WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 13, 760-767. Case Report ISSN 2277– 7105

WARFARIN TOXICITY WITH CHRONIC KIDNEY DISEASE: A CASE REPORT

Johnson V. Babu*[1], Timy Thomas[1], Neha Maria Augustine[2], Arpith Antony[1] and K. S. Irfan[1]

[1]Pharm. D Interns. Nirmala College of Pharmacy, Muvattupuzha.

[2]Assistant Professor, Department of Pharmacy Practice, Nirmala College of Pharmacy, Muvattupuzha.

Article Received on
25 August 2020,

Revised on 14 Sept. 2020,
Accepted on 05 October 2020

DOI: 10.20959/wjpr202013-18954

***Corresponding Author**
Johnson V. Babu
Pharm. D Interns. Nirmala College of Pharmacy, Muvattupuzha.

ABSTRACT

Background: Warfarin, a coumarin derivate which is the first anticoagulant used is a vitamin K antagonist mainly used as an anticoagulant. Unintentional toxicity is due to dosing, diet plan, drug interaction and liver disease. Not only these factors but also genetic polymorphisms can also affect the toxicity. The treatment or management of patients who had warfarin toxicity can vary based on their number of clinical symptoms or factors. **Case Presentation:** A 79-year-old male patient with 68 kg and 163 cm height was admitted in tertiary care hospital, with chief complaints of bleeding tendency, history of fall on the day before hospitalisation and history of blood in stool. Diagnosed as warfarin toxicity (Drug induced lower Gastric bleeding), Diabetes mellitus II, Chronic obstructive pulmonary disease, Atrial fibrillation, and Chronic kidney disease using physical and laboratory examination. Warfarin was stopped and administered vitamin K along with other regular medicines. Also converted the diet from normal to diabetic diet. The patient treated with fresh frozen plasma transfusion, Vitamin K, Insulin, Oral antihyperglycemic agent, antiplatelets, statins, diuretics and other supportive measures. Cardiology and nephrology management done as per advice. **Discussion:** The patients who are on warfarin need for a better communication between patient and health care providers by means of providing counselling regarding all aspects of medications as well as lifestyle modifications and by giving patient information leaflets.

KEYWORDS: Warfarin Toxicity, INR. Drug induced GI Bleed.

BACKGROUDND

Warfarin, a coumarin derivate which is the first anticoagulant used is a vitamin K antagonist mainly used as an anticoagulant for treatment and prevention of a variety of coagulopathic and thromboembolic disorders like deep vein thrombosis, pulmonary embolism, and to prevent stroke in people who have atrial fibrillation, valvular heart disease or artificial heart valves. [1 2] Warfarin exerts its anticoagulant effect by γ-carboxylation of the hepatic vitamin K-dependent clotting factors II, VII, IX, X, is impaired, leading to inhibition of coagulation.[3]

The toxicity can be due intentional, unintentional and paediatric ingestion. Mainly the unintentional toxicity is due to dosing, diet plan, drug interaction and liver disease. Not only these factors but also genetic polymorphisms can also affect the toxicity.[4] The treatment or management of patients who had warfarin toxicity can vary based on their number of clinical symptoms or factors. If the INR> 1.4 it can be called as coagulopathy in normal cases and >3.0 if the patient had valvular issues. The major signs and symptoms that will help suspect the cases are red spots on skin look like rashes, severe headache or dizziness, bleeding after injury heavily, stomach pain or vomiting blood, red, pink, dark brown urine, and blackish or bloody bowels etc.[5] In this article we describe a case of diagnosis, treatment and other issues of warfarin toxicity in an adult.

CASE PRESENTATION

A 79-year-old male patient with 68 kg and 163 cm height was admitted in tertiary care hospital, with chief complaints of bleeding tendency, history of fall on the day before hospitalisation and history of blood in stool. The medical history was significant for atrial fibrillation on warfarin, diabetes, chronic kidney disease, systemic hypertension, COPD and on regular treatment. Social habits of patients are drinking alcohol, smoking, and a non-vegetarian.

