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A CASE SERIES ON WARFARIN TOXICITY

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ABSTRACT

Background- Warfarin toxicity is relatively frequent in patients on long Warfarin therapy, presented with wide variety of clinical manifestation, often involving various organs and potentially fatal. Warfarin, an oral anticoagulant, is a vitamin K antagonist, is widely used for the prophylaxis and treatment of thromboembolic disease. In addition, warfarin is used to treat formed thrombus including those in the deep veins. Warfarin toxicity occurs due to intentional or unintentional overdose of warfarin as it has very narrow therapeutic index. Case presentation- We reported 2 cases of warfarin toxicity in two different conditions, in one patient warfarin was given in ischemic dilated cardiomyopathy (CMP) and in other for management of stroke. Both patients had raised PT-INR levels, a common indicator of warfarin toxicity with other symptoms showing active bleeding. Both patient were treated with holding tab Warfarin and inj. vitamin K along with inotropic support and rest treatment was continued as of earlier. Both patients PT-INR levels were dropped near to 1.5. Conclusion- the patients on warfarin must be closely monitored and counseled for the likely outcomes of this therapy.

KEYWORDS: Warfarin toxicity, anticoagulant, PT-INR, Vitamin K antagonist.

INTRODUCTION

Anticoagulants like warfarin are used widely to treat and prevent thrombus formation from mechanical heart valves, atrial fibrillation and dilated CMP. Despite being widely used, warfarin medication can lead to serious bleeding problems. The narrow therapeutic indexof

warfarin and high individual variability in the needed dose, primarily due to individual geneticpolymorphisms, make it challenging to achieve a safe therapeutic response. Clinicians are aware of this issue, and a wide range of warfarin maintenance doses, from 1 mg/day to 20 mg/day, are seen in the community. Warfarin therapy necessitates rigorous monitoring via the INR to direct dose in order to maintain a therapeutic level of anti-thrombosis and reduce the risk of bleeding problems. The INR is used to measure the blood coagulation pathway and track warfarin effectiveness. Prothrombin time data are standardized using the INR. The INR is defined as the prothrombin time ratio of a patient to a control sample multiplied by the index value for the analytical system being utilized.[1] [2]

Warfarin and vitamin K deficiency both induce coagulation disorders that are managed and treated with vitamin K. It belongs to the pharmacological class of fat-soluble vitamins.[1]

Dosing, diet, drug interactions, and liver disease are the main causes of accidental poisoning. Genetic variations can potentially have an impact on toxicity in addition to these other considerations. Depending on how many clinical symptoms or other factors a patient exhibits, their treatment or management may differ. In cases where the INR is >1.4, coagulopathy is diagnosed; if the INR is >3.0, valvular disease is diagnosed. Major warning signs and symptoms include red areas on the skin that resemble rashes, severe headaches or vertigo, heavy bleeding after injuries, stomach pain or blood in the vomit, red, pink, or dark brown urine, and blackish or bloody stools, among others. In this article, we discuss a case of warfarin toxicity caused at normal dose of warfarin, including the diagnosis, therapy, and accompanying problems.[1] [2]

CASE DESCRIPTION

Case 1

A 30 year old male patient with 97.5 kg weight was admitted in ICU in a tertiary care hospital, with complaints of increase in breathlessness, pedal oedema since 1 week and the hemoptysis since 3 days. The medical history was significant for Ischemic dilated CMP (Ejection fraction 25%) with left ventricular apical clot, and he was on warfarin and other regular treatment. Social habits of patient are drinking alcohol, tobacco chewing and a non vegetarian.

Past medication history- He was taking T. warfarin 4mg 0-0-1, T. MET XL (metoprolol succinate) 25mg 1-0-1, T. Lasilactone (furosemide+spironolactone) 40/50 mg 1-1-0, T. RL

(ramipril) 5mg 0-0-1 and T. Ecosprin Gold (Atorvastatin, Clopidogrel and aspirin) 75/75/25mg 0-0-1 for management of his condition.

On examination patient was found to be conscious, oriented, obese and afebrile. Pulse rate was 84/min and Blood pressure was 78/50mmHg; along with petechiae on trunk and straie on abdomen with bilateral pitting pedal oedema, elevated Jugular Venous Pressure (JVP), fine crepitations in bilateral base of lung and hepatomegaly. Systemic examinations have revealed that the cardiovascular system have normal S1 and S2 and no murmurs present. Respiratory system- normal breath sounds, withbilateral basal fine crepts sounds present. Gastro-intestinal tract, per abdomen- soft, non tender, bowel sounds present. Central nervous system- higher mental function normal, no focal neurological deficits. A specific investigation like Ultra Sonography was suggestive of borderline hepatomegaly and some renal concretions. From initial assessment and complaints the Warfarin toxicity with Heart failure with reduced ejection fraction(25%) with DCMP was suspected and confirmed with INR monitoring.

