Dabigatran Associated Acute Renal Failure (DAARF)

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ABSTRACT
Context: Dabigatran is a recently approved direct thrombin inhibitor widely advertised and used for stroke prevention in atrial fibrillation. Presumably, no blood tests monitoring is recommended.

Objective: To report two cases of DAARF seen in hospitalized patients 5 to 15 days after the initiation of Dabigatran therapy.

Setting: Consultative inpatient and outpatient nephrology private practice.

Interventions: Dabigatran was discontinued in both cases followed by acute hemodialysis, ablation of arrhythmias and transfusions in Case 1 and transfusions, medical care of atrial fibrillation, gastrointestinal bleeding and hyperkalemia in Case 2.

Outcome: Resolution of DAARF, hyperkalemia and anemia after medical interventions post withdrawal of Dabigatran.

Conclusions: Elderly patients or chronic kidney disease patients should be closely monitored before and after initiation of Dabigatran.

Background: Atrial fibrillation (AF) affects more than 3 million Americans and 10% of adults older than age 80 years.1 AF is responsible for 15% of strokes/year in the United States leading to annual costs in excess of $57 billion.12 Dabigatran (Pradaxa®) was recently approved in United States and is being widely advertised as alternative to warfarin for stroke prevention in AF. However, the pivotal RE-LY (Randomized Evaluation of Long Term Anticoagulation) trial14 did not include patients with a creatinine clearance less than 30 ml/min/1.73 m² a situation frequently present in the elderly. Herein, two cases of DAARF are described which have not been reported in the medical literature.

Case Reports:
Case 1: 69-year-old Hispanic male admitted because of epistaxis, increased bruising and bleeding on open scars, nausea and loss of appetite. The initial evaluation showed hyperkalemia, acute renal failure, coagulopathy and cardiac arrhythmias. A year ago, he had an implantable cardioverter-defibrillator (ICD)/pacemaker insertion post cardiopulmonary arrest. His past medical history included hypertension, diabetes mellitus, obesity, gout, hypercholesterolemia, chronic obstructive pulmonary disease and mild renal insufficiency. He had been doing well on his regular twelve outpatient medicines—that did not include nonsteroidal or potentially nephrotoxic agents—until five days before admission when he was started on dabigatran 150 mg twice daily. This was discontinued after nine doses due to above complaints. Prior outpatient serum creatinines ranged from 2.0 to 1.3 mg/dL.

On admission, he appeared in no distress, the blood pressure was 104/50mmHg, pulse 81/min, respiratory rate 18/min, temperature 97.3 F, pulse oxymetry 96% on room air, weight 250 pounds and height 64 inches. The remainder of the exam was negative except for epistaxis, bleeding on open scars and bruises on arms. See Table for admission laboratory studies.

He was treated overnight for hyperkalemia, given normal saline bolus of 250 ml/hr for six hours, and continued at 150 ml/hr for 24 hours. He received Vitamin K, fresh frozen plasma and desmopressin for the coagulopathy. Later, he also required two units of red blood cells.

Because of recurrent episodes of malignant tachyarrhythmias, after the first hemodialysis, he underwent an electrophysiologic study with ablation of atrial and ventricular tachycardia and reprogramming of the dual chamber ICD. He required a total of seven hemodialysis treatments, daily for four days and then three times every other day. The serum creatinine decreased to 1.8 mg/dL and he was discharged in an improved condition.

Case 2: 84 year-old Hispanic female admitted for evaluation of bloody diarrhea, anemia, hyperkalemia, arrhythmias and acute renal failure. She had a history of hypertension, diastolic heart failure and left ventricular hypertrophy. She had non valvular atrial fibrillation and paroxysms, difficult to control despite beta blockers and dronedaron. Two and half weeks prior to admission warfarin was discontinued and then started on dabigatran 150 mg BID and continued on dronedaron 400 mg po BID, metoprolol 50 mg po BID, spironolactone 25 mg daily, lisinopril 40 mg daily, sertraline 50 mg/day and fludrocortisone 0.1 mg bid. Her past surgical history included cholecystectomy, right mastectomy and bilateral knee arthroplasties.

