Original Article

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Coagulopathy Caused by Concurrent Ciprofloxacin and Warfarin Use: What Other Factors Induce Coagulopathy ?

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Background: To assess factors affecting the prolongation of the international normalized ratio (INR) with concurrent warfarin and ciprofloxacin use.
Methods: A retrospective case-control study was performed at a single, 2,000-bed tertiary hospital between January 2007 and December 2009. Thirty-three patients who were on warfarin and ciprofloxacin concurrently were enrolled. Demographics and clinical data were collected from medical records.
Results: Nine patients were assigned to the case group (prolonged INR) and 19 patients to the control group (normal INR). Activities of daily living (ADL) and total number of classes of medications taken demonstrated significant differences between the groups (15.33 vs. 7.11, p<0.001; 7.11 vs. 5.47, p=0.041). No bleeding complications occurred during this study.
Conclusion: As ADL reflects patient performance status and general condition of an individual, we conclude that a poor general condition is associated with coagulopathy in persons concurrently using warfarin and ciprofloxacin.

Key Words: Warfarin, International normalized ratio, Ciprofloxacin, Coagulopation disorders, Activities of daily living

INTRODUCTION

Warfarin has been the most frequently used oral anticoagulant agent for the past 50 years and is used for deep vein thrombosis, pulmonary thromboembolism, atrial fibrillation, valvular heart disease, and postprosthetic heart valve replacement[1-3]. It is an effective oral agent that can be taken easily. However, because of its narrow therapeutic index, the international normalized ratio (INR) has to be continually monitored[1]. Despite regular INR monitoring, warfarin has a risk of hemorrhage and can result in major bleeding including intracranial hemorrhage and gastrointestinal (GI) bleeding[1,2,4].

Warfarin is a hydroxycoumarin and a vitamin K antagonist which inhibits synthesis of vitamin K-dependent clotting factors (factor II, VII, IX, and X) in the liver[2,4,5]. Therefore, vitamin K-containing foods or drugs can affect the INR and warfarin's anticoagulation effect[6]. Many drugs and foods that affect the liver function also can change warfarin's anticoagulation effect because warfarin metabolism occurs primarily in the liver, involving the cytochrome P450 isoenzyme[2,5]. Other drugs can interact with warfarin when taken concurrently[1,4]. Patient conditions including fever, declined liver function, and hyperthyroidism can increase the anticoagulation effect of warfarin, and there are several reports that antibiotics can increase the anticoagulation response[6-8].

Fluoroquinolones are broad spectrum antibiotics used frequently in infectious diseases. Their oral and intravenous agents have many advantages including excellent bioavailability, low toxicity, and high volume of distribution that allow the antibiotics to reach effective concentrations in most tissues[6,8,9]. Ciprofloxacin has been used frequently for urinary tract infections (UTI)[9]. Levofloxacin and moxifloxacin, which achieve high intracellular concentrations, have been used for community aquired pneumonia as these antibiotics can effectively treat intracellular pathogens including Legionella pneumophilia and Myocobacterium tuberculosis. The frequency of their use has also increased in hospitalized patients[8,10]. However, because

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many elderly hospitalized patients have medical comorbidities and some patients take warfarin, the concurrent use of these antibiotics can result in drug interactions[8,10].

There are many reports of INR prolongation in patients on warfarin with concurrent use of antibiotics[7-13]. There are several hypotheses to explain INR prolongation. First, gut flora disruption resulting from antibiotic use can inhibit vitamin K2 synthesis[13,14]. Second, antibiotics that inhibit cytochrome P450 isozyme 2C9 can debase metabolism of the S-enantiomer of warfarin[13,15,16].

However, most studies have not shown statistical evidence of INR prolongation resulting from concurrent warfarin and fluoroquinolone use[7-13,17-20]. Therefore, we considered other factors affecting previously reported INR prolongation in addition to concurrent use of warfarin and fluoroquinolone. The purpose of this study was to determine what factors can affect INR prolongation in the setting of concurrent drug use.

