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Case Report

Warfarin-Induced Coagulopathy: Is Digoxin the Culprit?

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ABSTRACT

Warfarin is a notorious drug for drug interactions. Certain situations like severe Mitral Stenosis and Atrial Fibrillation still necessitate the use of warfarin, which increases bleeding risk. Here, we describe a case of warfarin-induced coagulopathy which may have occurred due to unusual interaction with digoxin.

Keywords: Atrial fibrillation, Digoxin toxicity, Rheumatic heart disease, Warfarin-induced coagulopathy.

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INTRODUCTION

Digoxin is used for rate control in atrial fibrillation and provides symptomatic relief in patients with symptoms of heart failure and pulmonary congestion.[1] Warfarin is a coumarin anticoagulant, used to prevent and treat the thromboembolic complications in valvular and non-valvular Atrial Fibrillation.[2] Digoxin rarely interacts with warfarin. However, toxic serum levels of digoxin may displace warfarin from the plasma protein binding site, leading to increased anticoagulant activity.[3] Previously, very few cases of warfarin-induced coagulopathy, consequent to toxic levels of digoxin, have been reported. We report a case of warfarin-induced coagulopathy while having therapeutic serum digoxin levels.

CASE REPORT

A 40-year old female presented to the Emergency department with hematuria and altered sensorium for 1 day. She was a known case of advanced Rheumatic Heart Disease with severe Mitral Stenosis, moderate Mitral Regurgitation, moderate Aortic Regurgitation, severe Tricuspid Regurgitation, and severe Right Ventricular Dysfunction. She had a history of recent hospital admission 2 weeks prior, on account of atrial fibrillation with a fast ventricular rate. Her medication included warfarin 5mg, digoxin 0.25µg, bisoprolol 2.5 mg, and spironolactone 50 mg once a day. She was referred for dual valve replace-ment (DVR) but was declared high risk due to severe Right Ventricle (RV) dysfunction. On examination, her blood pressure was 110/70, pulse 76/min regular, and GCS 11/15. The power of the right half of the body was reduced by 4/5. Her ECG showed regularized at-rial fibrillation with a heart rate of 66 bpm (Figure-1). Given her symptoms, her CT brain plain was advised which showed intra-parenchymal brain hemorrhage with communicating hydrocephalus (Figure-2). Her labs showed an Hb of 7.5g/dL, Total Leucocyte Count (TLC): 14.43x10^3, Platelet count: 289x10^3, ALT: 32 U/L, Total bilirubin:3.0 mg/dL, Urea: 72mg/dL, Creatinine: 1.4 mg/dL, Serum Na=130 mmol/L, and Serum K=4.6 mmol/L whereas the coagulation profile, i.e., Prothombin time (PT), and International Normalized Ratio (INR) showed a failure to clot. Her prior reports revealed normal coagulation profile with PT: 14s and INR: 1.0. She was transfused with 4 units of fresh frozen plasma (FFPs) to normalize her INR. The opinion of a neurosurgeon was sought and it was advised to manage the patient conservatively for the intracranial bleed and start intravenous mannitol 3-times a day. On the 3rd day of mannitol therapy, patient became anuric, her urine output fell to 20ml/24hrs and arterial blood gases revealed severe metabolic acidosis. Mannitol was stopped and fluid boluses were given, but the patient did not respond and eventually died before dialysis could be started. Her serum digoxin levels were 0.9 ng/ml (0.8-2.0ng/ml), which were in the therapeutic range. However, the sample was taken more than 24hrs after the last dose (which was taken on the morning before her presentation). After ruling out other concomitant drug interactions, use of macrolide antibiotics, dosing errors, possible lab errors, and keeping in view the ECG changes, digoxin was considered as the possible cause of her warfarin-induced coagulopathy.

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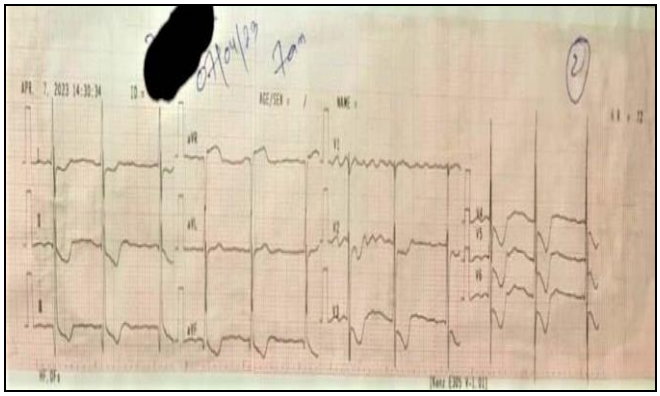

Figure-1: ECG showing Atrial Fibrillation with Regularized Ventricular Conduction.

