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Case Report

Profound Coagulopathy and Lactic Acidosis in a Diabetic Patient with Acute Renal Failure Taking Dabigatran and Metformin

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Abstract

A 71-year-old female was admitted for treatment of a left hemispheric stroke secondary to uncontrolled hypertension and carotid artery stenosis. Despite worsening renal function, she was initiated on dabigatran 150 mg twice daily. Upon discharge her home medications, including aspirin and metformin, were restarted. Two weeks after discharge she presented to the Emergency Department lethargic and in moderate respiratory distress. An extensive workup revealed lactic acidosis, acute kidney failure, and profound coagulopathy. Pertinent labs on admission included: hemoglobin = 7.5 g/dL, hematocrit = 23.8%, potassium = 7 mmol/L, anion gap 29 mmol/L, bicarbonate = 7mmol/L, BUN = 191 mg/dL, creatinine = 4.87 mg/dL, lactate = 9.8 mmol/L, prothrombin time (PT) greater than 100 seconds, INR greater than 10, and arterial blood gases (ABG): pH=7.2, pCO_2 =15 mm Hg, pO_2 = 227 mm Hg, HCO_3 = 6.3 mmol/L.

Transfer to a tertiary care hospital resulted in a nephrology consult and continuous renal replacement therapy (CRRT) to remove accumulated metformin and dabigatran. After 72 hours of supportive treatment, CRRT was discontinued and the profound coagulopathy and lactic acidosis resolved.

The absence of dabigatran renal dosage adjustment combined with the metformin-associated lactic acidosis contributed to a life-threatening adverse event. This event potentially could have been avoided had the risk factors been identified and appropriate drug adjustments made prior to her initial discharge.

Keywords: Dabigatran; Metformin; Profound Coagulopathy; Lactic Acidosis

Introduction

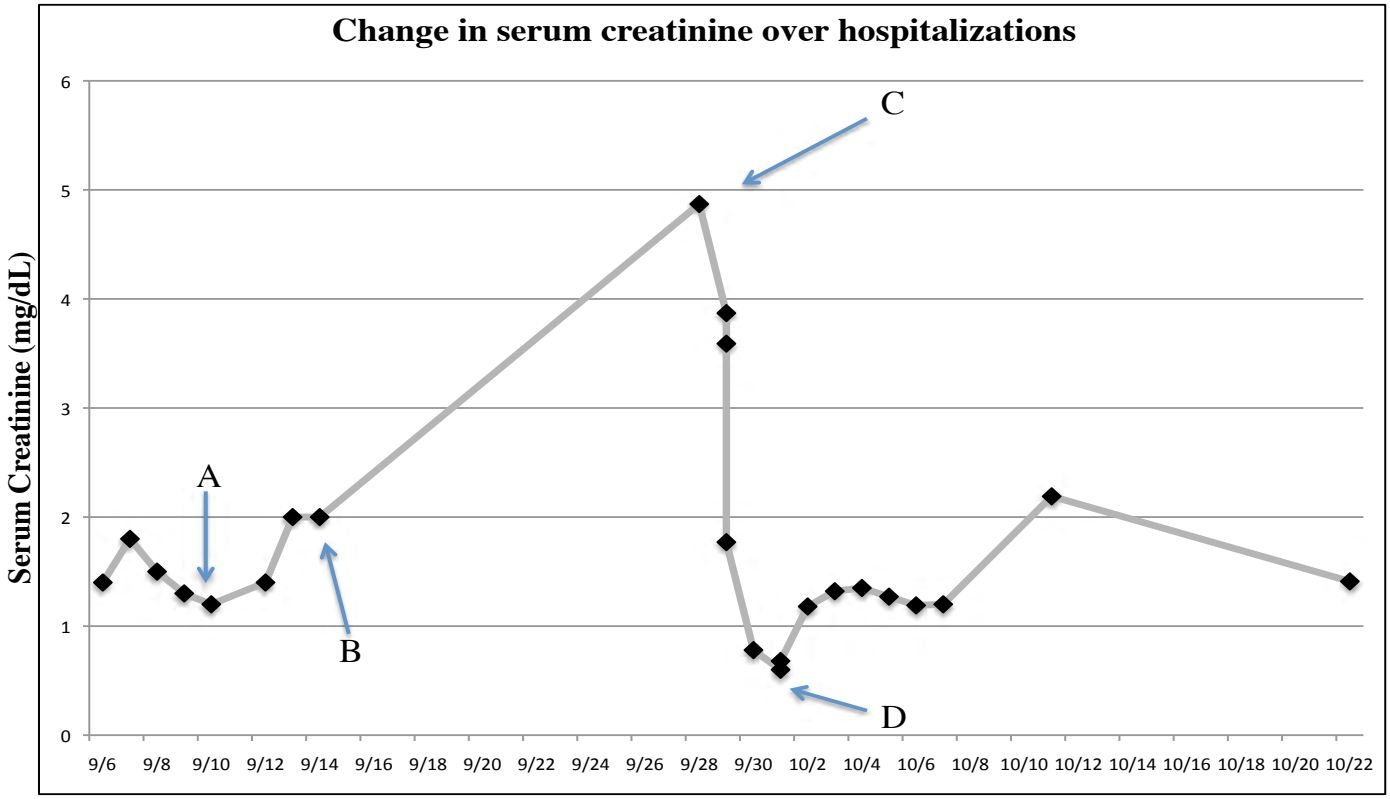
Dabigatran (Pradaxa®) is a direct thrombin inhibitor anticoagulant indicated for treatment and prevention in patients with pulmonary emboli, deep vein thrombosis, and for risk reduction of stroke and systemic emboli associated with non-valvular atrial fibrillation[1]. Until recently, dabigatran did not have a reversal agent, rendering patients taking dabigatran at an increased risk of major bleeding consequences. There is no commercially available biologic surrogate marker to monitor for efficacy and safety or to optimize dabigatran dosing in specific patient populations (e.g, renal insufficiency, obese patients, etc). Dabigatran is eliminated primarily in the urine (80% of total clearance), thus dosing adjustments are warranted for patients with renal insufficiency [1].

