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Case Report of Warfarin Induced upper gastrointestinal bleeding

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ABSTRACT

Warfarin is an oral vitamin k antagonist prescribed to those patients for the treatment and prevention of venous thromboembolism. The major challenges to be faced during the therapy were a greater risk for both major as well as minor bleeding, which makes the regular monitoring of INR (international normalized ratio) mandatory. Here we report a case study of 80 year old male who presented to casualty with the complaints of vomiting fresh blood in large quantities due to consumption of warfarin three times in a day for past 2 weeks. Patient was on anticoagulation therapy for paroxysmal atrial fibrillation since 2012 and was taking all his medications alone, he was independent in activities of daily living and instrumental activities of daily living. The blood investigation revealed anemia (Hemoglobin:6.1g/dl).He was immediately transfused with packed RBC and fresh frozen plasma to replenish the body reserves. Prothrombin time (PT)/INR was reported undetectable and warfarin was withheld from the past medications and was restarted at INR 1.56.The overdose has led to additional monitoring and prolonged hospital stay. Furthermore this case highlights the need for a better communication by providing counselling regarding all aspects of medications as well as lifestyle modifications and also by giving patient information leaflets.

INTRODUCTION

Warfarin is a coumarin derivative widely prescribed vitamin K antagonist as an oral anticoagulant which is discovered serendipitously in early 1980s. It is approved by FDA (food and drug administration) for various therapeutic indications and thereby considered to be a cornerstone in the prevention and treatment of venous thromboembolism, as well as for the prevention of thromboembolic complications associated with atrial fibrillation(AF), heart valve replacement and myocardial infarction. Pharmacological principle behind warfarin is inhibition of C1 subunit of Vitamin K epoxide reductase enzyme, whereas it is essential for the activation of vitamin k dependant coagulation factors such as Factor II,VII,IX, X and regulatory proteins such as C,S and Z (Prashanth *et al.,* 2012). Even though it is considered to be a drug of choice for long term anticoagulation, due to its narrow therapeutic index a regular patient monitoring INR is mandatory in order to attain desirable outcomes (Jayesh *et al.,* 2006). As the elderly population is more sensitive towards the effects of warfarin, lower initial doses were preferred followed by maintenance dosing with 2-4mg.

Warfarin associated bleeding

In fact warfarin is known to be a life saving medicine it is linked with various drug related problems such as drug-drug interactions, drug-food interactions as well as major bleeding (Pautas *et al.,* 2006). Among significant bleedings associated with warfarin Intraperitoneal bleeding is termed as major complications (Jayesh *et al.,* 2006). Patients treated with oral anticoagulants predispose to certain risk factors that contribute significant bleeding includes elderly population with an age greater than 75yrs, presence of comorbidities such as systemic hypertension, old stroke, paroxysmal atrial fibrillation etc. (Prashanth *et al.,* 2012).

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Besides the risk factors mentioned, certain facts that supports a greater risk for bleeding complications arises from concurrent use of aspirin or any other antiplatelets, due to polypharmacy and patient related factors such as poor compliance, inadequate knowledge about warfarin usuage, confusion etc. (Marinigh *et al.,* 2010). Warfarin associated bleeding mainly presents in gastro intestinal tract, urinary tract, soft tissues and orophartynx whereas GI bleeds is considered to be more fatal (Pautas *et al.,* 2006). However the use of warfarin in elderly population shows a good safety profile when the dose is adjusted and INR is monitored accordingly. For an elderly population, inorder to prevent the bleeding complications the INR with 2.5 is considered to be a gold standard and the commonly suggested therapeutic range is 2.0 – 3.0 (Prashanth *et al.,* 2012). As the elderly patients are more towards the bleeding risk the factors that increase INR and thereby bleeding includes drug-drug interactions, drug-food interactions and accidental overdosing.

Treatment & management of Bleeding

Bleeding manifestations were presented in those patients with a slightly elevated INR within a range of 3.5 - 5.0 **(**Kagansky *et al.,* 2004). Numerous methods have been implemented inorder to reverse the anticoagulant effect of warfarin includes administration of intravenous(IV) vitamin K1 (phytonadione), Fresh frozen plasma (FFP) in case of severe bleeding and by omission of warfarin dose, prothrombin complex concentrates (PCC) etc. The choice of therapy depends on individual's bleeding risk and core indication for anticoagulation.