He was taking warfarin 3mg, Inj. Lantus 18-0-6, T. Amaryl (Glimepiride) 2 mg 2-0-1, T. Calaptin (verapamil) 40 mg 1-1-1, T. Deplatt (Clopidogrel) 75 mg 1-0-0, T. Tide (Torsemide) 20 mg 1-0-0, T. Jovast (Atorvastatin) 10 mg 0-0-1, T. Doxolin (Doxofylline) 400mg $^{1}/_{2}$ -0-$^{1}/_{2,}$ T. Clonicare (clonazepam) 0.5mg 0-0-2,T. Amlodac (Amilodipine) 5mg 0-0-1,, T. Diaxriptin (bromocriptine) 0.8mg 2-0-0, T. Sobisis (sodium bicarbonate) $^{1}/_{2}$ -0-$^{1}/_{2}$, T. Zitaplus (teneligliptin) 20 mg 1-0-0, T. Alfoo (alfuzosin) 10mg 0-0-1 as own medicines.

On physical examination patient was found to be conscious, oriented, alert, moderate built, normal oral cavity. Tonsils, thyroid and no rashes, pallor or pedal edema. The body temperature was 37 °C, Pulse rate- 62/mts, Respiratory rate-20/mts, Blood pressure-120/70mmHg and SPO_2 -98%. Systemic examinations have revealed that the Cardiovascular system have S1 S2 normal and no S3 sounds but murmurs are present. Respiratory system-normal breath sounds, no added sounds, Gastro intestinal tract- soft, non-tender, bowel sounds + and Central nervous system- Higher mental function normal, no focal neurological deficits. From initial assessment and complaints, the Lower GI bleeding due to warfarin toxicity were suspected and confirmed with INR monitoring.

Lab Investigations: The ECHO showed no RWMA, satisfactory Left ventricular systolic function, Dilated LA, No obvious clots. The result of stool occult blood was negative. The INR was found to be 9.93 during admission time. On the 1st day of admission lab data was platelet count-218000, urea-35.5, Creatinine 2.1, Bilirubin total-0.6, Direct-0.2, SGPT-9, SGOT-13, Alkaline phosphate -69, Total protein-6.8, Albumin-3.7, Globulin-3.1, Albumin/Globulin ratio-1.2:1 Sodium-138, Potassium-4 and RBS-200. 3rd day HB found to be 11 and on 5 day it was 10.8. packed cell volume was checked due to low Hb and found to be 32.4. The urea on 2nd and 3rd day reported as 37.5 and 38.1mg/dl. The serum creatinine, Serum sodium and Serum potassium levels remain as same as the previous day.

Table No.1: INR and Glucose level of patient.

LAB	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 6
PTT Test	112 sec	43.0 sec	31.2 sec	22.2 sec	16.8 sec	16 sec	14.5 sec
PPT Control	11.3 Sec						
INR	9.93	3.80	2.76	1.96	1.48	1.41	1.28
FBS		284	297	223	265	240	227
RBS Morning		252	138	209	124	112	-
RBS Afternoon	200	218	200	202	201	165	-