On admission she was in no distress, the blood pressure was 143/75 mmHg, pulse 120/min irregularly irregular, respiratory rate 29/minute, temperature 97.6 F, height 62 inches, and weight 126 pounds. The remainder of the exam was negative except for presence of S4 gallop, surgical scars and hematocrizia.

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Dabigatran Associated Acute Renal Failure (DAARF) (Continued)

The electrocardiogram revealed AF with rapid ventricular response. The BUN was 29 mg%, creatinine 1.71 mg%, potassium 6.7 mEq/L, sodium 140 mEq/L. The white cell count was 13, 940/mm³ and the hematocrit was 31% and later dropped to 26.5% requiring two units of red blood cells. The platelet count was 193,000/mm³. The prothrombin time was 13.3, INR 1.43, and partial thromboplastin time 57. She was treated with diuretics for AF and for the hyperkalemia with calcium gluconate, oral dextrose and insulin hourly x 5 with improvement. Dabigatran, spironolactone and isonipril were discontinued. The endoscopic studies were negative. The creatinine gradually decreased over the next 5 days to 1.09 mg% and a month later to 0.8 mg% with conservative non dialytic renal care.

Discussion: Dabigatran etexilate (Pradaxa®) is a potent, reversible, direct thrombin inhibitor, approved in the United States, and in more than 70 countries worldwide, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.1,2 This approval followed the publication of the RE-LY trial, comparing warfarin with dabigatran.3 This approval followed the publication of the RE-LY trial, comparing warfarin with dabigatran.1 The most frequently reported adverse reactions were bleeding and gastrointestinal events. Hypersensitive reactions occurred in less than 0.1%.3,4 Acute renal failure has not yet been reported in the literature but 80 cases were noted in the Boehringer Ingelheim RE-LY study which also includes additional 34 cases of unspecified renal failure. Adding the two groups totals 114 cases of renal failure out of 1304 patients treated with dabigatran for a new adjusted percentage of 0.95 not previously noted.

The RE-LY trial studied 18,040 patients comparing two different doses of dabigatran (110 mg po BID and 150 mg po BID) versus warfarin. In brief, in the RE-LY trial, less bleeding occurred with dabigatran 110 mg twice a day than with warfarin but the higher dose of dabigatran 150 mg twice a day was more effective than warfarin in preventing stroke and systemic embolism.4,5 Acute renal failure was noted in 0.7% of patients using dabigatran 110 mg BID, 0.6% of patients treated with Dabigatran 150 mg BID and in 0.6% of patients using warfarin, respectively.5 The RE-LY trial excluded patients with a creatinine clearance less than 30 ml/min/1.73 m².

In our two DAARF cases described, dabigatran was discontinued upon admission. Both patients had received dabigatran at doses of 150 mg twice daily as suggested by the manufacturer and approved by the FDA. The etiopathogenesis of DAARF in these patients is not completely known but resolved with frequent hemodialysis treatments in case 1 and without non dialytic renal care in case 2. This may be classified as bizarre or delayed adverse drug reaction.7 Dabigatran is a pro-drug that has low protein binding, 85% elimination via the kidneys and can be dialyzed.6,7 It has a rapid onset of action and achieves therapeutic levels within two hours and steady state concentration in 2-3 days. It is probable that hypoperfusion and impaired kidney function led to dabigatran accumulation. The area under the curve of dabigatran is respectively 2.7 fold or 6 fold higher in volunteers with moderate (creatinine clearance less than 50 ml/min/1.73 m²) or severe (creatinine clearance less than 15 ml/min/1.73 m²) renal insufficiency.8,9 It should be noted that about 60% of dabigatran is removed with a 2-3 hour hemodialysis.10,11 Our report confirms such a benefit and hemodialysis may be considered in severe cases of DAARF as an alternative treatment in the absence of a specific dabigatran antidote.