The commonly recommended treatment options have been summarized in Table 1(Prashanth *et al.,* 2012).

Table 1: Treatment options.

Clinical setting	Management of Bleeding	Comments
INR with 3.5 - 5.0	Administer IV Vitamin K1inorder to achieve correction of coagulopathy rapidly (10-15 min)	*Oral vitamin K is preferred for prompt resolution in the absence of severe bleeds. * Dose of warfarin is either reduced or witholded in order to attain slow reversal within 24hrs.
INR 5.0-9.0 with Presence of clinically relevant bleeding not life threatening	Discontinue warfarin and administer : - IV Vitamin K1 5-10mg - Prothrombi nex-VF 35-50IU/kg	Low doses of Oral Vitamin K ≤ 5mg were also preferred to achieve a reduced INR levels within 24hrs.
INR > 9.0 with Presence of life threatening bleeding	Dose of warfarin should withheld and administer : - IV Vitamin k1 5-10mg - FFP 150-300ml - Prothrombi nex-VF 50IU/kg	Even though the higher doses of Vitamin K such as 10mg are linked with prolonged resistance and incidence of thromboembolic complications, the lower dose of 5mg is suggested for slow reversal

There shows a clear evidence of warfarin on its good positive response, but the outcomes can only be finalised by measuring the adherence of the patients towards warfarin. The possible ways to maximize patient adherence related to warfarin treatment includes improving patient education, dosing schedules and better communication. In order to improve medication adherence, valuable interventions should be put forward by registered medical practioner's, clinical pharmacists, behavioural specialists or nursing staffs thereby a better results could be achieved. In concern with elderly population, valuable interventions should be centred on patient attitudinal factors such as memory other cognitive-behavioural status (Dean *et al.,* 2010). Here we report a case study on upper gastro-intestinal bleeding due to accidental overdosing of warfarin therapy in an elderly male with paroxysmal atrial fibrillation who presented with chief complaints of vomiting fresh blood in large quantity since one day.

CASE HISTORY

Patient was a conscious oriented 80 year old male who was brought to causality with the complaints of vomiting fresh blood in large quantities. He was tired and had light-headness. He consumed warfarin three times in a day for past 2 weeks. Patient was on anticoagulation therapy for paroxysmal atrial fibrillation since 2012 with INR was maintaining within the normal range (2-3) and was taking all his medications alone, he was independent in activities of daily living and instrumental activities of daily living. Patient is a known case of type 2 diabetes(on diet), systemic hypertension, dyslipidemia, idiopathic parkinsonism and old cerebrovascular accident and was on medications such as T.Ecospirin AV 75mg (Aspirin 75mg +Atorvastatin 10mg) 0-1-0, T.Amiodarone 200mg 1-0-0, Cap. Esmoprazole 20mg 1-0-0, T.Clonidine100mcg 1-1/2-1,T.Warfarin 3mg,3mg,3mg in 3 days cycles (at 6pm), T.Remylon D 0-1-0 and T.Syndopa 110mg (Carbidopa (10mg) + Levodopa (100mg)) 1-0-1.

Investigation

On examination the patient had bradycardia (HR:4Obts/min) and hypotension(90/60mmHg), also the blood investigation revealed anemia (Hb:6.1g/dl). He was immediately transferred to medical ICU (intensive care unit) and transfused with packed RBC (red blood cell) and fresh frozen plasma to replenish the body reserves and to counteract the warfarin and aspirin, amiodarone. PT/INR was reported undetectable at the time of admission so warfarin was withheld from the past medications.

Electro Cardiogram- Sinus bradycardia with features of type 1 second degree heart block

Computed Tomography Brain- showed no intracranial bleed

Upper GI endoscopy- showed polypoidal lesion with stigmata of recent bleed in the antrum part of the stomach.

Ultrasound of abdomen- showed mild fatty liver,right simple renal cortical cyst.