From the available resources it was found that patient was alcoholic since 3 years and has chronic tobacco intake for last 15 years. He was diagnosed with Ischemic dilated CMP 5 years ago but has no proper documentation for same. In January'2022 he came to hospital with complaints of breathlessness and orthopnea and after all evaluations he was started on Inj. Heparin (for 7 days till he was admitted) and Tab Warfarin for 3 days and was discharged with advise to continue tab warfarin 4mg once every day in evening and had PT-INR of 1 before discharge. And patient returned 1 month later with symptoms of warfarin toxicity.

Laboratory investigations- The 2D ECHO showed Left Ventricular (LV) global Hypokinesia with ventricular systolic function- LV EF 25% and LV apical clot. Sputum test showed few epithelial cells along with some red blood cells. The INR was found to be 6.82 IU and APTT was 54.3 seconds (control 30 seconds) during admission time. On the first day of admission lab data were: platelets- 1.71 lacs/cumm, urea- 35.5mg%, creatinine- 0.8mg%, uric acid-7.3mg/dl Bilirubin total- 0.6mg%, direct-1.3mg% and indirect-2.8mg%, SGPT- 89 IU/L, SGOT- 70 IU/L, sodium- 132 mmol/L, potassium-6.8%, chloride-97 and RBS-110mg/dl, D-dimer- >4000ng/ml, BNP- 172.18 pg/ml, CRP- 72 mg/dl and HbA1c- 5.7 mmol/mol.

Table No. 1: INR, Glucose and input output charting of case 1.

Lab Test	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
PT TEST(seconds)	54		58		30		
PTT CONTROL	30 seconds						
INR (IU)	6.8		4.6	2.4	1.57		
FBS (mg/dl)	173	139	110				
INPUT (ml)	1300	1950	700	1000	1000	600	900
OUTPUT (ml)	4000	2300	850	1200	1200	700	1000

Based on all investigations, the patient was diagnosed with Acute Decompensated Heart Failure with reduced EF (15-20%) with LV Apical clot with Warfarin toxicity. After the admission warfarin was stopped immediately and Vitamin K was started along with ionotrop support and other regular medication.

Individualized therapy for the patient- medications like inj. Piperacillin + tazobactum 4.5g intravenously every 8 hourly as an antibiotic, inj. Metronidazole 500mg intravenously every 8 hourly as an prophylactic antibiotic, inj. Vitamin K (1 ampule) in 100ml normal saline OD as an antagonist for warfarin, inj. Furosemide 40mg intravenously in morning (7am) and afternoon (2pm), inj. Optineuron 2 ampules in 10 ml normal saline (0.9%) intravenously every 24 hours, tablet Aldactone 50mg in morning(8am) and afternoon(3 pm) as an antihypertensive, tablet Unizuva gold (aspirin 75mg + rosuvastatin 20mg + clopidogrel 75mg) at night as anti-platelet therapy, tablet Ivabradine 5mg one in morning and one at night, inj. Pantoprazole 40mg intravenously every 12 hourly, inj. Ondansetron 4mg intravenously every 8 hourly, tablet Digoxin 0.25mg once in morning [Monday to Friday], nebulizer Ipratropium bromide every 8 hourly were given to the patient. In addition to them, on day 5 medications like tablet Rivaroxaben 10mg once in morning, tablet Pregabalin + Nortriptyline 75/10mg twice a day, tablet Benfotiamine 100mg twice daily, tablet Febuxostat 40mg once in morning, tablet Indomethacin 75mg once in morning and capsule lysulin 1110mg once at night, were added to treatment regimen. The only therapeutic intervention was to stop tabWarfarin initially and after stable condition adding of other anticoagulant.

Patient's complaint of hemoptysis and pedal edema were resolved and INR was reduced to 2.4 IU. Alternate day monitoring of PT INR was done. Patient was counseled for newer anticoagulants but due to issue of affordability, patient was started again on warfarin with a lower dose and was kept on home based on PT INR monitoring and was explained for same. Furthermore patient was counseled about diet and was asked to visit doctor in case of any

new symptom. Patient failed to show up for follow up as he died a week later of discharge at home with no justification of death.