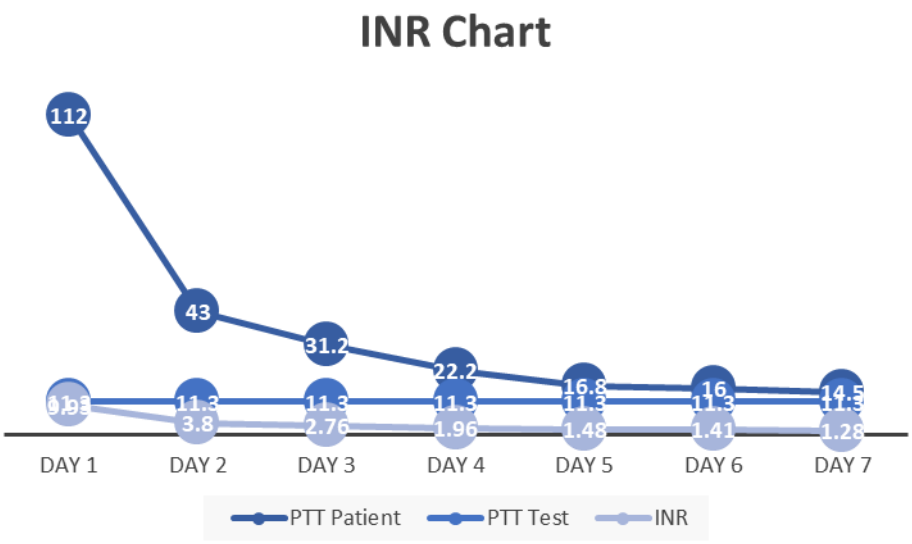

Figure No: 1 INR Chart.

Based on the physical, laboratorial investigation it was diagnosed as warfarin toxicity (Drug induced lower GI bleeding), DM II, COPD, AFIB, and CKD. On admission time itself the warfarin was stopped and administered vitamin K along with other regular medicines. Also converted the diet from normal to diabetic.

Day 2- on checking vitals BP- 110/80 SpO2-90%, RR-20, PR-56 were found. Constipation, malena were complained. On day 3 BP was 140/90, SpO2- 96%, RR-20 and PR-60. Patient found to be better and no fresh complaints. Day 4- BP-120/80, SpO2-96%, RR-20, PR-60. Presented complaint of Giddiness and on ECG nothing significant found. But pre syncope were found during the examination. This may due any of the drugs because the anti-diabetic, benzodiazepines, others drugs in the medication can cause dizziness. But it didn't last for long. The BP, Sugar checked. Day 5- BP-150/80, SpO2-96%, PR-90 and RR 20. Restarted the Warfarin at 1 mg and planned to increase the dose slowly. No fresh complaints. On 6th day chief complaint of black coloured stools (malena) reported, no vomiting, giddiness was reported and chest found to clear. Temperature found to be normal. Pulse rate -78/mts, RR-20/mts, Bp-130/80 mmHg, SpO2-98%. Day 7- No new fresh complaints were reported. BP-130/80, RR-22, PR-80. Patient were discharged.

The patient treated with fresh frozen plasma transfusion, Vitamin K, Insulin, OHA, antiplatelets, statins, diuretics and other supportive measures. Cardiology and nephrology management done as per advice. (Table no: 2)

Table No: 2 Treatment Given.

Drugs	1st	2nd	3rd	4th	5th	6th	7th
T. Clonicare 0.5mg 0-0-2	*	*	*	*	*	*	*
FFP 500ml	*						
Inj. Vitamin K 1 amp IV OD	*	*	*	*	-	-	-
Inj. Lantus	16-0-8	18-0-12	25-0-18	25-0-25	*	*	*
T. Calaptin 40mg 1-1-1 (verapamil)	*	*	*	*	*	*	*
T. Amaryl 2mg 2-0-1 (Glimepiride)	*	*	*	*	*	*	*
T. Deplatt 75mg 1-0-0 (Clopidogrel)	*	*	*	*	*	*	*
T. Tide 20mg 1/2 -0-0 (Torsemide)	*	*	*	*	*	*	*
T. Jovast 10mg 0-0-1 (Atorvastatin)	*	*	*	*	*	*	*
T. Doxolin 400mg ½-0-½ (Doxofylline)	*	*	*	*	*	*	*
T. Diaxriptin 0.8mg 2-0-0 (bromocriptine)	*	*	*	*	*	*	*
T. Glucobay 50 mg 1-0-0 (acarbose)	*	*	*	*	*	*	*
T. Amlodac 5mg 0-0-1 (Amilodipine)	*	*	*	*	*	*	*
T. Thiamine 1-0-1	*	*	*	*	*	*	*
T. Dulcolax 2tab stat HS	-	*	-	-	-	-	-
T. Sobosis ½ -0-½	-	*	*	*	*	*	*
T. Cremalax	-	1-0-1	1-0-0	*	*	*	*
Inj. HAR	-	0-6-0	0-6-0	0-4-0	*	*	0-0-6
T. Zitaplus 20mg 1-0-0 (teneligliptin)	-	-	*	*	*	*	*
T. Alfoo 0-0-1 (alfuzosin)	-	-	*	*	*	*	*
T. Warf 1mg 0-0-1(6pm)	-	-	-	-	*	*	*