Patient was restarted with a low dose of 2mg of warfarin when the INR was 1.56. Patient was planned to do a 24 hour holter monitoring for the evaluation of bradycardia. Patient's hospital duration was for 7 days and discharged with medications like:

T. Warfarin 2mg 0-0-1 at 6pm for 4 days (dose to be adjusted on review)
T. Pantoprazole 40mg1-0-0 for 1 month
T. Arkamine (Clonidine) 100mcg 1-1-1 to continue
T. RemyelinD(nutritional supplement) 0-1-0to continue
T. Syndopa110mg (Carbidopa (10mg) + Levodopa (100mg)) 1-0-1
T. Shel D (Calcium Supplement) 500mg 1-0-0

Patient had to review in Cardiology after 1week with the holter monitoring reports and also in the Geriatric medicine with CBC (complete blood count),PT/INR reports. Patient was advised to follow a diabetic diet and also warned to seek immediate care when any bleeding manifestations like vomiting blood, gum bleeds, excess tiredness, headache, blurring vision, palpitations, breathlessness or chest discomfort.

DISCUSSION

The coumarin derivative warfarin an anticoagulant works by preventing platelets from sticking from each other to form blood clots. It can cause serious bleeding so proper monitoring is required which is by INR monitoring (Kessler *et al.,* 2006).The warfarin toxicity or overdose results from administering high dose, altered protein binding ,low potassium intake, reduced synthesis or increased clearance of vit K dependent clotting factors and more important the use of Erythromycin, Fluconazole, Amiodarone, Propranalol, Proxicam and Omeprazole which compete for the protein binding sites with the warfarin(David *et al.,* 1998). As the warfarin has narrow therapeutic index, they result in major or life threatening bleeding (Baglin *et al.,* 1998) and most of the bleeding are from gastrointestinal, urinary, soft tissues (6.5%), intracranial hemorrhage (1%). The target INR of warfarin patients is 2-3 bleeding is hiked even at low anticoagulation of INR <2 and increased exponentially when INR > 5 (Meena *et al.,* 2011).

The treatment used mainly depends on the rectal bleeding and if there is a significant bleeding, we start with immediate transfusion of the packed red blood cells, fresh frozen plasma and also using an IV/oral vitamin K1 and other evaluation depends on the situation ahead (Chua *et al.,* 1998).

A research article published in British Journal of Medicine on 2015 in which they compared the risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin. They came with a conclusion that the risk of gastrointestinal bleeding increased after age 65, such that by age 76 the risk exceeded that with warfarin among atrial fibrillation patients **(**Neena *et al*.,2015).

Another research article in the Circulation, American Heart Association on 2013 conducted a study on the management and Outcomes of major bleeding during therapy with Dabigatran or Warfarin. They found out that the patients who had major bleeding on Dabigatran required more red cell transfusions but received less plasma, required a shorter stay in intensive care and had a lower mortality compared with that of warfarin induced major bleeding (Ammar *et al.,* 2013). A study in the New England Journal of Medicine on 2013 showed the extended use of Dabigatran, Warfarin and placebo in venous thromboembolism where Dabigatran was effective in venous thromboembolism and also carried a lower risk of bleeding compared to warfarin but carried a higher risk than placebo (Sam *et al.,* 2013).

Even though Warfarin serves as cornerstone for the prevention and treatment of diverse indications, due to greater incidence of bleeding many physicians hesitate in prescribing warfarin to very elderly population having a previous history of atrial fibrillation (Lip *et al.,* 2002). On evaluation of study conducted by BAFTA trial (Birmingham Atrial Fibrillation Treatment of the Aged), which is considered to be the foremost randomised trial exclusively in the elderly population. Here two groups were treated with aspirin and warfarin and they compare for possible bleeding risk. A comparable severe bleeding was encountered by both groups, hence they came into a clear evidence of advantage of warfarin over aspirin by highlighting a better anticoagulation with warfarin. Likewise a similar results from various clinical trials encourage the physicians prescribing warfarin in elderly population with AF (Mant *et al.,* 2007).

CONCLUSION

The case report highlights the accidental overdose of warfarin due to poor adherence in a well cognitive oriented elderly patient with atrial fibrillation. Hence the patient presented with spontaneous upper gastric bleeding which has led to initial ICU stay followed by episodes of bradycardia and hypotension. Due to this patient required additional monitoring and prolonged hospital stay. Furthermore this case projects the need for a better communication by means of providing counselling regarding all aspects of medications as well as lifestyle modifications and by giving patient information leaflets.

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