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# An Experience with Reversal of Dabigatran with Two Doses of Idarucizumab, Hemodialysis, and Time in the Setting of Anuric Renal Failure and Major Gastrointestinal Bleeding

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**Abstract**

*Dabigatran is a direct oral anticoagulant (DOAC) FDA approved for nonvalvular atrial fibrillation and venous thromboembolism. Benefits of dabigatran when compared to warfarin sodium include a shorter half-life and lack of need for routine monitoring. Recently idarucizumab was FDA approved for dabigatran reversal in the setting of life-threatening bleeding. Idarucizumab binds dabigatran neutralizing its activity. There is limited data regarding efficacy of redosing of idarucizumab as well as clearance of dabigatran in the setting of anuric renal failure. We present a case of a patient on chronic dabigatran for atrial fibrillation who was admitted for septic shock and developed gastrointestinal bleeding, anuric renal failure requiring dialysis for several days; despite two doses of idarucizumab and hemodialysis, the thrombin time remained elevated. Subsequently dabigatran levels returned and confirmed delayed clearance despite these interventions.*

**Keywords:** *dabigatran, DOAC, reversal, idarucizumab, bleeding, anuric renal failure, hemodialysis*

## Introduction

Dabigatran is the first FDA approved direct acting oral anticoagulants (DOAC) based on a landmark non-inferiority multicenter, parallel group, randomized controlled trial (RE-LY) [1]. Dabigatran has also been approved for venous thromboembolism (VTE) based on the RE-COVER trial, a randomized, double blind, non-inferiority trial [2]. Dabigatran as well as the other DOAC's are being increasingly used in place of warfarin sodium based on ease of administration, lack of need for routine monitoring, and improved efficacy. Current American College of Cardiology, American Heart Association, and Heart Rhythm Society guidelines from 2014 give class I recommendations for DOACs in patients with nonvalvular atrial fibrillation with prior stroke, TIA, or CHADSVASC2 scores greater than two. According to the 2016 American College of Chest Physicians VTE guidelines, dabigatran is a first line option for patients with VTE or PE in patients without active malignancy. Since the introduction of the DOACs considerable concern regarding the lack of a clear reversal agent and reversal strategy has been a topic of discussion [2]. Dabigatran is currently the only DOAC with areversal agent (idarucizumab) approved based on themulti center prospective REVERSE-AD trial in 2015 [3]. In this study normalization of dilute thrombin time was achieved in 98% of patients presenting with active bleeding[3]. There is limited data on efficacy of idarucizumab in the setting of acute renal failure. We highlight a case in which dabigatran levels remained elevated despite two doses of idarucizumab, five days of continuous veno-venous hemofiltration (CVVH) and one session of hemodialysis (HD).

## Methods

Coagulation studies were all performed on the *STA®Compact* analyzer (DiagnosticaStago, Parsippany,

NJ07054). Citrated platelet-poor plasma from the patient was analyzed by one of the techniques outlined below.

1. The aPTT reaction uses *STA® PTT-Automate 5* as the partial thromboplastin, together with 0. 025 M $CaCl_2$.
2. The thromboplastin for the PT/INR reaction is the *STA®-Neoplastine CI PLUS* which has an International Sensitivity Index (ISI) of 1. 23 when used on our instruments.
3. The thrombin time was performed using *STA®-Thrombin* which contains human thrombin at approximately 1.5 NIH units/ml when reconstituted.
4. Fibrinogen was determined with *STA® Fibrinogen 5* containing human thrombin at ~ 80 NIH units per mL as well as a heparin inhibitor. The procedure is insensitive to heparin (up to 2 IU/mL). The reaction is performed with a precalibrated bar-coded fibrinogen curve. Plasma dilutions are made in StagoOwren-Koller buffer.
5. The anti-Xa reaction (*STA® Liquid anti-Xa*) uses a liquid chromogenic substrate and a liquid bovine factor Xa. Calibration is performed with a STA®-Multi Hep Calibrator which creates a hybrid curve using both unfractionated heparin and low molecular weight heparin standards.
6. D-Dimers are measured with the *STA®-Liatest assay*. This assay is based on an immunoturbi dimetric assay that uses latex microparticles. The reaction is pre-calibrated with the data from the standards stored on a bar code.
7. Assays for Dabigatran were performed on plasma specimens at NMS Laboratories (3701 Welsh Road, Willow Grove, PA 19090) using High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS). Information was made available after hospital discharge.

