

## Interaction between warfarin and tamoxifen: A case report

Mishra D<sup>1</sup>, Paudel R<sup>2</sup>, Kishore PV<sup>3</sup>, Palaian S<sup>4</sup>, Bista D<sup>5</sup>, Mishra P<sup>6</sup>

<sup>1</sup>Medical Intern, <sup>2</sup>Lecturer, <sup>3</sup>Assistant Professor, <sup>4</sup>Lecturer, <sup>5</sup>Post graduate student (MSc, Medical Pharmacology), <sup>6</sup>Assistant Professor, Manipal Teaching Hospital / Manipal College of Medical Sciences Pokhara, Nepal

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### Abstract

Warfarin is a commonly used anticoagulant with documented reports of drug interactions. Tamoxifen is used in the adjuvant hormonal treatment of women with oestrogen-receptor- positive breast cancer. Warfarin and tamoxifen are known to interact with each other with a resultant increase in the bleeding tendency. These reports are mainly from the white population. We report a case of drug interaction between warfarin and tamoxifen with an acute onset. This report suggests that when these drugs are co administered, careful monitoring of the coagulation profile is needed.

**Key words:** Drug interaction, Tamoxifen, Warfarin

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Warfarin is a coumarin type anticoagulant that acts by preventing the gamma-carboxylation of several glutamate residues in prothrombin and factors VII, IX and X as well as the endogenous anti-coagulant proteins C and S. It is used as an anticoagulant in several high risk patients like prophylaxis of embolism in rheumatic heart disease and atrial fibrillation, prophylaxis after insertion of prosthetic heart valve, prophylaxis and treatment of venous thrombosis and pulmonary embolism, transient ischemic attacks<sup>1,2</sup>. Tamoxifen is an oestrogen-receptor antagonist used as an adjuvant hormonal treatment of choice in women with oestrogen-receptor- positive breast cancer. It is also used in anovulatory infertility<sup>2,3</sup>. We report a case of Drug Interaction (DI) between warfarin and tamoxifen in a patient on long term tamoxifen therapy.

### Case report

A 53 yr old lady, a known case of invasive ductal carcinoma of left breast underwent surgery 5 years back. Following the surgery, the patient was subjected to chemotherapy during the post operative period that included Inj. Adriamycin. The post operative chemotherapy was followed by prophylactic chemotherapy with Tab. Tamoxifen citrate 20 mg once daily.

Five years later, (January 2006) the patient got admitted to the Manipal Teaching Hospital, Pokhara, Nepal with cardiac complaints. The echocardiography revealed Left Ventricular Ejection Fraction (LVEF) of 30% with moderate mitral regurgitation and moderate pulmonary arterial hypertension and moderate tricuspid regurgitation. Investigations on the day of admission showed a

bilirubin 0.9mg/dl, direct bilirubin 0.4 mg/dl, indirect bilirubin 0.5 mg/dl, AST: 22 U/l, ALT 14 U/l, ALP 122 U/l, the serum albumin was 3.5 g%, serum globulin:2.2 g%, albumin/ globulin ratio of 1.6: 1, blood urea 28 mg/dl, serum creatinine 0.8 mg/dl serum calcium: 8.2 mg/dl, Haemoglobin 13.3 g%, Total count 7,9000 cells per cubic mm, differential count Neutrophils 67 %, Lymphocytes 30 %, Monocytes 01 %, Eosinophils 1 % Basophils 1 %, ESR 06, platelet count was 293000 cells/mm.<sup>3</sup> The urine routine and microscopy results were within the normal limits, creatinine phosphokinase (CPK) total 200 units/litre, CPK MB 7 units/litre. Sonography of the abdomen showed hepatomegaly. A diagnosis of adriamycin induced dilated cardiomyopathy was made. On taking the history it was found that the patient was taking her Tamoxifen regularly and did not come for follow up for a longer period. The hepatic and renal status of the patient was normal.

Her cardiac status deteriorated further and repeated echocardiography revealed dilated left ventricle with global hypokinesia. Based on the diagnosis, and the patient status it was decided to start the patient on warfarin 5 mg once daily.

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### Correspondence

Dr. Deepak Mishra  
Medical intern  
Department of Medicine  
Manipal College of Medical Sciences  
Pokhara, Nepal  
E-mail: deepakmishra46@hotmail.com

The patient was also given Cap. Omeprazole 20 mg once daily, T. Digoxin 0.25 mg once daily, T. Carvedilol 3.125 mg once daily, T. Losartan 25 mg once daily, T. Frusemide+ Spironolactone(:20/50 mg) once daily, T. Tamoxifen citrate: 20 mg once daily, T. Frusemide 20 mg once daily and

T. Metoclopramide 10 mg eight hourly and Cap. Vitamin B complex once daily. Since the patient was on warfarin and warfarin has been reported to have major drug interactions, we carefully monitored the International Normalized ratio (INR). The details of the patients INR is tabulated in Table 1.

**Table 1:** The coagulation profile and the dose of warfarin

Day of admission	INR	Dose of warfarin
1	1.59	5 mg
3	3.75	2.5 mg and 5 mg on alternate days
5	10.27	Drug was stopped
7	3.11	Drug was stopped
9	2.73	1 mg
11	1.67	2 mg
13	1.76	2 mg
16	2.34	2 mg
25 (7 <sup>th</sup> day of discharge)	10.78	2.mg

On the third day of starting the warfarin, the patient's INR reached 10.27 and hence the warfarin was stopped immediately. Since the patient was also on omeprazole, a possible interaction between warfarin, omeprazole and tamoxifen was suspected and omeprazole was also stopped. Warfarin was restarted again on day 9 at a low dose (1 mg) with regular INR monitoring. The dose was titrated to reach the desired INR (nearly 2) on 2mg of warfarin.

