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Acute Warfarin Toxicity due to Interaction between Warfarin and Amiodarone

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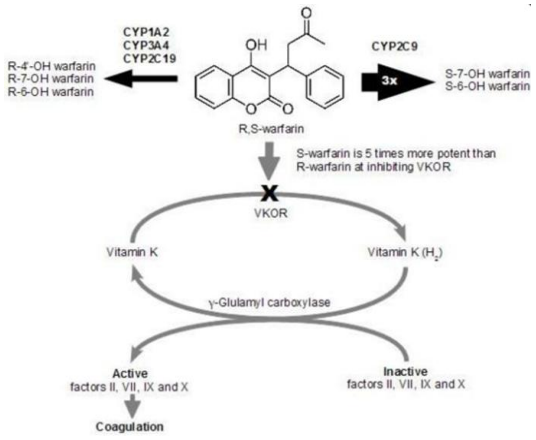
Abstract
Warfarin is an anticoagulant that's broadly used in the treatment and prevention of thrombosis, in the treatment of dilated cardiomyopathy, mechanical valves, pulmonary embolism and atrial fibrillation. Amiodarone was initially introduced as an anti-anginal drug over 40 years ago but is now used therapeutically as a Class III antiarrhythmic agent. Amiodarone is associated with adverse effects like pulmonary toxicity, hepatotoxicity and thyroid disorder. There have been reviews of unfavorable drug interactions when amiodarone is administered together with a wide range of different therapeutic agents like theophylline and flecainide . However, the most common, probably the maximum risky drug interaction that amiodarone exhibits is its potentiation of the anticoagulant effect of warfarin, which substantially increases the patient's risk of hemorrhage. Polymorphisms in cytochrome P450 genes and drug interactions are accountable for most of the warfarin toxicity. Each person is different in their susceptibity to drugs. Here we report a case in our article, which is an example of one such interaction of warfarin with amiodarone.
Keywords: *Warfarin, Amiodarone.*

Introduction

Warfarin was approved as a drug in the early 1950s and is widely prescribed. It is an anticoagulant which is broadly used in the prevention of thrombosis, for dilated cardiomyopathy, mechanical valves, pulmonary embolism and atrial fibrillation.[1] Warfarin use can be associated with serious bleeding risks. Warfarin has narrow therapeutic index and greater variability among individuals in the dosage required, which may be due to individual genetic variations. Also warfarin has interactions with many drugs which potentiates the anticoagulant effect of warfarin. To maintain adequate anti-thrombosis and to prevent bleed, monitoring through the INR is necessary. The INR is used to reveal the effectiveness of warfarin and measures of the pathway of blood coagulation. The INR is used to standardize the consequences for a prothrombin time. The INR is the ratio of a affected person's prothrombin time to a control sample, raised to the power of the index fee for the analytical machine used.

Elements which increase the risk of bleeding: genetic polymorphisms affecting the metabolizing enzymes, impaired liver function, drug interactions, congestive heart failure, fever.[2] Genetic elements and drug interactions basically account for the hazard of over-anticoagulation. Warfarin metabolism involves often the cytochrome P450 (CYP) enzymes. Vitamin K is needed by proteins C and S, and for clotting factors II, VII, IX, and X to allow assembly of the procoagulant enzyme complexes vital to generate fibrin. Warfarin has the ability to interfere with



Warfarin metabolism. (Warfarin is metabolized inside the liver. CYP1A1, CYP1A2, and CYP3A4 metabolize the (R)-enantiomer and CYP2C9 metabolizes the stronger (S)-enantiomer. Warfarin inhibits vitamin K reductase complex subunit 1 to intervene with the diet-K-based carboxylation of clotting factors prothrombin II, VII, IX, and X.).

the recycling of diet K in the liver. The pharmacologic impact of warfarin is mediated by the inhibition of nutrition K epoxide reductase complex subunit.[3,4]

Metabolism

Warfarin comprises of (R) - and (S)-warfarin enantiomers. The levorotatory S-warfarin is five times stronger than the dextrorotatory R-warfarin and approximates for 60% to 70% of warfarin's anticoagulant action. (S)-warfarin is metabolized almost exclusively by CYP2C9.[5,6,7]

