Management of a Patient with a Thoracic Epidural After Accidental Clopidogrel Administration

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We report a case of accidental clopidogrel administration in a patient receiving ongoing epidural analgesia postoperatively. The epidural catheter was removed 7 hours after the clopidogrel dose without incident. The onset of inhibition of adenosine diphosphate–induced platelet aggregation in healthy individuals has been reported at 12 to 24 hours after administration of a single 75-mg dose of clopidogrel. This case demonstrates the importance of understanding clopidogrel's pharmacology to avoid ordering unnecessary tests, which may delay catheter removal. Consideration of appropriate testing and limitations in the context of unintentional antiplatelet administration with indwelling neuraxial catheters is discussed. (A&A Case Reports. 2015;5:18–20.)

Although there are guidelines regarding the discontinuation of clopidogrel before engaging in neuraxial techniques,[1] no definitive recommendations address the issue of epidural catheter removal in the event of accidental administration of clopidogrel. One of the main concerns of concomitant epidural analgesia and clopidogrel exposure is the formation of an epidural hematoma, with consequences ranging from back pain, lower-extremity weakness, and radicular pain, to complete paraplegia.[2–4] The toxicity of clopidogrel is highlighted by reported cases of spontaneous spinal epidural hematoma.[5–10] We report the case of a patient who received a single 75-mg dose of clopidogrel postoperatively in the presence of an indwelling epidural catheter.

Verbal consent was obtained from the patient to publish this report, and the case report was in compliance with IRB requirements.

CASE DESCRIPTION

A 68-year-old man, ASA physical status IV, was scheduled for a pseudoaneurysm repair of a saphenous vein to the obtuse marginal graft via a left thoracotomy incision with cardiopulmonary bypass on standby. The graft pseudoaneurysm measured 7.8 cm and was impinging on the lingular bronchus, causing shortness of breath and dyspnea on exertion. His medical history included obstructive sleep apnea, tobacco abuse, congestive heart failure, and coronary artery disease as well as a non–ST-segment elevation myocardial infarction in 1992. He underwent coronary artery bypass graft surgery in 1992 with a saphenous vein graft to the obtuse marginal followed by stent placement in the graft in 2005. The venous pseudoaneurysm arose distal to the stent. His medications included carvedilol, lorazepam, isosorbide mononitrate, lisinopril, rosuvastatin, hydrochlorothiazide, aspirin, and clopidogrel. Aspirin and clopidogrel had been discontinued 7 days before hospital admission. Preoperative blood work, including renal function, prothrombin time (PT), activated partial thromboplastin time, and platelet count, was normal.

The evening before surgery, a T5-6 epidural catheter was placed via a left paramedian approach with a 17-g Tuohy needle while the patient was in the sitting position. A single, nontraumatic needle pass was made without visualization of blood or cerebrospinal fluid from the Tuohy needle or the epidural catheter. The patient tolerated the procedure well without complications. The surgical team and the patient were notified that clopidogrel should not be restarted until after the epidural catheter was removed postoperatively.

The following day, the patient underwent surgery without cardiopulmonary bypass and was taken to the intensive care unit for observation. An epidural infusion (bupivacaine 0.25% at 6 mL/h and hydromorphone 0.2 mg/h) was started with adequate pain control. On postoperative day (POD) #2, the patient reported minimal pain. A 75-mg dose of clopidogrel was accidentally administered one hour before the pain management team was notified of the administration. The patient was immediately counseled regarding the medication error and instructed to inform his nurse if he had any symptoms of an epidural hematoma, including back pain, radicular pain, sensory changes, weakness, and bowel/bladder changes; serial hourly neurologic checks were initiated.

The results of stat laboratory tests revealed the patient had a normal complete blood count and smear. The platelet function analyzer (PFA)-100 collagen/epinephrine closure time (CEPI CT) was low. Thromboelastogram (TEG®) parameters were normal (Table 1). Also, the PT and international normalized ratio were elevated minimally (Table 1). On the basis of the verified administration time, laboratory results, and normal neurologic examination in conjunction with guidelines recommending epidural catheter removal at an international normalized ratio less than 1.5,[1] the catheter was removed 7 hours after the dose of clopidogrel. The pain management team was notified about an hour after the clopidogrel dose was administered, and the following 6-hour delay before epidural catheter removal was primarily due to awaiting the results of the aforementioned laboratory tests. There was no visualization of blood on the catheter tip upon removal. The patient continued to have neurological checks every 2 hours for the next 24 hours.

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Table 1. Laboratory Results Before Removal of Epidural Catheter

	Results	References
TEG® analysis		
R, reaction time	8.5 min	5.2–9.0 min
α angle, fibrinogen activity	63.2 degrees	54.0–73.0 degrees
MA, platelet function	69.1 mm	57.0–77.0 mm
EPL, estimated lysis	0%	0–15%
PT/INR		
PT	16.0 s	11.4–14.0 s
INR	1.4	0.9–1.2
PFA		
Collagen/epinephrine closure time	91 s	94–193 s

TEG® = thromboelastogram; MA = maximum amplitude; EPL = estimated percentage lysis; PT = prothrombin time; INR = international normalized ratio; PFA = platelet function assay.

On POD #3, the patient resumed clopidogrel and continued to do well postoperatively without incident after hospital discharge on POD #7.

