



The risk of over-anticoagulation during concomitant treatment of warfarin and proton pump inhibitors

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INTRODUCTION

Proton pump inhibitors (PPIs) are known to have protective effect on the risk of gastrointestinal bleeding for patients on warfarin. However, increased international normalized ratio (INR) and prothrombin time (PT) has been reported when PPIs use concomitantly with warfarin. Competitive inhibition of CYP2C19 is proposed as possible mechanism for interactions between PPIs and warfarin.

Although effect on clinical outcomes have not been determined, there are still concerns of increased anticoagulation of warfarin and even increased bleeding risk when taking warfarin and PPIs concomitantly.

This study aims to evaluate the risk of over-anticoagulation in patients receiving warfarin and PPIs.

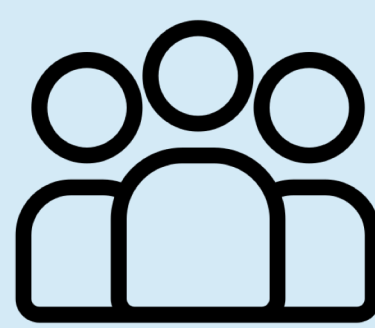
METHOD

Database source



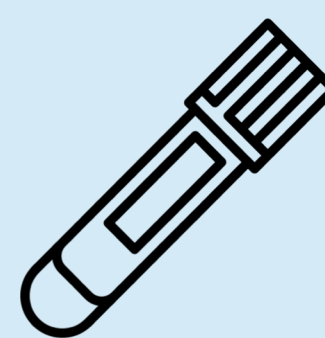
Electronic medical records from a medical center in Southern Taiwan

Population



Patients who were prescribed PPIs within 7 days of warfarin prescriptions during 2021/1/1 to 2021/12/31.

Outcomes



1. Change in INRs
2. The proportion of over-anticoagulation (defined as INR level ≥ 4)

Statistical analysis



Dichotomous variable presented in number and proportion, and continuous variable presented as mean $\pm$ standard deviation (SD). INR levels at baseline and after concurrent use of warfarin and PPIs were compared by two-sample *t* test.

RESULTS

Table 1. Baseline characteristics of total cohort

Variables	Total cohort (n=249)	
	N (%) of patients or Mean $\pm$ SD	
Mean age (years)	64.36 $\pm$ 12.44	
Male sex	136 (54.6%)	
Comorbidity		
DM	29 (11.7%)	
CKD	24 (9.6%)	
Liver disease		
Mild	9 (3.6%)	
Moderate to severe	0 (0%)	
CCI (previous year)		
0	155 (62.6%)	
1	55 (22.1%)	
≥ 2	12 (4.8%)	
Concomitant medications		
Antiplatelets	59 (23.7%)	
NSAIDs	0 (0%)	

CCI: Charlson Comorbidity Index; CKD: chronic kidney disease; DM: diabetes mellitus; NSAIDs: non-steroidal anti-inflammatory drugs

There were only 8 and 7 included patients reported over-anticoagulation events at day 30 and 90 after concurrent use of warfarin and PPIs, respectively. Among over-anticoagulant events, patients were taking esomeprazole (n=5 and 4 at day 30 and day 90 after concomitant use) and lansoprazole (n=2 and 3 at day 30 and day 90 after concomitant use) along with warfarin (table 2).

There was no significant change in INR levels at baseline and at day 30 and 90 after concomitant use of warfarin and PPIs (table 3).

Table 2. Proportion of patients with over-anticoagulation under warfarin and PPI treatment

	Cases with over-anticoagulation, N (%)	
	After 30 days concomitant use	After 90 days concomitant use
	(n=178)	(n=144)
PPIs	8 (4.5)	7 (4.9)
Esomeprazole	5 (2.8)	4 (2.8)
Pantoprazole	1 (0.6)	0 (0)
Lansoprazole	2 (1.1)	3 (2.1)

PPIs: proton pump inhibitors

Table 3. Change in INR value under warfarin and PPI treatment

Variable	Baseline	After 30 days concomitant use			After 90 days concomitant use		
			Change	P-value		Change	P-value
INR value, Mean±SD	1.75±0.71	1.76±0.92	0.08±0.87	0.87	1.76±0.97	0.06±0.95	0.85

PPI: proton pump inhibitor; SD: standard deviation

A total of 249 patients concomitantly using warfarin and PPIs were enrolled in this study.

Of included patients, the mean age was 64.4 $\pm$ 12.4 years, 54.6% were male, 62.7% had Charlson comorbidity index (CCI) score = 0, 23.69% had concomitant use of antiplatelets and no concurrent prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs) (table 1).

CONCLUSIONS

In our study, patients who taking warfarin with PPIs had lower bleeding tendency at baseline, and concurrent use of warfarin and PPIs may not significantly increase anticoagulant effect of warfarin. However, we still found that a small number of patients may encounter over-anticoagulation after use warfarin with PPIs, especially for esomeprazole and lansoprazole.

Close monitoring of INR levels may be warranted when using warfarin and esomeprazole or lansoprazole concomitantly, especially for patients have higher bleeding risk. Further studies are required to provide a comprehensive understanding on this drug interaction issue.

REFERENCES

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