The activity of the CYP2C9 enzyme has an important effect on the clearance of (S)-warfarin and as a result has effects on anticoagulant effect. In the presence of genetic variations in which the activity of CYP2C9 is reduced, clearance of (S)-warfarin is also reduced. Activity of CYP2C9 between people can range by greater than 20-fold. (R)-warfarin is metabolized through a couple of varying CYP enzymes.[8]

Pharmacokinetics

- By oral route,warfarin has a bioavailability of 100%, peaks in blood in 1 hour, and has a protein binding of 98 to 99%.
- It is metabolised to 6-hydroxywarfarin and seven-hydroxywarfarin (inactive).
- Half life is about 40 hours. Duration of action might be as long as 5 days.

Drug Interactions Involving Coumarins[9]

Increased Anticoagulant Effect	Decreased Anticoagulant Effect
Alcohol, allopurinol, NSAIDs, anabolic steroids, amiodarone, ciprofloxacin, erythromycin, sulfonamides, tetracyclines, SSRI antidepressants, thyroxine, cisapride, disulfuram, simvastatin, cimetidine, omeprazole.	carbamazepine, phenobarbitone, sodium valproate, griseofulvin, oral contraceptives, vitamin k, vitamin C and disopyramide.

Case Report

Sixty eight years old male came to ER with complaints of giddiness, swelling, pain and redness which started to begin in the right knee joint one week before and also involved the right arm and left elbow joint. No other significant present history. Patient was on Acenocoumarin 3mg once a day, and Amiodarone 200mg twice a day for 4 months as his previous Echocardiogram revealed hypokinesia of non dilated LV with irregular rhythm. No history of trauma, fever, allergic exposure, rashes and bleeding diathesis. No history of bleeding diathesis in family members.

On Examination: Patient was drowsy, oriented, PR- 92 / min, BP - 90/60 mm Hg, RR- 20 / min,

redness and swelling was present over right knee joint, right arm and left elbow joint. Diffuse ecchymosis was present over right knee joint,right arm and left elbow joint. Systemic examination revealed no abnormality. Investigations showed elevated prothrombin time, activated partial thromboplastin time, INR, anemia and thrombocytopenia. Arterial and venous Doppler of both upper limb and lower limb were normal. X ray right knee joint and elbow joint showed no evidence of bony injury. Aspiration of right knee joint showed bloody aspirate suggestive of heamarthrosis.

Investigations

	DAY 1	DAY 2	DAY 3	DAY 4
Hemoglobin	4.6	6	8.2	8.3
Total count	10,300	7200	5500	4200
Neutrophills	74%	78%	79.2%	72.6%
Lymphocytes	15%	28%	14.5%	20.1%
Platelet	2,13,000	1,30,000	1,09,000	1,09,000
urea	123	105	70	44
creatinine	3.6	3.0	2.1	1.1
Na	140	128	132	136
K	4	3.5	4.0	4.4
Cl	96	89	99	99
PT	>400 seconds	60	32	14
INR	Could not be measured	6.6	2.9	1.21
Albumin	2.9			
Globulin	3			
Bilirubin(total)	0.7			
Direct	0.2			
Indirect	0.5			
SGOT	21			
SGPT	18			
ECG :	HR – 75 /min, regular rhythm, ST depression in 2,3,avf, V2-V6	Trop T-negative	2D ECHO :	EF- 65 % Dilated RA/ RV PAH moderate Adequate systolic function No RWMA

Patient was admitted with the provisional diagnosis of acenocoumarol toxicity. He was treated with vitamin K1 infusion, 4 units of fresh frozen plasma in a dosage of 15ml/Kg, 1 unit of packed cell, 1 unit of whole blood transfusion. Patient improved hemodynamically and all the signs of acenocoumarol toxicity reversed over four days and was discharged. Patient is under follow up for past 5 months and patient is doing well.

Conclusion

The motive for thinking about a drug interaction of warfarin whilst beginning amiodarone is the impact of amiodarone on warfarin metabolism. It is vital to recall this drug interplay in any person receiving both of these drugs due to the severity and consistency of this interaction. It is better to reduce the dose of warfarin to one-half when beginning amiodarone therapy.[10,11,12] Due to long half life of amiodarone it is imperative to do several dose adjustments before the patient is maintained on a particular dosage of warfarin.

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