Lactic acidosis is a serious, life-threatening but rare adverse reaction that can occur with metformin accumulation [2]. Patients with decreased renal clearance, hepatic disease, and other conditions consistent with hypoperfusion or hypoxemia are at a higher risk for metformin accumulation and possible development of metabolic acidosis [2].

Case Presentation

We describe a case of a 71-year-old female with recent admission for management of a left hemispheric stroke, thought secondary to a 90% left carotid artery stenosis and uncontrolled hypertension. She was initially hospitalized at a critical access hospital facility (CAHF) for eight days. She became medically resistant and was discharged prematurely against medical advice; on discharge, she was prescribed dabigatran 150 mg twice daily and aspirin 81 mg in addition to the rest of her usual medications, which included metformin 1000 mg twice daily, despite declining renal function markers (SCr 1.2 mg/dL at baseline; increased to 2 mg/dL two days after beginning dabigatran [Figure 1]). Two weeks later, she presented to the Emergency Department (ED) at the same CAHF appearing lethargic and in moderate respiratory distress with audible rhonchi in her lung bases, unable to reveal much history because of her respiratory difficulty. Extensive evaluation in the ED resulted in a diagnosis of profound coagulopathy, acute renal failure and lactic acidosis.

Upon physical exam, she was observed to have extensive ecchymoses on her arms and her capillary refill was sluggish. The patient was hemoccult-positive. She had epistaxis, hematemesis, melena, and vaginal bleeding. She was hypertensive with systolic blood pressure readings between 144-150 mm Hg (148/35 mm Hg). An EKG revealed sinus tachycardia (117 bpm) without ischemic changes or QRS widening but peaked T waves, presumably associated with her hyperkalemia (7 mmol/L). On room air her pulse oximetry (SpO_2) was 83%. The patient's remaining laboratory results were significant for WBC = 19.2 103/uL, hemoglobin = 7.5 g/dL, hematocrit = 23.8 %, potassium = 7 mmol/L, anion gap 29 mmol/L, serum glucose = 305 mg/dL, BUN = 191 mg/dL, serum creatinine = 4.87 mg/dL (estimated glomerular filtration rate 9 ml/min/1.73m^2), lactate = 9.8 mmol/L, prothrombin time (PT) greater than 100 seconds, INR greater than 10, troponin = 0.03 ng/mL, BNP = 545 pg/mL, albumin = 3.1 g/dL and a normal urinalysis. The patient's arterial blood gases were as follows: pH=7.2, pCO_2 =15 mm Hg, pO_2 = 227 mmHg, HCO_3 = 6.3 mmol/L, and O_2 saturation = 96.8%.