Case 2

A 64 year old female patient was admitted in female medicine ward in a tertiary care hospital. Patient came with complaints of breathlessness (NYHA grade 2) since 4 days, hematuria since 2 day and pedal oedema. The medical history was significant for Atrial fibrillation, Cerebrovascular accident aka CVA stroke and hypertension, and was on warfarin 5mg. Patient had no addiction. She achieved menopause 20 years ago. She was a non vegetarian by diet.

Past medication history- she was taking T Warfarin 5mg 0-0-1, Inj enoxaparin 0.6mg 0-0-1, T atorvastatin 40mg 0-0-1, T Aspirin 75mg 0-1-0, T clopidogrel 75mg 0-1-0, T Metoprolol 25mg 1-0-1, T furosemide 20mg 1-1-0, T spironolactone 25mg 1-0-0 for management.

On examination patient was found to be conscious, oriented, obese, afebrile and pallor. Pulse ratewas 76/min and Blood pressure was 190/60mmHg.systemic examination revealed that the cardiovascular system have normal S1 and S2, no murmur and arrhythmia. Respiratory system- normal breath sounds. The INR was found to be 8.6 IU and APTT wasm120 seconds (control 30 seconds) during admission time.

Patient has hypertension since past 16 years (year 2006). In December'2021 she had left sided CVA and then in Feburary'2022 she had right CVA and also was diagnosed with Inflammatory bowel disease (IBD). From 2nd episode of stroke she was kept on tab. Warfarin 5mg along with other medications to manage hypertension and Stroke. 1 month later in March'2022 she came with complaints of warfarin toxicity.

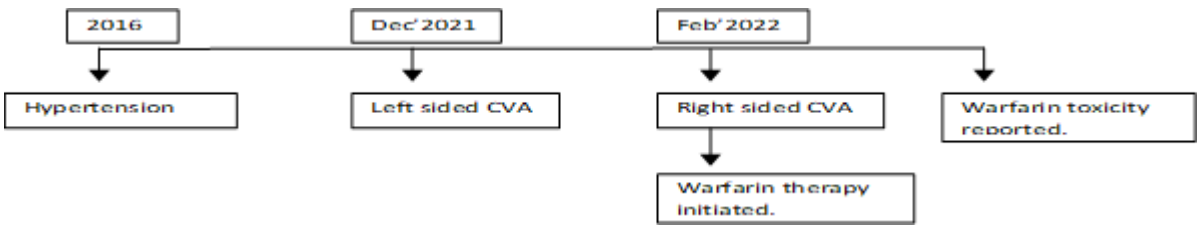

Figure 1- Timeline about historic and current information of Case 2.

Laboratory investigations- the 2D ECHO showed mild Tricuspid valve regurgitation (TR) and LVEF 60%. The CT scan of abdomen- pelvis was suggestive of inflammatory bowel

disease along with partial thrombosis. Colour Doppler examination of left lower limb veins was suggestive of Popliteal vein, posterior and anterior veins appear thrombosed. MRI of brain (stroke protocol)- Focal areas of restricted diffusion along bilateral fronto-parietal lobes represented recent sub-acute non haemorrhagic infarct. On the first day of admission lab data were: platelets- 3.74 lacs/cumm, urea- 75mg%, creatinine- 1.8mg%, total bilirubin- 0.3mg%, Protein- 2.9gm%, Sodium- 129mmol/L, Chlorides-91mmol/L and RBS- 208mg%.

Table No. 2: INR, Glucose and input output charting of case 2.

Lab Test	Day 1	Day 2	Day 3	Day 4
PT TEST (seconds)	120		21.6	
PTT CONTROL	30 seconds			
INR (IU)	8.6		1.5	
RBS (mg/dl)	208	160	109	130
INPUT (ml)	600	600	1100	400
OUTPUT (ml)	400	500	1800	600

Based on all investigations, the patient was diagnosed with Warfarin toxicity with left Left lowerlimb Deep vein thrombosis, in known case of IBD and hypertension and past history of CVA stroke.

After the admission, warfarin was stopped immediately along with T. Lasix and T. spiranolactone and Vitamin K was started along with other regular medication.