The warfarin restarted from 5th day of admission by reducing the dose to 1mg and planned to maintain the INR below 1.8.

The condition improved and coagulopathy corrected also no complaints were reported during the 7th day therefore with medications Inj. Lantus 25-0-25, T. Amaryl (Glimepiride) 2 mg 2-0-1, T. Calaptin (verapamil) 40 mg 1-1-1, T. Deplatt (Clopidogrel) 75 mg 1-0-0, T. Tide (Torsemide) 20 mg $^1/_2$ -0-0, T. Jovast (Atorvastatin) 10 mg 0-0-1, T. Doxolin (Doxofylline) 400mg $^1/_2$ -0-$^1/_2$, T. Clonicare (clonazepam) 0.5mg 0-0-2,T. Amlodac (Amilodipine) 5mg 0-0-1, T. Thiamine 100mg 1-0-1, T. Diaxriptin (bromocriptine) 0.8mg 2-0-0, T. Glucobay (acarbose) 50 mg 1-0-0,T. Sobisis (sodium bicarbonate) $^1/_2$ -0-$^1/_2$, T. Cremalax 0-0-1, T. Zitaplus (teneligliptin) 20 mg 1-0-0, T. Alfoo (alfuzosin) 10mg 0-0-1, T. Warf (warfarin) 1mg 0-0-1 (5 pm) patient were discharged. Advised to review after 7 days with Erythrocyte sedimentation rate, Fasting blood sugar, post prandial blood sugar, PT, INR, sodium, potassium, Renal function test. After 9 days patient follow up was done. The patient found to be better. Blood sugar-130/80, Hemoglobulin -12.2mg/dl, Urea-28, Creatinine-1.9, Total count-7100, Neutrophils-55, Lymphocyte-37, Esnophills-8, Erythrocyte sedimentation rate-

25, Platelet-2.4, Fasting blood sugar-74, post prandial blood sugar-111 Uric acid-6.6, sodium-132 and potassium-3.9. The INR found to be within limit (1.23). Advised some modification in present therapy.

ADR: Drug induced lower GI bleeding is dose dependent adverse reaction of type A. It can also address a symptom of warfarin toxicity. The reaction is severe in nature can lead to life threatening complication and can be preventable one. Causality assessment of ADR were done using Naranjo, and WHO scale. The ADR was confirmed by using these scales.

The occurred event cause could be related with Laboratory test variation, had probable time relationship to drug intake, the ADR could not be explained by disease or other drugs, response to withdrawal was acceptable (pharmacologically, pathologically). Therefore, the casualty assessment from WHO scale found to be certain.[6]

As per the Naranjo scale the ADR was found to be a Probable (8) explained in Table no. 3.[7]

Table No. 3: Naranjo Scale based causality assessment.

Sl. No	Questions	Yes	No	Don't Know	Score
1	Are there previous conclusive reports of this reaction?	+1	0	0	+1
2	Did the adverse event appear after the drug was given?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
4	Did the adverse reaction reappear upon readministering the drug?	+2	-1	0	0
5	Were there other possible causes for the reaction?	-1	+2	0	+2
6	Did the adverse reaction reappear upon administration of placebo?	-1	+1	0	0
7	Was the drug detected in the blood or other fluids in toxic concentrations?	+1	0	0	+1
8	Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose?	+1	0	0	0
9	Did the patient have a similar reaction to the drug or a related agent in the past?	+1	0	0	0
10	Was the adverse event confirmed by any other objective evidence?	+1	0	0	+1
TOTAL					8

Definite - 9 or higher, Probable - 5 to 8, Possible - 1 to 4, Doubtful - 0 or less.