Point A: Dabigatran 150 mg twice daily started
Point B: Patient discharged against medical advice
Point C: Patient presents to ED with profound coagulopathy and lactic acidosis. CRRT began and dabigatran and metformin discontinued
Point D: CRRT discontinued on 10/1

Figure 1. Change in Serum Creatinine before and after Dabigatran was initiated

The patient was started on 15 L of O_2, given 1 L normal saline (NS) IV fluid bolus, 1 unit of cross-matched blood, 2 units of fresh frozen plasma (FFP), 1 unit of packed red blood cells (PRBC), and 1 dose of levofloxacin was administered for concern of hospital acquired pneumonia due to her recent hospitalization. Additionally, she was administered 1 gram calcium gluconate IV, 50 mEq of $NaHCO_3$ IV, and 15 units of regular insulin subcutaneously and placed on Bilevel Positive Airway Pressure (BiPAP) breathing apparatus to reduce the work of breathing.

At this point, the decision to transfer her to a tertiary hospital was made and she was transported via helicopter. She was admitted to the tertiary hospital ICU (via ED) with a diagnosis of acute blood loss anemia, hemorrhagic shock, profound coagulopathy, acute kidney injury, and respiratory distress, with a background setting of poorly controlled hypertension and diabetes, cerebrovascular disease, and recent left hemispheric, ischemic stroke.

Initial management was supportive. The volume-associated hypotension was treated with IV fluid resuscitation (2 more liters of 0.9% NS), with continuous monitoring and resuscitative adjustment, including pharmacologic.

Initially, she was not intubated. Her gastrointestinal (GI) bleeding, precipitated by her profound coagulopathy, made correcting the coagulopathy paramount.

The patient was started on a twice-daily proton-pump inhibitor. Her acute kidney injury and hyperkalemia were thought secondary to global hypoperfusion. She continued to receive FFP and PRBC transfusions as necessary and the ED physician at the receiving hospital administered 10 mg intravenous vitamin K. Potential fibrinogen depletion was also monitored. After initial resuscitation and stabilization, she underwent upper GI endoscopy, which revealed diffuse mucosal bleeding, but no ulcerations or arterial bleeding sources. GI mucosal prophylaxis with proton pump inhibitors was continued. With regard to her acute kidney injury, the impression at this point was that cumulative poor renal clearance of both the dabigatran and metformin resulted in severe metformin-associated lactic acidosis and profound dabigatran-associated coagulopathy related to thrombin inhibition. The patient also developed fever with rigors, acute respiratory depression and aspirated blood from an acute epistaxis episode; therefore, antimicrobials (piperacillin/tazobactam and vancomycin) and mechanical ventilation were added to the patient's treatment plan, respectively.

	9/30 04:20	9/30 10:05	9/30 16:40	9/30 22:15	10/1 03:50	10/1 13:00	10/1 15:50	10/2 04:16
Hgb (g/dL)	8.8	9.0	6.1	7.7	7.2			9.4
Hct, Final (%)	26.4	26.2	17.7	21.8	20.1			27.6
Platelet count ($x10^9$/L)	92	77	68	47	44			79
Protime (seconds)	97.2	84.3	49.9	25.1	20.4		15.9	15.1
Prothrombin Time (PTT) (seconds)		122.2			59.1		40	
INR	12.6	10.5	5.4	2.3	1.7		1.3	1.2
Thrombin Time (seconds)						266		71
BUN/CREA Ratio	42.06		48.58		33.33			13.33

Table 1. Pertinent Laboratory Values

Nephrology consult assessed her renal function as critical and remarked that the severe lactic acidosis was not likely to improve without metformin removal through continuous renal replacement therapy (CRRT), thus CRRT was initiated. Additionally, the CRRT could be used to treat dabigatran toxicity. [1,3,4] Ultra-filtration was used given the development of generalized edema and a low albumin (2.4 gm/dL). The losartan, a potentially renal compromising drug at this point, was discontinued. Thrombin time was utilized as a biologic marker to assess dabigatran activity and to assess fibrinogen. [5,6] While the immediate concern was correcting and managing her coagulopathy, strict attention was paid to the antithrombotic reversal and subsequent increased risk for thromboembolic events, especially recurrent stroke.

