DABIGATRAN INDUCED ECCHYMATOUS PATCHES: A RARE CASE REPORT

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Abstract-

Anticoagulants are the class of drug that is frequently used for treating and preventing thromboembolism. Generally Vitamin K antagonists (Warfarin) have been the usual treatment and the merely orally available agent for more than 60 years. Dabigatran was the first new oral anticoagulant and their metabolites (acyl glucuronides) are competitive, direct thrombin inhibitors. We know that in the coagulation cascade thrombin converts fibrinogen to fibrin. Dabigatran acts by inhibiting thrombin which thereby prevents the development of thrombus. Active moieties inhibit thrombin induced platelet aggregation as well as free and clot-bound thrombin. We report a case of 65 years old female patient who have experienced nasal bleed, per-rectal bleed and ecchymatic patches all over the body after 10 days of administration with Dabigatran. Patient had a previous history of admission to hospital for treatment of Deep vein thrombosis. Ecchymosis is a uncommon but potentially fatal complication caused by Dabigatran, which necessitates careful monitoring of patients receiving this medication. Because of the efficacy and good safety profile of Dabigatran, clinicians should be informed about this rare adverse effect.

Index Terms- Dabigatran, Ecchymatous patches, Prothrombin time, INR.

I. INTRODUCTION

Anticoagulants are the class of drug that is frequently used for treating and preventing thromboembolism. Generally Vitamin K antagonists (Warfarin) have been the standard treatment and the merely orally available agent for more than 60years [1][2]. Despite its widespread use, it has a number of drawbacks, including a limited therapeutic index, the need for frequent laboratory monitoring, and the fact that it is affected by diet, genetics, and illnesses [1]. Drugs that overcome these limitations would offer great potential was necessary and was approved by US Food and drug administration.

Novel Oral Anticoagulants (NOACs) are a new type of aanticoagulant drug that is used to treat and prevent stroke in people who have non-valvular AF (AF not associated with a problem in heart valve) and used to treat venous thromboembolism. Dabigatran was the first new oral anticoagulant that was introduced into the market in 2010. Direct thrombin inhibitors (e.g.,Dabigatran) and direct factor Xa inhibitors (e.g., Rivaroxaban, Apixaban, and Edoxaban) are the 2 classes of currently available NOACs[3]. Dabigatran is used to treat deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have received parenteral anticoagulant for 5-10 days, and to lower the risk of DVT recurrence in patients with non-valvular atrial fibrillation and PE in patients who have been previously treated, prophylaxis of DVT and PE in patients who underwent hip replacement surgery. Dabigatran is known to cause bleeding and symptoms similar to gastritis. Hypersensitivity to drugs (including urticaria, rash and pruritus), allergic edema, anaphylactic reaction and anaphylactic shock are all examples of drug hypersensitivities are the other side effects which were reported in <0.1% of patients who received Dabigatran[4]. Ecchymosis is a flat, blue or purple patchy discoloration of skin resulting from blood leaking from vessels. Ecchymosis is characterised by discoloured skin. If the leakage is recent, the affected area will appear dark blue, black, or purple, and when the bleeding stops, the colour may change to yellow or green. Ecchymosis usually clears up in 1-3 weeks. Studies in Spain found that leukocytoclastic vasculitis affects 10–30 people per million per year [5].

II. CASE HISTORY:

A 65 years old female patient was admitted to the hospital with chief complaints of nasal bleed, per-rectal bleed, ecchymatic patches all over the body and dizziness for a period of 3 days. Patient had a history of fall 3 months back that resulted in fracture of right femur, which was operated (modular bipolar implant insertion). Following which patient was bedridden and developed swelling of left lower limb, which was insidious in onset and gradually progressive. For this complaint patient had a history of admission to hospital and was diagnosed with Deep vein thrombosis (DVT). DVT was managed with Tab Dabigatran 110mg BD, Tab Aspirin 75mg OD, and Tab Clopidogrel 75 mg OD. Patient has a past medical history of Diabetes and hypertension (10 years). After 10days of Dabigatran administration patient developed nasal bleed, rectal bleed, ecchymatic patches all over the body, for which patient was

admitted to the hospital and diagnosed with Dabigatran toxicity& severe anemia. Dabigatran, aspirin, Clopidogrel was stopped and Dabigatran toxicity was treated with Inj Vit K 30mg stat followed by 10mg 1-0-0 for 11 days, Inj Pause 500mg 1-0-1 for 10 days, Inj Iron sucrose 100mg for 4 days, blood and fresh frozen plasma (FFP) transfusion. Patient condition got resolved and was started with Tab Warfarin 2mg 0-0-1 and was stopped on 5th day since patient developed gastrointestinal bleeding. When gastrointestinal bleeding got resolved patient was discharged and advised to review after 7 days with PT-INR report.

	1st day of admission	7th day of admission	During warfarin administration	After stopping Warfarin
PT Time	25.51	18.47	23.74	32.20
INR	1.06	1.43	1.83	2.48

Other investigations like bilateral lower limb venous doppler showed left lower limb swelling, Renal Artery Doppler showed no case of stenosis, both kidney small in size with increased parenchymal echo texture with thinned out parenchyma. Ultrasonography revealed presence of bilateral chronic kidney disease.