## Case Description

We present a 54-year-old woman with a past medical history of atrial fibrillation prescribed dabigatran 150mg twice daily, hypertension, obesity (BMI 31. 3), chronic obstructive pulmonary disease, and gastrointestinal erosive reflux disease who presented to Shands hospital at The University of Florida with anuria, volume overload, decreased oral intake for 4 days, and a gastrointestinal bleed (GIB). The patient came from home and is used to managing her own medications. The patient additionally has been prescribed amlodipine 5mg, albuterol as needed, and omeprazole 20mg daily. She had been on dabigatran for several years, had not missed any doses, did not take more than prescribed, and did not open the capsule prior to self-administration. There is no history of chronic kidney disease with recent blood work a month prior showing a normal creatinine. At presentation, the patient was in hemorrhagic shock with volume overloadthat requiredvasopressor support for 48 hours. The patient was given supportive transfusions with four units of fresh frozen plasma and two units of packed red blood products (hemoglobin was 6. 6 g/dl) level of early upon admission. Our hematology service was consulted for recommendations for reversing dabigatran in the setting of a life-threatening GIB. Refer to figure 1 whichsummarizes results of the prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), dabigatran levels (DL), before and after idarucizumab was administered, and when CVVH/HD was performed. DL levels were sent to a referral lab and resulted after the hospital course and were not available in real time to impact treatment decisions. Treatment decisions was based on the clinical picture and thrombin time as a surrogate marker for dabigatran activity. Idarucizumab was administered in the emergency department prior to obtaining the initial thrombin time. DL was 4200ng/ml. On the following day CVVH was started due to anuric renal failure with volume overload and was chosen instead of traditional hemodialysis due to persistent hypotension on presser support (blood pressure was 78/51 with a pulse of 130). Her creatinine was 14. 02mg/dl with a EGFR of 3 ml/min/1. 73$m^2$upon admission. Initially the patient was not started on any anticoagulation with CVVH due to risk of bleeding, fortunately there was no clotting issues. The patient was subsequently re-dosed with idarucizumab 24 hours later due to continual bleeding and inability to localize and cauterize a source of bleeding. DL levels remained elevated and actually increased after CVVH was initiated. TT also remained elevated after two doses of idarucizumab and CVVH. Shortly after the patient had an urgent bi-directional scope and local attempts at hemostasis was successful

with cautery for two bleeding gastric ulcers. Bleeding eventually ceased and the patient remained on CVVH for a total of four days followed by one day HD. TT and dabigatran levels trended down over the 14 total days. Once the patient demonstrated clinical stability without evidence of bleeding she was started on deep vein thrombus prophylaxis with heparin subcutaneous, as needed heparin flushes for CVVH/HD, and transitioned to apixaban5mg twice a day. One year follow up demonstrates that the patient remains dialysis independent and is tolerating apixaban well without any side effects discernable to the patient.