Over the next 72 hours, the patient's acid/base balance, blood pressure, and electrolyte status were managed appropriately, the patient was extubated, and the CRRT was discontinued. Over the course of the hospital stay, the patient received 8 units of PRBC, 1 unit of platelets, and 10 units of FFP. The patient was transferred from the ICU to a step-down unit and continued to slowly convalesce. The gastrointestinal bleed significantly diminished with resolution of the coagulopathy.

Discussion

Metformin is an oral dimethylbiguanide antihyperglycemic drug used in the treatment and management of Type II diabetes [2]. Metformin has a relatively short half-life (~6 hours) and accumulation does not occur in normal circumstances [2] .However, in situations of reduced renal clearance, lactic acidosis can occur [2]. Lactic acidosis can impact approximately 1% of hospitalized patients and is one of the most common causes of high serum anion gap metabolic acidosis [7]. Lactic acidosis occurs in 0.03 cases per 1000 patient years [8]. Out of those patients who develop lactic acidosis 50-80% will end in death [1,7,8]. Precipitating factors that increase the propensity for developing lactic acidosis include hepatic disease, antiretroviral therapy, cancer, acute renal failure, metformin therapy, and respiratory failure, the latter three which were present in our patient [7,9-11]. Treatment with metformin, angiotensin II antagonists, and/or non-steroidal anti-inflammatory agents is not uncommon in elderly individuals with multiple comorbidities and this combination can be detrimental in the event of dehydration or severe hypovolemia. Our patient was concomitantly taking losartan, an angiotensin receptor antagonist, which may have been a contributing factor and this was discontinued on nephrology evaluation.

In patients with renal insufficiency and decreased creatinine clearance, the half-life of metformin may be prolonged increasing the risk of lactic acidosis. Metformin serum levels were not obtained in our patient, although there were markedly elevated serum lactate levels (9.8mmol/L) and an elevated anion gap (25 mEq/L). There was no evidence of ketonuria, toxic ingestion (e.g., ethylene glycol, salicylates), sepsis, or tissue hypoxia therefore, an iatrogenic cause of the lactic acidosis was predominantly suspected owing to hypoperfusion-associated acute renal injury from the profound dabigatran-associated hemorrhage and subsequent metformin accumulation (Type B lactic acidosis) [12].

Metformin therapy should be reviewed and considered for discontinuation if the renal clearance function (estimated GFR) decreases below 45 ml/min/1.732 and discontinued if the estimated GFR falls below 30 ml/min/1.73m2.2,[13] Interruption of metformin should be considered with states of tissue hypoxia (e.g., myocardial infarction, sepsis), use of contrast media, or use of general anesthesia [8, 10, 13, 14].

Dabigatran (Pradaxa®) is a direct thrombin inhibitor anticoagulant. A subset analysis from the RE-LY trial compared dabigatran use in patients with atrial fibrillation and diabetes mellitus (DM) to patients without DM [15]. The primary outcome of the study was to determine if two different doses of dabigatran were non-inferior in preventing strokes compared to the standard treatment of warfarin. The two therapies were considered non-inferior in preventing stroke events. Patients with DM were more likely to have an intracranial bleed while taking 150 mg dabigatran twice a day compared to 110 mg dabigatran twice a day, although this occurrence was less likely than in those patients taking warfarin. This study may suggest that patients with DM should be on a lower dose of dabigatran to prevent adverse hemorrhagic reactions [15].

A significant limitation of the RE-LY trial was that patients with severe renal impairment were excluded [15]. Given that dabigatran is 80% renally eliminated, patients with severe renal impairment are at an increased risk for major bleed secondary to dabigatran accumulation and toxicity [3,15]. While our patient did not have a history of documented renal disease, it was thought that her global hypoperfusion brought about by the dabigatran-associated hemorrhage resulted in acute renal injury, which subsequently increased her risk for metabolic acidosis from the metformin. Further, at the time of her initial discharge, her renal function markers (e.g., serum creatinine) were trending upward, suggesting compromised filtration and perhaps warranting drug adjustments.

The lack of a biologic surrogate marker to monitor for efficacy, toxicity and dose adjustment of the dabigatran is vividly illustrated in this case. An argument can be made that had a marker been available, monitoring and dose adjustment of dabigatran may have, indeed, abated the cascade of events that ensued.