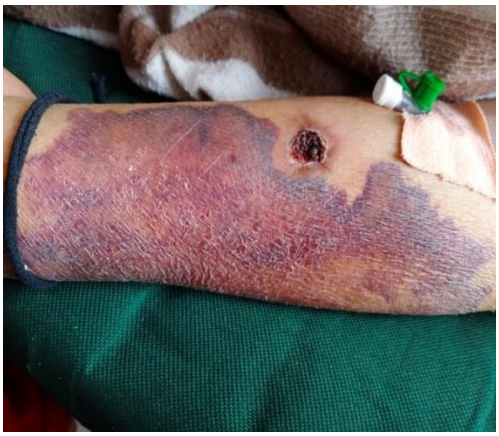

Fig 1: Ecchymatic patches in hand

III. DISCUSSION:

Dabigatran and its metabolite (acyl glucuronides) are competitive, direct thrombin inhibitors. As we know that in the coagulation cascade thrombin converts fibrinogen to fibrin. Dabigatran acts by inhibiting thrombin which thereby prevents the development of thrombus. Active moieties inhibit thrombin induced platelet aggregation as well as free and clot-bound thrombin. It is available in the form of oral tablets of 75mg, 110mg and 150mg. Dabigatran is widely used to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, as well as to treat deep venous thrombosis (DVT). It is given to patients with DVT and PE at a dose of 150mg BD orally and 110 mg orally on the first day, then 220 mg once per day for DVT and PE prevention following hip replacement surgery. Dose reduction is needed in older patients (>75years), in patients with increased bleeding risk and acute renal failure [4]. Dabigatran etexilate will extend clotting indicators like aPTT, ECT, and TT at beneficial doses. Because Dabigatran's action bypasses the extrinsic pathway, INR is relatively unaffected by its exposure. Hence it cannot be used to interpret the way it is used for warfarin monitoring [6]. The most common side effects are symptoms of gastritis and bleeding. Esophagitis, gastritis, GERD, GI haemorrhage, GI ulcer, and indigestion are all gastrointestinal symptoms. Epidural hematoma, intracranial haemorrhage, anaphylaxis (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction and shock are all serious side effects.

Ecchymosis is a flat, blue or purple patchy discoloration of skin resulting from blood leaking from vessels [7]. The spots in ecchymosis will be larger than 10mm in diameter when compared with other two types of bleeding like petechiae (<2mm in diameter) and purpura (2mm-1cm in diameter). Ecchymosis is characterised by discoloured skin, with the colour of the patch corresponding to the age and severity of the injury. If the leakage is recent, the affected area will be dark blue, black, or purple, changing to yellow or green as it heals. It usually takes 1-3 weeks to resolve [7]. Ecchymosis appears similar to hematoma. Ecchymosis is a relatively rare, potentially fatal adverse effect of Dabigatran. It is most commonly reported within 10 days of initiation of therapy[8]. Ecchymosis can be managed by giving nonsteroidal and anti- inflammatory drugs, topical steroids, application of ice pack/ heat pack, and elevation of affected area to reduce swelling [9].

Here a 65 years old female patient who had a history of fracture of right femur which was operated. Following that she developed deep vein thrombosis, which was confirmed by bilateral lower limb doppler. For management of DVT patient was started on Dabigatran 110mg 1-0-1. After 10 days of treatment with Dabigatran patient developed nasal bleed, per-rectal bleed and Ecchymatic patches all over the body. It is well known that the primary route of excretion of Dabigatran is renal (up to 80%) and has a short half-life of 12-17h. In renal impairment half-life will be increased to 15-34.1hours. USG revealed that patient is having bilateral chronic kidney disease. This suggests that the current condition of Dabigatran toxicity might have resulted from renal impairment. This along with the laboratory values such as PT, INR led to confirming the condition as Dabigatran induced Ecchymatic patches. Other potential risk that might have led to bleeding includes Tab Aspirin and Tab Clopidogrel. Since it was confirmed that the current condition was caused by the drug Dabigatran it was stopped and antiplatelet drugs like Aspirin and Clopidogrel were also stopped. Inj Vitamin K 30mg followed by 10mg, Inj Tranexamic acid 5oomg was used to stop bleeding. Blood, fresh frozen plasma transfusion and iron sucrose were also given to manage severe anemia that resulted from bleeding. Other treatment alternatives include Warfarin, heparin, low-molecular weight heparin and factor Xa inhibitors. When ecchymatic patches got resolved, Tab warfarin 2mg was started for treating DVT. Later it was stopped when patient developed

gastrointestinal bleeding. Considering all the available information, causality assessment of the current medical condition of the patient was analyzed using Naranjo Causality Assessment Algorithm. Naranjo score of 5 was attained which indicates that reaction occurred is probable.

IV. CONCLUSION:

The current case highlights the importance of Novel Oral Anticoagulants (NOACs), including Rivaroxaban and Dabigatran, have been widely used as warfarin replacements, considering their efficacy and safety. Ecchymosis is a rare but potentially fatal complication caused by Dabigatran, which necessitates careful monitoring of patients receiving this medication. The increased use of Dabigatran due to its efficacy and good safety profile, clinicians should be aware of this rare adverse effect. This condition can be reversed by holding the drug until patient's achieves stable condition.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

ACKNOWLEDGEMENT:

The research team would like to express their gratitude the patient and consultant doctors who took part in the study and gave their valuable feedback.

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