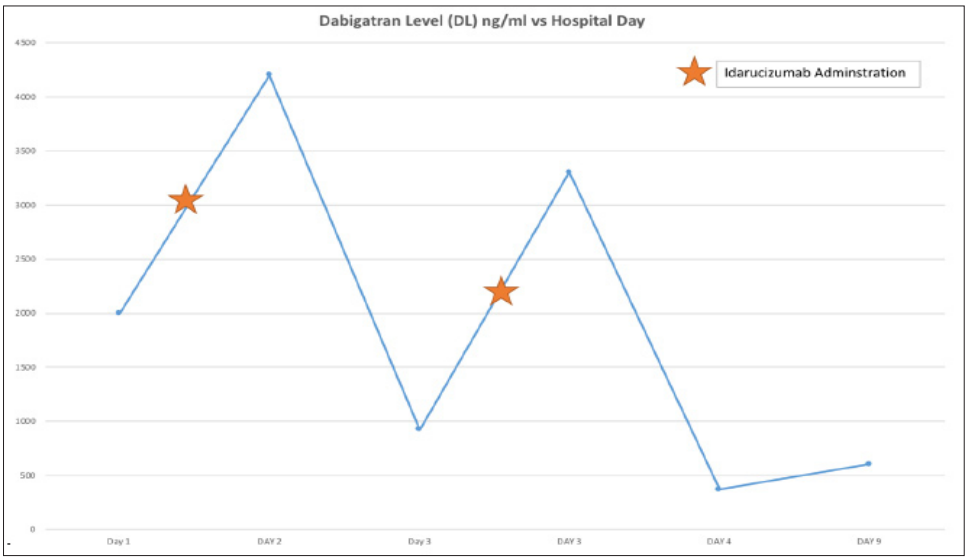


**Fig 1.** *Comparing Dabigatran Levels versus Hospital Day and observation of rebound levels after idarucizumab administration*

## Discussion

There is minimal data regarding dabigatran reversal in the setting of anuric renal failure. This case is presented to highlight the need for effective treatment strategies for dabigatran reversal in the setting of anuric renal failure. Dabigatran is a small, lipophilic molecule with a moderate volume of distribution of 0. 9-1 L/kg. Approximately 80-85% of dabigatran is excreted by the kidneys. Due to extensive renal elimination, the terminal half-life of dabigatran is prolonged (25-30 hours) in the setting of severe renal dysfunction, as defined by a creatinine clearance less than 30 mL/min [4,5]. Peak dabigatran plasma concentrations are dose dependent and are observed approximately 1. 5-3 hours post oral dosing. Steady state plasma peak and trough dabigatran in patients with CrCl> 50 mL/min are 180 ng/mL and 90 ng/mL, respectively [6]. Two case reports suggest the terminal half-life of dabigatran is prolonged to 25-30 hours in the setting of a creatinine clearance less than 30 mL/min compared to 9 hours for healthy individuals [4,5]. Due to dabigatran's low protein binding (~35%), small molecular size, high water solubility and renal elimination, renal replacement therapy has been recommended in the setting of dabigatran-associated major bleeding. There has been literature highlighting the efficacy of HD vs CVVH with the former having better efficacy [6]. Approximately 48-68% of dabigatran has been shown to be removed during a four-hour hemodialysis session with higher blood flow rates leading to greater dabigatran clearance with patients with renal insufficiency [7]. Idarucizumab has been shown to reverse dabigatran activity within minutes of administration in patients with life threatening bleeding [3]. Data on efficacy with acute renal failure is lacking as the RE-LY trial excluded patients with a creatinine clearance less than 30mL/min or less [3]. Some literature suggests that in the setting of renal impairment the idarucizumab/dabigatran complex are not cleared in time, and this may cause dissociation of the complex and perhaps re-activation of dabigatran [8,9]. Marino et al. reports dabigatran levels were seen to decrease 4 hours after administration but at the 12-hour mark DL were elevated once again [10]. This is supported by a similar hypothesis seen in a randomized, double-blind, crossover phase Ib study that looked at idarucizumab

efficacy in patients with mild to moderate renal insufficiency not needing dialysis [8]. Rebound dabigatran plasma concentrations have also been observed following hemodialysis and administration of idarucizumab possibly due to volume of distribution which is attenuated by obesity [11,12]. This highlights the need for a longer duration of hemodialysis in treatment of dabigatran reversal.