DISCUSSION/ CLINICAL IMPLICATION

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.

As the warfarin has narrow therapeutic index, they result in major or life-threatening bleeding and most of the bleeding are from gastrointestinal, urinary, soft tissues (6.5%), intracranial haemorrhage (1%). The target INR of warfarin patients is 2-3 bleeding is hiked even at low anticoagulation of INR 5.

The case report highlights the overdose of warfarin due to poor adherence in a well cognitive oriented elderly patient. Patient presented with gastric bleeding which has led to hospital admission. Case projects the need for a better communication between patient and health care providers by means of providing counselling regarding all aspects of medications as well as lifestyle modifications and by giving patient information leaflets.

The warfarin induced gastric bleeding is common but can lead to a very serious and fatal condition to the patient. If the condition is unnoticed, it can lead to severe bleeding which may lead to life-threatening complications and death.[8,9]

Thus, leading to a conclusion, that the patients who are on warfarin should be advised with all kinds of positive and negative effects along with diet. Also, counsel with proper time management and dose management for better outcome.

CONCLUSION

All anticoagulant especially warfarin will induce severe life-threatening complications may lead to death. Early identification with proper symptoms and management is necessary to eliminate these reactions. Patient education had an important role in prevention of ADR and better therapeutic outcome.

ABBREVIATIONS

INR- International normalized ratio, COPD- Chronic obstructive pulmonary disease, GI- gastric intestinal, HMF- high mental function, DM- diabetes mellitus, PPBS- Post prandial blood sugar, FBS- fasting blood sugar, ECG- electrocardiogram, AFIB- atrial fibrillation, ADR- adverse drug reaction, SPO2- partial pressure of oxygen, PR- pulse rate, RR- respiratory rate, BP-blood pressure, CKD- chronic kidney disease, IV- intravenous, OD-once

daily, HS- Night time, RBS- random blood sugar, PTT- partial thromboplastin time, RWMA- regional wall motion abnormality, SGOT- serum glutamic-oxaloacetic transaminase, SGPT- Serum Glutamic Pyruvic Transaminase.

REFERENCES

1. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Therapeutics and clinical risk management, 2015; 11: 967.
2. Lee A, Crowther M. Practical issues with vitamin K antagonists: elevated INRs, low time-in-therapeutic range, and warfarin failure. Journal of thrombosis and thrombolysis, 2011; 31(3): 249-58.
3. Vermeer C, Schurgers LJ. A comprehensive review of vitamin K and vitamin K antagonists. Hematology/oncology clinics of North America, 2000; 14(2): 339-53.
4. Deaton, J.G. and Nappe, T.M., 2017. Warfarin toxicity.
5. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines. Chest., 2008; 133(6): 160S-98S.
6. Zaki SA. Adverse drug reaction and causality assessment scales. Lung India, 2011; 28(2): 152-3. doi: 10.4103/0970-2113.80343. PMID: 21712934; PMCID: PMC3109846.
7. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury. https://www.ncbi.nlm.nih.gov/books/NBK548069
8. Devereaux PJ, Duceppe E, Guyatt G, Tandon V, Rodseth R, Biccard BM, Xavier D, Szczeklik W, Meyhoff CS, Vincent J, Franzosi MG. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial. The Lancet, Jun 9, 2018; 391(10137): 2325-34.
9. Falamić S, Lucijanić M, Ortner-Hadžiabdić M, Marušić S, Bačić-Vrca V. Pharmacists' influence on adverse reactions to warfarin: a randomised controlled trial in elderly rural patients. International journal of clinical pharmacy, Oct 1, 2019; 41(5): 1166-73.