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THE ROLE OF CLINICAL PHARMACIST IN THE DETECTION AND MANAGEMENT OF DRUG INTERACTIONS WITH WARFARIN

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ABSTRACT

Warfarin is a drug which has a narrow therapeutic index and shows a severe bleeding when it is prescribed with other medications like NSAIDS, Phenytoin, which may lead to increase the INR levels in patients unless it is monitored. The present study is an observational, prospective, non-interventional which was carried out at KIMS hospital on 148 patients who were on warfarin therapy from November-2010 to August-2011. Among 148 patients 42 patients had shown an increase in INR levels during their warfarin therapy. Out of 42, 11 patients who were on other medications had shown a profound elevation in INR level, which clearly indicates that the INR level is to be monitored especially when warfarin is prescribed with other medications which may lead to cause a severe bleeding due to increased INR levels. Our study mainly concludes that as there is a risk in adding NSAIDS and other medications which increase the INR levels, an appropriate measure is to be taken to find the alternative drugs to avoid the chance of drug interactions with warfarin and whenever it is possible a proper monitoring is to be done to prevent the risk of bleeding due to elevated INR levels. It is the prime role of a pharmacist to educate the patients to undergo for a regular INR check and provide appropriate advice to physicians and other health care team for alternative drugs which lacks drug interactions with warfarin.

KEY WORDS: Non-Steroidal Anti-inflammatory Agents, Anti-Epileptics, Cyclo-oxygenase 2 inhibitors, International Normalized Ratio.

INTRODUCTION

Co administration of non-steroidal anti-inflammatory drugs (NSAIDs) and warfarin increases

the risk of bleeding. The mechanisms of this interaction are antiplatelet effect and gastric mucosal damage, because most NSAIDs do not produce a hypothrombinemic response. [1,2] When given to or withdrawn from patients maintained on warfarin, NSAIDs may actually alter anticoagulant control as a result of changes in the amount of circulating warfarin released from plasma albumin binding sites. Preliminary data suggest that the cyclooxygenase-2 inhibitors celecoxib and rofecoxib may be safer options in patients requiring an NSAID and warfarin, because these agents have reduced antiplatelet properties compared with traditional NSAIDS [3,4] Concomitant use of NSAIDs and warfarin should be avoided, especially in patients who are at increased risk for NSAID gastropathy (e.g., age greater than 65 years, history of peptic ulcer disease, systemic steroid therapy, heavy smoking or high NSAID dosage). If NSAID therapy is necessary, a cyclooxygenase-2 inhibitor should be used, and the INR should be closely monitored [5, 6, 7]. Patients also should be informed about the risk of bleeding associated with combined warfarin and NSAID therapy. Many studies showed that high maintenance dose of warfarin (>40mg/week), the presence of co morbid medications (ex: NSAIDS) were the risk factors for INR increase in respect to NSAID-warfarin interaction. [8]

Table 1. Some of the main medicines, medicine classes and other agents that can interact with warfarin.

	Risk of Bleeding	Mechanism
Antibiotics		
Most antibiotics but especially macrolides, metronidazole, quinolones and cotrimoxazole	↑	Inhibition of vitamin K synthesis by intestinal flora, inhibition of warfarin metabolism or both
Rifampicin*	↓	Induction of hepatic metabolism
Antifungals		
Fluconazole, miconazole (including gel and vaginal preparations)	↑	Inhibition of warfarin metabolism
Antidepressants		
Serotonergic agents (SSRIs and venlafaxine)	↑	Inhibition with platelet function – increased bleeding risk without

		alteration of INR. Some, e.g. fluoxetine, paroxetine, can also inhibit warfarin metabolism
Antiplatelet agents		
Aspirin, clopidogrel, dipyridamole	↑	Interference with primary haemostasis – increased bleeding risk without alteration of INR
Amiodarone	↑	Inhibition of warfarin metabolism
Anti-inflammatory agents		
NSAIDS, Cox-2 inhibitors	↑	Direct mucosal injury, antiplatelet effects may also have a role. Increased bleeding risk without alteration of INR. Inhibition of warfarin metabolism and an increase in INR rarely reported with some NSAIDs
Analgesics		
Tramadol	↑	Inhibition of warfarin metabolism
Paracetamol	↑	Direct interference with vitamin K cycle Interaction possible with chronic, regular use of paracetamol, short-term (a few days) unlikely to interact
Alternative remedies/foods		
Ginkgo, fenugreek, chamomile, dong quai, cranberry products	↑	Unclear, multiple mechanisms
St John's wort*	↓	Unclear, possible effects on warfarin metabolism
Foods with high vitamin K content, e.g. leafy greens, broccoli*	↓	Increased vitamin K synthesis antagonises anticoagulant effect of warfarin

St johns wort, vitamin K rich food substances like leafy vegetables, broccoli are the agents which will reduce the bleeding risk but the INR may become sub-therapeutic and warfarin dose may need to be increased.

The following are the measures to be taken to decrease the risk of warfarin associated hemorrhage.

1. **Optimise Warfarin Therapy**

A key element for reducing bleeding in patients taking warfarin, especially if they are also taking an antiplatelet drug is to optimize warfarin therapy.

2. **Appropriate Target INR**

The INR should be maintained at the appropriate target level (i.e. 2-3) depending upon the indication for the use of warfarin like Deep Venous Thromboembolism, Pulmonary Embolism, trial Fibrillation. [9]

3. **Appropriate Duration of Therapy**

When patients are prescribed warfarin the duration of therapy should be determined in advance. Periodic re-evaluation of the patients harm: benefit ratio of warfarin should also occur. The optimum duration needs to be tailored to the individual and specialist advice may be warranted [10, 11, 12].