In our patient, we do not believe the TT remained elevated due to alternative causes as the patient had a normal fibrinogen level, no liver disease, no evidence of disseminated intravascular coagulation, and was not receiving other anticoagulants such as heparin. After administration of idarucizumab twice, four days of CVVH, one session of HD, the thrombin time and dabigatran levels remain elevated but decreased over the span of 14 days. Figure one summarizes results of the prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), dabigatran levels (DL), before and after idarucizumab was administered, and when CVVH/HD was performed. Figure 2 shows rebound dabigatran levels after the administration of the reversal agent idarucizumab. DL were measured 185 minutes after the first idarucizumab dose and 148 minutes after the second dose. This phenomenon is possibly due to volume of distribution as dabigatran moves into the blood from the periphery [10]. We hypothesize that idarucizumab as inactivates dabigatran in the blood, this may decrease levels of dabigatran thereby creating a gradient of concentrations for dabigatran and allowing a flux from the periphery into the blood and thus creating a rebound effect after administration of idarucizumab. This was noted in our patient after both doses of idarucizumab and may have been exacerbated by dabigatran's moderate volume of distribution which is attenuated by the patient's obesity (BMI 31. 3). Another hypothesis is thatidarucizumab-dabigatran complexes in renal failure lead todissociation of idarucizumab from the complex and re-activation of dabigatran [8,9]. In our patient, we noted an abrupt rebound effect after administration of idarucizumab suggesting this could be due to volume of distribution rather than disassociation as the levels trended down. Also, a possibility could be that when measuring levels of dabigatran, the spectrometry machine could measure both free dabigatran and dabigatran-idarucizumab complexes, thereby creating an elevated level. Lastly, prior studies suggest high flow traditional HD may be more efficient for drug elimination rather than CVVH. Our patient utilized CVVH out of necessity due to persistent hypotension. We report prolonged high levels while on CVVH supporting the necessity for traditional high flow HD compared to CVVH [6].

| Test | Normal Range | Day 1 | Idarucizumab | DAY 2 | Day 3 | Idarucizumab | DAY 3 | DAY 4 | DAY 5 | DAY 6 |
|---|---|---|---|---|---|---|---|---|---|---|
| Dabigatran Level (DL) ng/ml | 0 | 2000 | | 4200 | 920 | | 3300 | 370 | | |
| Thromobin Time (TT) sec | 12.0-18.8 sec | | | | | | 53.8 | 150 | 122 | 124.9 |
| Cr (mg/dl) | 0.40-0.90 | 14.34 | | 8.16 | | | 7.39 | 4.69 | 1.78 | 1.22 |
| INR | 0.9-1.2 | >8.0 | | 3.8 | | | 5 | 2.1 | 1.7 | 1.5 |
| PT sec | 11.9-15 sec | 77.3 | | 48.3 | | | 19.1 | 23 | 20.3 | 18.4 |
| aPTT | 23-38 sec | 158 | | 143 | | | 41 | 77 | 66 | 53 |
| CVVH | | | | | | | | | | |
| HD | | | | | | | | | | |
| **Test** | **Normal Range** | **DAY 7** | **DAY 8** | **DAY 9** | **DAY 10** | **DAY 11** | **DAY 12** | **DAY 13** | **DAY 14** | **DAY 15** |
| Dabigatran Level (DL) ng/ml | 0 | | | 600 | | | | | | |
| Thromobin Time (TT) sec | 12.0-18.8 sec | 78.2 | | 53.4 | 48.2 | 56.3 | | | 28.3 | |
| Cr (mg/dl) | 0.40-0.90 | 1.19 | 1.86 | 2.5 | 1.82 | 2.37 | 2.09 | 2.71 | 2.96 | 3.09 |
| INR | 0.9-1.2 | 1.4 | 1.3 | 1.2 | | | | | | |
| PT sec | 11.9-15 sec | 17.4 | 16.2 | 15.5 | 15 | 14.9 | | | 17.1 | |
| aPTT | 23-38 sec | 41 | 39 | 36 | 35 | 38 | | | | |
| CVVH | | | | | | | | | | |
| HD | | | | | | | | | | |

**Fig 2.** *Table depicting Dabigatran levels, thrombin time, Cr, INR, PT, aPTT, and days of dialysis in relation to hospital day.*

This case highlights the importance of cautious use of dabigatran in patients with renal dysfunction and the need for very close clinical follow up of renal function in those receiving the drug. There is little experience and evidence suggesting an increased efficacy when redosing of idarucizumab [3]. Case reports demonstrate a rebound effect of DL and it is uncertain if this equates to increased action of dabigatran [10]. In one case, they did see success with re-dosing (which was prompted by the rebound effect) and HD while the patient progressed from anuric renal failure to recovery [10]. We show that after second dose of idarucizumab and after the expected rebound effect, DL and TT trended down with CVVH as well as an improved clinical picture and one round of HD.

