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"DELAYED/CONTINUOUS ADVERSE DRUG REACTION"- VAGINAL BLEEDING INDUCED BY SYNERGISTIC EFFECT OF DABIGATRAN AND EPLERENONE: A CASE SERIES

KEY WORDS: Dabigatran, Eplerenone, Vaginal Bleeding, Adverse Drug Reactions, endometrial thickening

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ABSTRACT

Dabigatran associated gynecological bleeding are less common when compared to warfarin and been widely used to decrease the risk of stroke and venous thromboembolic events in patients were anti-coagulant therapy is needed, because its effects are predictable and lab monitoring are not required. But we observed a contrary effect, incidence of severe vaginal bleeding in the following case series that had been switched to dabigatran after receiving warfarin for many years. Even though, dabigatran is known to cause vaginal bleeding, it has been not widely reported. Hence, we are suspecting one more drug eplerenone which is used to treat hypertension and heart failure, along with dabigatran for the occurrence of vaginal bleeding.

INTRODUCTION:

Dabigatran etexilate,an oral pro-drug, has been widely used in treating patients with non-valvular atrial fibrillation for prevention of stroke and venous thromboembolism by the approval of US Food and Drug Administration in 2010[1].It prevents thrombin-induced platelet aggregation. Dabigatran reversibly binds to the active site on the thrombin molecule, preventing thrombin-mediated platelet aggregation. Dabigatran has inherent bleeding risk[2]. The RE-LY trial demonstrated that dabigatran was associated with a lower incidence of major hemorrhage than warfarin[3]. However, several studies and case reports has been published citing specifically major gastrointestinal bleeding rather than vaginal bleeding due to dabigatran[4]. But we have observed vice-versa in case of vaginal bleeding. Our case series describes the delayed adverse drug reaction of vaginal bleeding in patients with cardiac conditions due the synergistic effect of drugs such as dabigatran and eplerenone.

Eplerenone is the oral aldosterone antagonist for the treatment of essential hypertension and heart failure has been associated with reduction in blood pressure and improved survival for patients with heart failure who are in stable condition after a myocardial infarction[5]. Due to the selectivity of aldosterone receptor, adverse effects such as gynecomastia (0.5%) and vaginal bleeding (0.6%)are rare[6]. But the Adverse drug reaction vaginal bleeding cannot be completely ignored since the structural similarity of eplerenone to estrogen and progesterone. Eplerenone –Selective aldosterone receptor antagonist has high affinity for the aldosterone receptor and low affinity for androgen and progesterone receptor[7]. There is only less than 1% chance of vaginal bleeding as per available reports[8,9]. However, to our knowledge no published studies or case report citing specifically major vaginal bleeding induced due to synergistic effect of dabigatran and eplerenone.

CASE REPORT 1:

31-year-old female patient, a known case of complete Atrioventricular canal defect with Eisenmenger's syndrome, atrial flutter with complete heart block and hypothyroidism underwent permanent pacemaker implantation for low ventricular rate. This patient had been receiving oral anticoagulant warfarin 5mg once daily for stroke prophylaxis in view of atrial flutter. She was shifted to dabigatran 75mg once daily post-procedure and initiated on oral medications like macitentan 10mg once daily, torsemide 5mg once daily, eplerenone 25 mg twice daily, pantoprazole 40mg once daily and oral calcium supplements. After 22 days she presented to emergency room with complaints of severe vaginal bleeding since evening.She has changed 6 pads and not associated with abdominal pain (or) clots. She has no drug allergies and no gynecological issues in the past. Her thyroid function test was normal. Gynecologist opinion was obtained to rule out any gynecological cause for her bleed. Her USG-abdomen revealed endometrial thickening. Her last menstrual period was normal and was on regular menstrual cycle. In view of low hemoglobin, she was transfused 2 units of packed red blood cells. On third day the suspected drug dabigatran was withheld and eplerenone was changed to once daily. Since bleeding persisted the eplerenone was withheld. After the washout period of the drug, bleeding stopped. Patient was discharged home with tablet rivaroxaban 15mg once daily instead of dabigatran and her hemoglobin remained stable with no further bleeding. Patient was under warfarin for more than a year and later changed to dabigatran. We suspect dabigatran and eplerenone for the 'Delayed/Continuous-Adverse drug reaction' since the patient did not develop the adverse drug reaction for the 22 days after pacemaker implantation even though she was on these medications and mechanism of delay is unknown. Causality assessment for the suspected drugs was done through Naranjo scale and found a score for 'possible' adverse drug reaction.