4. **Prevention of Co-Medications**

Polypharmacy may lead to increase the risk of drug interactions especially when the patients are unaware of the drugs which may interact with warfarin. Pharmacist should educate the patients to avoid taking drugs or food substances which may lead to increase the INR levels.[13, 14, 15] In this study, we evaluated the risk factors for international normalized ratio (INR) increase, which is a surrogate marker of bleeding, after addition of an NSAID in a total of 42 patients who used warfarin.

MATERIALS AND METHODS

Study Population

A total of 42 warfarin users were confirmed who began to take NSAIDS at KRISHNA INSTITUTE OF MEDICAL SCIENSES from November 2010 to August 2011, it is a 10 months prospective, non-interventional, study carried out in department of cardiology the data was collected from both the inpatient, outpatient pharmacies of the hospital. Initially 148

patients who were using warfarin were selected, of these 148 patients 42 (62%) are using both warfarin and NSAIDS concomitantly.

The patients who fulfill the following criteria were recruited for the study:

1. Maintenance warfarin dose was stabilized for at least 3 months before adding a NSAID. Stabilization was defined as INR change within 15.0% of baseline values. Target INR value was 2.0-3.0.
2. INR values after addition of NSAIDs were available.
3. The warfarin dose did not change after adding a NSAID, and the administered NSAID dose remained constant.
4. The age of the patient was 18 yr and older.

   42 patients fulfilled all of the above criteria.

Study Design

It is an observational, non-interventional, prospective study carried out at KIMS hospital during November 2010 to August 2011.

Risk Factors for Haemorrhage Due To Elevated Inr Are

1. Older age group
2. High target INR
3. Cerebrovascular disease
4. History of gastrointestinal bleeding or ulceration
5. Liver disease
6. Renal disease
7. Other co morbid disease such as heart failure, anemia, hypertension, malignant disease and diabetes
8. Personal or family history of bleeding disorders.

RESULTS

In this study out of 148 patients, 42 patients who were using other medications like NSAIDS, Antiepileptics along with warfarin were selected and enrolled in the study. Among 42 patients 11 patients (26.1%) showed an INR elevation of >15 %.the normal INR for these patients suffering from thromboembolic disorders is 2-3, but the INR level has been increased to 13 to 14 i.e approximately 15% fo the normal value.out of 11 patients 5 patients has shown a severe gastrointestinal bleeding due to the use of NSAIDS with warfarin. 4patients of the 11

who experienced an increased INR to 15 %had to decrease the dose of warfarin after stopping it atleast for 1 day and the remaining 7 patients had withdrawn the use of co-medications (like Ibuprofen,Aspirin, Fibrates,Phenytoin)along with warfarin and shifted to other alternatives which has less interactions with warfarin.

Table 2: The following table illustrates the increase in INR values and its percentage among the patients with and without co-medications.

S. NO	INDICATION FOR WARFARIN	NUMBER OF PATIENTS	DESIRED INR LEVELS	ELEVATED INR VALUE	%OF INR ELEVATED	Use of Co-Medications Like NSAIDS, ANIT-EPILEPTICS
1	Venous thromboembolism	4	2-3(target INR of 2.5)	16	15	YES
2	Pulmonary embolism	3	2-3(target INR of 2.5)	14	15	YES
3	Atrial fibrillation	4	2-3	13	<15	YES
4	DVT+PE+AF	7	2-3	7-13	<15	NO
5	DVT+PE+AF	8	2-3	5-10	<15	NO
6	DVT+PE+AF	14	2-3	4-6	<15	NO
7	DVT+PE+AF	108	2-3	2-3	NORMAL	NO

DISCUSSION

This study was carried out in 148 patients who were using warfarin, out of 148 patients selected 42 patients , who were using other medications like NSAIDS, Antiepileptics along with warfarin were selected and enrolled in the study. Among 42 patients 11 patients (26.1%) showed an INR elevation of >15 %.the normal INR for these patients suffering from thromboembolic disorders is 2-3, but the INR level has been increased to 13 to 14 i.e approximately 15% for the normal value. From the table 2 it is clear that the increase in INR can be seen specially when the patients use other medications like NSAIDS, Anti-epileptics etc when compared to those who are not on co-medications. From this it is clear that a thorough monitoring of INR values is essential in the hospitals to prevent the risk of complications associated with elevated INR levels of Warfarin.

Limitations

There are two major limitations in this study. First, the number of patients was limited so that all of the potential confounding variables which could affect the INR level could be evaluated simultaneously. We could enroll only 42 patients because INR was not measured in most of the cases after the addition of a NSAID. The low number of patients might produce a type I and II errors in the interpretation. Second, the endpoint of the study was the INR value, a

surrogate marker of hemorrhage rather than bleeding although bleeding may be more clinically important endpoint. However, considering the potential seriousness of bleeding, clinicians may still have to use INR as a guideline for deciding their strategy when using warfarin.

CONCLUSION

Our study mainly concludes that as there is a risk in adding NSAIDS and other medications which increase the INR levels, an appropriate measure is to be taken to find the alternative drugs to avoid the chance of drug interactions with warfarin and when ever it is possible a proper monitoring is to be done to prevent the risk of bleeding due to elevated INR levels.It is the prime role of a pharmacist to educate the patients to undergo for a regular INR check and provide appropriate advice to physicians and other health care team for alternative drugs which lacks drug interactions with warfarin.

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