Because of the lack of data with the use of idarucizumab in the setting of severe renal failure, dosage remains experimental and its efficacy remains uncertain. In our patient, even with re-dosing of idarucizumab combined with CVVH/HD DL; TT took 14 days to clear, suggesting there may be a decrease efficacy in anuric renal failure. Our data also supports that a rebound is possibly due to dabigatran's moderate volume of distribution which is worsened by patient obesity. A recently published article suggests that perhaps re-dosing could be utilized to diminish the rebound effect, although no standardized trial has looked at this indication [13]. Lastly, we want to implore the possibility of needing multiple doses of idarucizumab for reversal. Five cases have recently been described with incomplete reversal of dabigatran with the recommended 5g of idarucizumab, suggesting perhaps additional doses may be required in certain populations of patients, notably those with severe renal failure [13,14].

Further information and data is needed with dabigatran and idarucizumab in the setting of anuric renal failure to address the question of re-dosing and the utility of CVVH/HD. We hope for future studies addressing reversal in renal insufficiency and renal failure. We hope to see studies that address the optimum duration of dialysis needed to create standard regiment for dabigatran reversal in the setting of a major bleed and anuric renal failure. The updated REVERSE AD publication includes re-administration and at least one patient received three doses, and we suggest further studies imploring re-administration in specific patient populations. The final learning points of this case include the necessity to localize a bleeding source as quickly as possible as if the source is not localized and corrected, bleeding will continue even if no anticoagulant is present.

## References

[1] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009; 361(12): 1139-51.

[2] Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009; 361(24): 2342-52.

[3] Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015;373(6):511-20.

[4] Stangier J, Rathgen K, Stahle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *British Journal of Clinical Pharmacology*. 2007; 64(3): 292-303.

[5] Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. 2007; 36(2): 386-399.

[6] Bouchard J, Ghannoum M, Bernier-jean A, et al. Comparison of intermittent and continuous extracorporeal treatments for the enhanced elimination of dabigatran. ClinToxicol (Phila). 2015; 53(3):156-63.

[7] Chai-adisaksopha C, Hillis C, Lim W, Boonyawat K, Moffat K, Crowther M. Hemodialysis for the treatment of dabigatram-associated bleeding: a case report and systemic review. *Journal of Thrombosis and Haemostasis.* 2015; 13: 1790-1798.

[8] Glund S, Stangier J, Van ryn J, et al. Effect of Age and Renal Function on Idarucizumab Pharmacokinetics and Idarucizumab-Mediated Reversal of Dabigatran Anticoagulant Activity in a Randomized, Double-Blind, Crossover Phase Ib Study. ClinPharmacokinet. 2016.

[9] Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. ThrombHaemost. 2015; 113 (5): 931-42.

[10] Marino KK, Santiago RA, Dew RB, et al. Management of Dabigatran - Associated Bleeding with Two Doses of Idarucizumab Plus Hemodialysis. Pharmacotherapy. 2016; 36(10): e160-e165.

[11] Kashiura M, Fuijita H, Sugiyama K, Akashi A, Hamabe Y. Hemodialysis for removal of dabigatran in a patient with gastric hemorrhage. *Acute Medicine & Surgery*. 2016; 3: 132-134.

[12] Chang D, Dager W, Chin W. Removal of dabigatran by hemodialysis. *American Journal of Kidney Disease.* 2013; 61(3): 487-489.

[13] Simon A, Domanovits H, Ay C, Sengoelge G, Levy JH, Spiel AO. The recommended dose of idarucizumab may not always be sufficient for sustained reversal of dabigatran. J Thromb Haemost. 2017;15(7):1317-1321.

[14] Steele AP, Lee JA, Dager WE. Incomplete dabigatran reversal with idarucizumab. ClinToxicol (Phila). 2017;:1-3.

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