DISCUSSION

This case highlights an unnecessary delay in epidural catheter removal in the setting of accidental clopidogrel administration while awaiting uninformative laboratory results that did not directly assess clopidogrel's antiplatelet effect. Instead, the epidural catheter should have been removed immediately based on clopidogrel's known pharmacology. Fortunately, this patient did not experience any adverse effects. A number of reports highlight the spectrum of complications associated with clopidogrel, including the development of a spontaneous, symptomatic epidural hematoma during the course of ongoing therapy.[7–9]

Clopidogrel is a prodrug, and although 50% of the prodrug is absorbed in the duodenum, only 15% of the absorbed prodrug is available for transformation by cytochrome CYP2C19 to the active agent.[11] Therefore, genetic polymorphisms of CYP2C19 and other cytochromes can account for variability in response to therapy. Similarly, varying rates of gastrointestinal absorption of clopidogrel can lead to variability in onset and effect of drug administration.[11] Medication interactions, diet, smoking, alcohol, demographics, and pretreatment platelet hyperreactivity all contribute to wide variability in the pharmacokinetics and pharmacodynamics of clopidogrel.[12] Generally, clopidogrel's antiplatelet effect on the P2Y12 adenosine diphosphate (ADP) receptor is slow in onset, irreversible, and highly variable. The onset of inhibition of ADP-induced platelet aggregation in healthy individuals has been reported at 12 to 24 hours after administration of a single 75-mg dose of clopidogrel.[13] Maximum ADP-induced platelet aggregation is achieved 3 to 7 days after achieving a steady state with a 75-mg daily dose of clopidogrel.[14] In contrast, a 600-mg initial loading dose of clopidogrel achieves comparable platelet aggregation inhibition within 8 hours.[15]

Complete blood count, PT, and activated partial thromboplastin time are not affected by clopidogrel. The PFA-100 (Siemens, Munich, Germany) test, designed to measure platelet adhesion and aggregation, initially was used to detect congenital or acquired platelet dysfunction.[16] The PFA-100 test uses 2 cartridges that contain a combination of collagen and ADP or collagen and epinephrine.[17] Initially, a prolonged CEPI CT in conjunction with a normal collagen/ADP (CADP) CT was thought to detect aspirin. However, subsequent research has demonstrated PFA-100's low sensitivity for detecting aspirin.[17] Similarly, it initially was considered that a prolonged CADP CT detected the effect of ticlopidine or clopidogrel. However, subsequent studies have demonstrated inconsistent prolongation in CADP CT by either medication, and both CEPI and CADP CTs may be normal in patients receiving ongoing clopidogrel therapy because the PFA-100 lacks sensitivity in detecting clopidogrel's effect.[17–19] In our case, only the CEPI CT was obtained, even though the CADP CT would have been more relevant. Furthermore, we would not have expected these tests to be abnormal 4 hours after clopidogrel administration (when the laboratory tests were drawn), given the onset time of platelet inhibition of at least 12 hours for a single 75-mg dose of clopidogrel.

The VerifyNow System (Accumetrics, San Diego, CA) uses measurement of the inhibition of light transmission by platelets and can specifically indicate a P2Y12 inhibitor effect reported in P2Y12 reaction units.[20] Although not available in our hospital, VerifyNow is approved by the Food and Drug Administration and available in the United States. In this case, with laboratory tests drawn 4 hours after administration of clopidogrel, this test should also have been within normal limits.

A number of tests address viscoelastic evaluation of clotting. The standard TEG® assay reagent is not able to determine clopidogrel's effect because it uses kaolin-related activation of thrombin. This thrombin-initiated platelet activation neutralizes the ability of a standard TEG® test to predict antiplatelet agent effects.[17] A newer TEG® assay and protocol called platelet mapping uses 2 TEG® machines to estimate clopidogrel's effect by using arachidonic acid and ADP as platelet activators in the setting of factor XIII-mediated diminished fibrin activation.[21] When the TEG® platelet mapping test is compared with a simultaneous standard TEG®, clopidogrel's effect can be reported in 15 to 60 minutes.[21] Rotation thromboelastometry is a variation of the TEG® concept with similar reagent-dependent limitations on antiplatelet agent detection.[17] Sonoclot (Sienco Inc., Arvada, CO) does not have an assay to identify clopidogrel's effect.[17] Traditional TEG®, used in our case, does not directly assess clopidogrel's effect on platelet function.

The "gold standard" of platelet function testing is considered to be light transmittance aggregometry, which uses several reagents to induce in vitro activation of platelets.[20] When an ADP assay is used, light transmittance aggregometry may estimate clopidogrel's effect, although it is not commonly used for this purpose. This test may take up to 6 hours to complete.

After verifying the administration time of the clopidogrel, and obtaining stat laboratory tests, we elected to remove the epidural catheter 7 hours after clopidogrel administration. Delaying further would have overlapped with the anticipated pharmacologic onset of clopidogrel at 12 hours. Ideally, we would not have awaited the results of platelet function tests, given their pitfalls and the likelihood that they would be normal. Instead, we should have chosen immediate epidural catheter removal with serial neurological checks for 24 hours after removal.

In summary, our case demonstrates the limitations of normal platelet function assays and thromboelastogram parameters and extrapolates from literature regarding the pharmacokinetics and pharmacodynamics of clopidogrel to safely remove an epidural catheter.

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