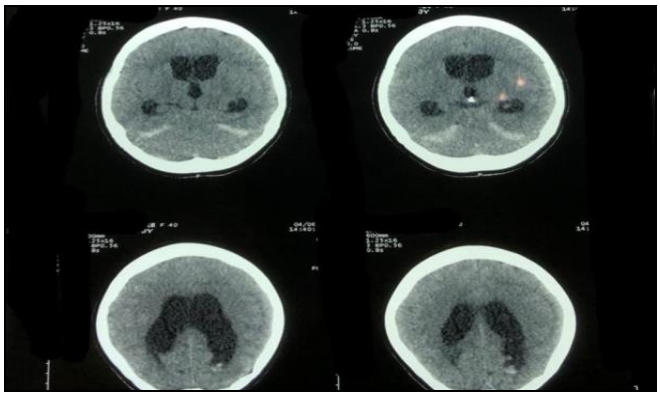

Figure-2: CT-Brain showing Intracranial Bleed (Subarachnoid Hemorrhage) and Communicating Hydrocephalus

DISCUSSION

Most of the drug interactions of warfarin are due to the inhibition or activation of the cytochrome enzyme CYP2C9.99% of ingested warfarin is bound to plasma proteins and may be displaced by increasing concentrations of weakly acidic drugs. Under normal conditions, only 1% of the unbound drug fraction exhibits metabolic activity.[4] Warfarin has various drug interactions through multiple mechanisms, like change in degree of absorption, activating or inhibiting effects of various drugs on liver enzymes and competitive binding to plasma protein binding sites.[5]

Digoxin is a cardiac glycoside with a bioavailability of 70-80%. The plasma protein-bound drug is around 25-30%. It has a large volume of distribution and is mostly found in the heart, kidneys, and skeletal muscles. The half-life of Digoxin varies from 26 to 45 hours in healthy individuals. The main route of excretion is via kidneys,[6,7] while administering digoxin, serious monitoring for side-effects should be done, as digoxin overdose may cause high degree AV-blocks, ventricular arrythymias[7] and even CNS depression.[8]

Previously, warfarin-induced coagulopathy, secondary to digoxin toxicity, has been reported by Bhattacharyya *et al*. The proposed mechanism of digoxin-induced, warfarin-induced-coagulopathy had been toxic concentrations of digoxin due to underlying renal impairment. These increased levels were supposedly enough to displace warfarin from its plasma protein binding site leading to an increase in its anticoagulant effect.[2] Similar interaction was reported by Raina *et al*.[9] They reported a similar case of warfarin-induced coagulopathy with toxic digoxin levels. The similarity with our case is in the ECG pattern of "regularized Atrial fibrillation" (atrial fibrillation with underlying high degree AV block) with the characteristic reversed tick appearance of the digoxin effect.[10] The fact that serum digoxin levels were within therapeutic range in our patient is a new finding however, that could be because the sample for digoxin levels was withdrawn late after presentation (when more than 24 hours had passed after the last digoxin dose). Another factor similar to the discussed case was simultaneous administration of Spironolactone which might have caused decreased digoxin excretion, but as the levels of digoxin came as therapeutic, this is less likely to be the underlying mechanism.

LIMITATIONS OF STUDY

None

CONCLUSION

Digoxin-warfarin interaction, although rare, should be kept in mind when starting both drugs together. Such patients should be called for follow-up in 5 to 7 days to monitor International Normalized Ratio (INR) and make changes in drug doses as required. Patients taking both drugs simultaneously and presenting with warfarin-induced coagulopathy should also be tested for digoxin toxicity.

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Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

SSK & SAA: Concept, drafting the manuscript, critical review, approval of final version to be published

BUHS & RUH: Study design, critical review, approval of final version to be published

HM & AY: Drafting the manuscript, critical review, approval of final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

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