessitated continuous antiplatelet therapy without the prolonged washout common to irreversible antiplatelet agents.

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