CASE REPORT 2:

A 51-year-old female patient, a known case of chronic pulmonary embolism with severe pulmonary arterial hypertension presented with complaints of postmenopausal bleeding. She attained menopause 2 years back. Her USG and CT abdomen revealed multiple intramural uterine fibroids and thickened endometrium. Her post-menopausal bleeding was initially attributed to uterine fibroid. In view of chronic pulmonary embolism, she has been receiving warfarin treatment for more than 5 years. She was recently shifted to dabigatran from warfarin one month back. This made us to suspect for the synergistic effect of dabigatran with eplerenone. The drugs dabigatran and eplerenone was started simultaneously, hence it could be the cause of endometrial thickening and intramural fibroids or else it

could have aggravated the uterine abnormal bleeding. This "Delayed/Continuous-ADR" would have been the caused or aggravated due to the simultaneous initiation of dabigatran with eplerenone.

Her oral anticoagulant was stopped. Subsequently, she underwent Total abdominal hysterectomy with bilateral salpingo-oophorectomy. Postoperatively she was restarted on dabigatran along with other medications and then discharged with stable hemodynamics. Hence, we are suspecting the cause of bleeding could be due to the initiation of dabigatran and eplerenone simultaneously.

DISCUSSION:

DABIGATRAN- Dabigatran is a member of the relatively new class of anti-thrombolytic drugs known as direct thrombin inhibitors. It may replace warfarin in several applications. Dabigatran shows lesser incidence of bleeding compare to warfarin[10]. But in contrast to available literatures, we observed the effect of vaginal bleeding. There is no much evident data to prove the effect of dabigatran in vaginal bleeding and mostly it causes major GI bleed rather than other form of bleeds[11]. But we have observed that there is an occurrence of gynecological bleeding due to dabigatran after the shifting of warfarin to dabigatran[12].The dabigatran induced endometrial hyperplasia is one of the possible similar findings in both the cases which elucidated the synergistic effect of dabigatran and eplerenone.

We also suspect eplerenone for a synergic effect on the adverse drug reaction observed. EPLERENONE –Selective aldosterone receptor antagonist has high affinity for the aldosterone receptor and low affinity for androgen and progesterone receptor, consequently eplerenone elicits some sex-steroid dependent effects[13]. In clinical trials 0.8 percent woman has reported vaginal bleeding as adverse drug reaction[14]. Since the vaginal bleeding-ADR of Eplerenone is rare we cannot ignore it completely.

Eplerenone is **chemically** described as **Pregn-4-ene**-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3oxo-, γ-lactone, methyl ester, (7α,11α,17α), was derived from spironolactone by introduction of a 9α,11α-epoxy bridge and by substitution of the 17α-thioacetyl group of spironolactone with a carbomethoxy group. Although eplerenone exhibits 10-to 20-fold lower affinity for the aldosterone receptor in-vitro compared with spironolactone[15]. The structural activity relation (SAR) of eplerenone and structural similarity of eplerenone with progesterone and estrogen shows its ability to cause hormonal (estrogen, progesterone) effects[16].

Progesterone pills can cause irregular bleeding and endometrial hyperplasia[17]. So, the substitution of 17α-thioacetyl group confers eplerenone with significantly increased selectivity for aldosterone receptor over other steroid receptor but the preg-4-ene structure is same as the progesterone so the chance of gynaecological adverse drug reactions should be noted with care and the chance of delayed/continuous adverse drug reaction cannot be ignored.

Hence, we observe a structural activity related effect of eplerenone to progesterone which causes the vaginal bleeding as adverse drug reaction[18].In both cases we have observed endometrial hyperplasia, that might have been there already which became aggravated due to the either or both drugs and may be the drugs itself might have induced it[19]. Here we are suspecting a temporal association between the two above mentioned cases and the time of onset of presenting complaints of vaginal bleeding. Mostly due the contributory relationship between the problems encountered in both the cases. Further studies and clinical trials on both drugs can give a clear picture of the suspicion.

CONCLUSION:

Dabigatran may be favored over warfarin considering its lesser adverse drug reactions and eplerenone is not having an established report of gynecological bleeding as an ADR. But in our cases, we have observed a contrary effect. Nearly 20-30 days after shifting from warfarin to dabigatran, we have observed a severe gynecological bleeding in both the cases. We do suspect eplerenone for the synergistic effect of the ADR in both cases due to the structural similarities.

In both cases we have observed endometrial hyperplasia, which might be aggravated suddenly due to the either drugs or both drugs and might have caused due to the either of the drugs. This case series is up to our knowledge and suspicion on both dabigatran and eplerenone. Even though several studies states that there are not much adverse drug reactions in the case of eplerenone alone, but it cannot be also completely ignored. Our findings will be adding knowledge to futuristic drug-drug interactions research studies. This might a possible cause for the vaginal bleeding as ADR. However, a need exists for more clinical trials of both drugs investigating the gynecological effect and drug-drug interaction of both dabigatran and eplerenone.

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