Medications like inj. H albumin (20%) intravenously at the rate of 20-25cc/h OD, Inj. Vitamin K (1 ampule) in 100ml normal saline OD, tablet atorvastatin 40mg at night, tablet aspirin 75mg in afternoon, tablet clopidogrel 75mg in afternoon, tablet metoprolol 25mg once in morning and at night, syrup lactulose 30ml in half glass water, tablet febuxostat40mg once in morning and at night and tablet phostat (calcium acetate) 667mg once in afternoon with meal tablet calcium+ vitamin D3 twice daily were given to the patient. Patients complain of hematuria was resolved in 2 days. Patient was kept on strict input/output monitoring and was cautiously monitored for bleeding episode. On discharge patient was counseled for newer anticoagulants, diet and lifestyle modification and was asked for follow up after 15 days for PT INR monitoring.

Patient came back after 5 day for follow up with no new complaints. PT-INR examination was not done as patient declined to give consent.

DISCUSSION/ CLINICAL IMPACT

Here we presented 2 cases, in both the cases warfarin was given as an anti coagulant even thoughthe primary condition, age and gender are different. Warfarin is the most commonly used anti coagulation agent with a lot of advantages despite its narrow therapeutic index. For this reason the treatment with warfarin must be very cautiously.

With oral vitamin K, brief warfarin withdrawal, and appropriate treatment of the bleeding cause, such as compression, packing, or topical antifibrinolytics, patients with increased INRs and mild-moderate bleeding can be treated. Major or life-threatening bleeding should first be treated with intravenous high-dose (10 mg) vitamin K and prothrombin complex concentrates or fresh frozen plasma for factor replacement.

The concomitant use of Warfarin along with other anticoagulants such as Aspirin can lead to increase bleeding related consequences. In our cases the concomitant use of warfarin along with aspirin was done, and it can be noted as drug-drug interaction. It is being assumed that bleeding and raised PT- INR is caused due to synergistic effect of Concurrent therapy as well as warfarin toxicity. Both factors add on to one other.

In a prospective observational study by Gebrehiwot Teklay et al. A conclusion was drawn that commonly prescribed drugs interaction with warfarin were antibiotics, anticoagulants, NSAIDS and diuretics. Drug-drug interactions were prevalent and bleeding consequences weresignificantly linked to raised INR values.[3]

In such cases, it is important for clinicians to be aware of potential interactions and monitor patients INR cautiously.

Patients with mechanical heart valves dysfunction and/or renal dysfunction will be required to continue warfarin instead of the currently available oral anticoagulant therapy agents.

Randomized thrombosis prevention trail by the medical research council's general practice research framework, interpretated that combined treatment with warfarin and aspirin is more effective in the reduction of Ischemic heart disease than single agent on its own.[4]

In the other randomized trial, by Gullov AL et al. which involved 328 patients, aspirin-OAC therapy was linked to a non-significantly decreased incidence of arterial thromboembolism.[5]

Given that individuals receiving OAC therapy typically have concurrent coronary artery disease (CAD) or are at high risk for stroke, some experts have proposed that adding aspirin to OAC therapy may be helpful in these patients despite the lack of evidence for therapeutic benefit.[6]

[7]The co-administration of an OAC with an anti-platelet medication may lower the risk of thromboembolic and other cardiovascular events in such patients by complementing antithrombotic events.[7]

In the study of The BAFTA trial (Birmingham Atrial Fibrillation Treatment of the Aged), which is regarded as the most important randomized trial conducted solely in the elderly population. Here, aspirin and warfarin were given to two groups, and the potential risk of bleeding was compared. Since both groups experienced similar levels of severe bleeding, they were able to demonstrate clearly the superiority of warfarin over aspirin by emphasizing warfarin's better anticoagulation.[8]

CONCLUSION

Warfarin is a coumarin derivative and acts as an anticoagulant by preventing aggregation of the platelets and its effect must be monitored regularly via the international normalized ratio (INR). Though every patient must be evaluated individually, the combination use of warfarin and aspirin for the prevention of cardiovascular events was found more useful than monotherapy and must be done after evaluating individual complications and risks of patient.

The patients taking warfarin therapy requires more attention from health care providers, constant care and frequent monitoring to prevent warfarin toxicity. Better communication between patients and medical professionals is also necessary. In cases of warfarin toxicity, quick and efficient action should be done to avoid potentially fatal complications.

ABBREVIATIONS

CMP-Cardiomyopathy

LV- left ventricle

EF- ejection fraction

CVA- cerebral vascular accident

BNP- B-type natriuretic peptide

TR- Tricuspid regurgitation

CRP- C reactive protein

LL DVT- lower leg, deep vein thrombosis

IBD- Inflammatory bowel disease.

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