Since the INR of the patient was stabilized with 2 mg of warfarin, the patient was discharged on 2 mg of warfarin. At the time of discharge, she was on T. Digoxin 0.25 mg once daily, T. Carvedilol 3.125 mg once daily, T. Losartan 25 mg once daily, T. Frusemide 40 mg once daily, T. Warfarin 2mg once daily, T. Metoclopramide 10 mg once daily, Cap. Alphacalcidol 1 Cap once daily and Cap B complex once daily.

On the 7<sup>th</sup> day after discharge the patient again got admitted in the emergency with complaints related to exacerbation of her underlying cardiac problems. Her routine INR was reported as 10.78 and a possible DI between warfarin and tamoxifen was established. Based on the diagnosis warfarin was stopped immediately. Oncology consultation was sought regarding stoppage of Tamoxifen citrate as she had already taken it for 4.5 years. Tamoxifen was stopped but high INR level continued. The altered coagulation profile resulted in bleeding per rectum. The patient was given Inj. Vitamin K in order to stabilize the coagulation profile. However, her chief

cardiac complaints further deteriorated. This was revealed by a very low ejection fraction. Finally the patient died due to her cardiac complications. We further carried out the details of the DI using the Micromedex database.<sup>4</sup> The Micromedex classifies a DI based on the reports/data available in the literature. The analysis revealed the severity of the DI to be 'major' and the onset to be 'delayed' and the documentation status to be 'good'. But clinically, in our patient the DI developed on the 3<sup>rd</sup> day of treatment an acute onset.

### Discussion

Drug interaction is an important cause of adverse drug reactions (ADRs) accounting for 6-30% of all ADRs.<sup>5</sup> A study has found drug-drug interactions (DDIs) to be the main cause for nearly 2.8 percent of all hospital admissions among persons older than 50 years taking medications.<sup>6</sup> The result of a DI may be an additive effect, antagonistic, alteration of effect or idiosyncratic effects.<sup>7</sup> Patients who take multiple drugs, elderly and seriously ill patients are more susceptible to DIs. One hospital study found an ADR rate of 7% in patients taking 6-10 drugs, which increased to 40% in those taking 16-20 drugs.<sup>8</sup>

Warfarin is a drug with multiple DIs and is well reported in the literature. Our patient was taking tamoxifen for a long period of time. The patient was prescribed warfarin due to her underlying cardiac complications. On addition of warfarin in the usual dose of 5 mg, the patient showed an erratic response presenting with an increased INR value. Since the

patient was on Omeprazole along with Tamoxifen, a possible interaction between Warfarin, tamoxifen and omeprazole was made. Later when the patients INR was stabilized and omeprazole was withdrawn, again a similar erratic INR value was reported leading to a possible DI between warfarin and tamoxifen. During our literature review, we could locate two case reports of interactions between these drugs, mainly from the white population. In these case reports, the addition of tamoxifen to the drug regimen of women stabilized on warfarin resulted in a 1.5-fold to 2-fold increase in the prothrombin time.<sup>9,10</sup> In our patient the INR raised to more than 10; which is considered as fatal. The mechanism behind this interaction is not established.

The clinical management of a DI can be done in many ways. In most of the cases, it is recommended to stop the offending drugs. In the case of DI between warfarin and tamoxifen, it is recommended that concurrent administration of tamoxifen and coumarin-type anticoagulants, including warfarin, is contraindicated in high-risk women where tamoxifen is indicated to reduce the incidence of breast cancer. In other clinical situations where tamoxifen is used concurrently with warfarin, the prothrombin time ratio or INR (international normalized ratio) should be closely monitored during the addition and withdrawal of treatment with tamoxifen, and should be reassessed periodically during concurrent therapy.

Changing the warfarin to Acenocoumarol may not be an alternative option in this patient. In the literature we could get a single reference of a DI between acenocoumarol and tamoxifen.<sup>11</sup> However, in our case, the tamoxifen was stopped in the patient.

Carrying out the severity analysis helps the clinicians to categorize the DI based on its severity and hence appropriate measures could be taken based on the severity. In our case the DI was found to be a “major” DI indicating that the DI may be life threatening and or require medical intervention to minimize or prevent serious adverse effects.

Carrying out the onset analysis of the DI can be helpful in identifying and preventing the occurrence of a DI in the future. In our case, the onset was found to “delayed” type as per the Micromedex categorization. However, clinically the DI occurred within a short duration of treatment (3 days) suggesting an acute onset. We could not identify the reason behind the sudden onset of the DI in our patient.

## Conclusion

Since warfarin is a commonly employed drug with DI, care should be taken in administering warfarin with other drugs. If warfarin is to be used, the patient should be continuously monitored with coagulation profile not only during initiation of therapy but also till the coagulation profile is stabilized at least for one month. There after the coagulation profile should be monitored as per the protocol of warfarin therapy.

Whenever an unknown drug or a drug with rare interaction with warfarin (other than reported earlier) is prescribed, continuous monitoring of coagulation profile may be warranted in view of the acute onset type of DIs enumerated in our case.

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