Impaired renal function is commonly overlooked in elderly patients who are frequently affected by atrial fibrillation. It is estimated that about seven million people have either paroxysmal or persistent atrial fibrillation in the European Union and the United States12 who may be considered candidates for dabigatran. This drug is being promoted as not requiring blood monitoring of its effect during treatment.1,13 However, the RE-LY trial patients with a creatinine clearance less than 30 ml/min/1.73 m² were not included.1,4 Dabigatran has received a class 1B recommendation (benefit greater than risk) for secondary stroke prevention in patients with non valvular AF. It costs about $6 to $8 per day and is more expensive than warfarin that is about 15 cents per day at Wal-Mart’s but requires regular PT/INR testing.

No drug plasma level is available for dabigatran in the USA,4 and none is recommended by the manufacturer but in France a haemolysis thrombin inhibitor assay: Hyphen™ BioMed is available and in clinical use.3 Dabigatran may be inadvertently used in the elderly and special caution is necessary in view of a recently published report with fatal consequences.16 Thereby, renal and hepatic function parameters should always be evaluated prior to and during dabigatran therapy in the elderly or renally impaired and discontinued in patients with worsening renal function or DAARF.

A creatinine clearance is a cumbersome test to obtain on a routine clinical situation but the estimated glomerular filtration rate (GFR) may be used instead in the outpatient setting.17 Dabigatran should be used cautiously and at decreased doses for patients with chronic kidney disease (CKD) stage 4 (estimated GFR of 15 to 29 ml/min/1.73 m²) and should not be used with CKD stage 5 (estimated GFR less than 15 ml/min/1.73 m² or dialysis).18,20 In stark contrast to the United States, the Canadian guidelines for Pradaxa™ contraindicate its use in patients with creatinine clearances less than 30 ml/min.19 Similar restrictions apply in Europe, United Kingdom, Japan, Australia and New Zealand. Is it time to reevaluate guidelines in the USA?

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Addendum: The above two cases were reported to the FDA six months ago. After submission of this article, the post marketing experience in Europe and USA10 has led Boehringer Ingelheim to change the dosages and administration of Pradaxa12 which include now:

- Assess renal function prior to initiation and in patients with creatinine clearance (CrCl) less than 50 ml/min or more than 75 years of age, at least once a year.

For patients with CrCl more than 30 ml/min: 150 mg, twice daily.

For patients with CrCl 15-30 ml/min: 75 mg twice daily, etc (The prior FDA approved dose for Pradaxa in the USA was 150 mg twice daily until recent changes in late November 2011)12

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TABLE OF LABORATORY STUDIES, Case 1

<table>
<thead>
<tr>
<th>Serum:</th>
<th>Blood:</th>
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<tbody>
<tr>
<td>Potassium</td>
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<tr>
<td>Sodium</td>
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<td>Blood urea nitrogen*</td>
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<td>Uric acid</td>
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<td>Lactic acid</td>
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<tr>
<td>Prostate specific antigen*</td>
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</table>

Urine:
- Analysis: negative
- Osmolality: 379 mOsm/kg H2O
- Toxicology Drug Screen: negative

Chest Radiography: mild cardiomegaly, pacer in place.

Complete Abdominal Ultrasound: negative, 6 cm right upper pole cyst noted.

Electrocardiogram: atrial fibrillation with rapid ventricular response.

* To convert the values for:
  - blood urea nitrogen to mmol/L, multiply by 0.357
  - creatinine to μmoles/L, multiply by 88.4
  - glucose to mmol/L, multiply by 0.0555
  - uric acid to μmoles/L, multiply by 60
  - lactic acid to mmol/L, divide by 10
  - prostate specific antigen to μg/L, multiply by 1000

REFERENCES

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