Additionally, at the time, no commercially available reversing agent (e.g., idurucizumab) was available and the use of prothrombin complex concentrates have shown little effectiveness in managing dabigatran-associated bleeding complications [5,16]. Therefore, supportive care, whole and fraction-

ated blood products, and continuous hemodialysis were used in our patient to manage and reverse the dabigatran toxicity. Of note, the ED physician ordered intravenous vitamin K, which was predictably ineffective for reversing the dabigatran – associated anticoagulation. The reversal of the antithrombotic state was with the understanding that this reversal could possibly render the patient susceptible for systemic thrombosis and emboli. The decision to use CRRT versus intermittent conventional treatment was to avoid possible dabigatran "rebound" [4,5].

Partial thromboplastin time (PTT) and thrombin time (TT) were selected as coagulation assays because they have been shown to detect the presence of dabigatran [5]. However, their imprecision and inability to detect very low or very high dabigatran concentrations in assessing accurate anticoagulation status in situations requiring more exactness, such as prior to emergency surgery or, as in our case, critical hemorrhage, renders these assays suboptimal. In retrospect, given this concentration insensitivity, a different assay for dabigatran assessment should have been selected. Dilute thrombin time (dTT) is a more sensitive assay and can measure the activity of thrombin in the plasma and thus directly measure the activity of the direct thrombin inhibitors, however this laboratory assay is not universally available [5,6,17]. Ecarin clotting time is considered a more precise method for assaying dabigatran, but is also not widely commercially available [17]. PTT and TT were felt to be appropriate monitors for detecting the presence of dabigatran while the patient was receiving CRRT and as one determines continuing or discontinuing the CRRT. After the patient's TT reached 71 seconds the CRRT was discontinued to prevent complete removal of dabigatran in order to prevent thromboembolism.

The patient's past medical history was significant for hyperlipidemia, hypertension, DM, gout, COPD, CVA, carotid artery stenosis (90% left), and current tobacco use (1 pack per day). After her recent CVA, the patient was started on (off-label) dabigatran (Pradaxa®) 150 mg twice daily and clonidine (Catpres®) 0.1 mg three times a day in addition to her other meds. Her history lacked detailed discharge information after her stroke but it was noted that she was initially started on 81 mg of aspirin daily. The dabigatran was then apparently added in lieu of aspirin because the aspirin was thought to be associated with a relative thrombocytopenia (175 →99 x 10^3/uL) during her hospitalization; Notably, she was also receiving enoxaparin 30mg daily at the time and after the low molecular weight heparin and aspirin were discontinued, the platelets increased to the normal range. A heparin-induced thrombocytopenia evaluation was not completed. At a follow up visit with her primary care physician (PCP) she complained of dizziness and her PCP reduced her clonidine to 0.1mg twice a day. However, the lack of monitoring as an outpatient and the continuation of her antihypertensive regimen might have accentuated her hypoperfusion given the hypotensive effects.

During her hospital stay for the CVA, the patient was discharged prematurely as she was starting to refuse care. Notably, her serum creatinine was increasing toward the end of her stay; this was addressed by lowering the chlorthalidone dose from 25 mg daily to 12.5 mg daily. Her serum creatinine continued to rise after the diuretic adjustment for the last two days of her visit, which should have prompted a more thorough evaluation of her medications and risk factors prior to discharge. Dose adjustment or discontinuation of dabigatran and metformin were warranted especially since patients with DM are at a higher risk of bleeding while using dabigatran [15].

The Naranjo Scale produces a score of 6 for the dabigatran (hemorrhage) and 8 for the lactic acidosis and results in a "*probable*" assessment for iatrogenic consequence in our patient [18].

Conclusion

This case illustrates the importance of drug therapy monitoring to optimize medication and reduce adverse events. While the absolute risk of adverse reactions to dabigatran and metformin are relatively small, the consequences of adverse events materializing are catastrophic. In our case, this was compounded by the pharmacodynamic interaction that presented itself, that being a dabigatran-associated hemorrhagic event, leading to global hypoperfusion and acute renal injury, which in the presence of metformin likely accelerated a lactate metabolic acidosis. In retrospect, this is a situation that may have been avoided with appropriate monitoring and medication adjustment. In a setting of compromised renal function, the metformin and dabigatran should have been dose adjusted or discontinued, albeit data to support to renal adjustment of dabigatran in this population are lacking and other antithrombotics may have been more rational to consider.

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