MATERIALS AND METHODS

1. Study patients, case and control groups

This single-center multivariable retrospective case-control study was conducted with hospitalized patients recruited from a 2,000-bed tertiary hospital located in Seoul, South Korea, between January 2007 and December 2009. We identified 1,308 patients who were prescribed ciprofloxacin and 495 patients who were prescribed warfarin during the study. Although 88 patients took both ciprofloxacin and warfarin, only 33 patients took the medications concurrently (Fig. 1). In these 33 chronically anticoagulated patients who then took ciprofloxacin, 9 suffered INR prolongation over 5.0 at any point without an increase to their warfarin dose. We enrolled these 9 patients for the case group. However, 19 patients did not show INR prolongation over 3.5 though taking ciprofloxacin and warfarin concurrently. These patients were assigned to the control group (Fig. 1). All data were obtained from medical records, and this study was approved by the institutional review board of our hospital.

2. Protocol

We undertook a multivariable study to determine which factors affect INR prolongation in patients who had concurrently taken ciprofloxacin and warfarin. The variables included age, sex, activities of daily living (ADL), comorbidities, concurrent use of medication except for warfarin and ciprofloxacin, and duration of hospitalization.

Comorbidities included diabetes mellitus, cancer, hypertension, chronic kidney disease, and other medical diseases. Previous bleeding histories included GI bleeding, intracranial bleeding, and anemia due to bleeding of any other parts of body as bleeding was a complication of warfarin use. Chronic liver disease was also regarded because liver disease can inhibit warfarin metabolism.

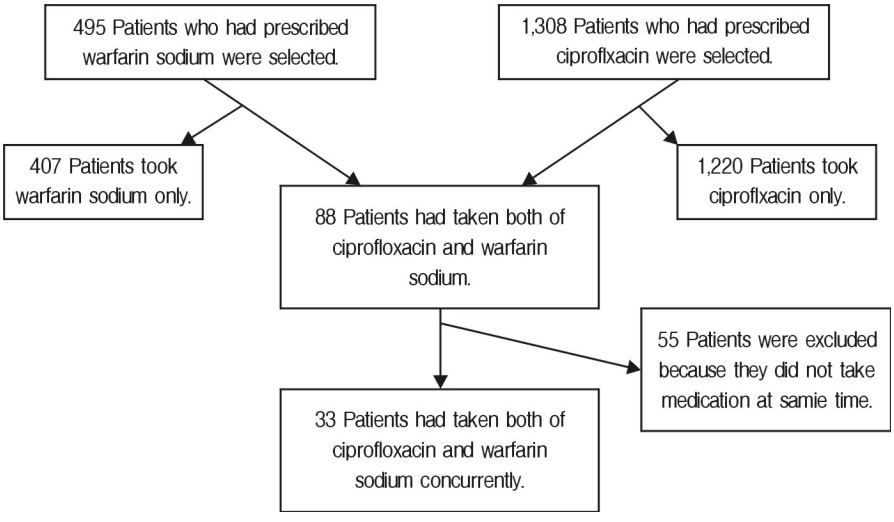

Fig. 1. Flow chart of subject identification for the study. Finally, 33 patients were on warfarin and ciprofloxacin concurrently.

The Katz ADL index was used to assess function including bathing, dressing, toileting, feeding, continence, and transferring. We scored one point for independent patients, two points for partially dependent patients, and three points for fully dependent patients. We added the scores for each item, and ADL values ranged from 6 to 18.

Medication histories, except ciprofloxacin and warfarin, included every drug suspected to affect the metabolism of warfarin. These included aspirin, antiplatelet agents, anti-inflammatory agents, steroids, other antibiotics, acetaminophen, selective serotonin reuptake inhibitor, and cytochrome P450 inducer or inhibitor. We also included the number of types of medication taken concurrently with warfarin as a variable.

In addition, the infectious disease for which the patients required ciprofloxacin, pressure sores, admission history, and residence in a health care facility were included as stastistical variables. Patients were excluded from the study if their antibiotic course was completed (due to recovery), if they expired due to disease progression, or if they had to stop the antibiotics because of severe adverse drug reactions including GI bleeding and other severe hemorrhaging. No subjects were excluded due of bleeding associated complications.

A 'pre-INR' was measured at admission or 3 days before the concurrent use of ciprofloxacin and warfarin. After beginning the concurrent administration of ciprofloxacin and warfarin, the INR was measured every 3 or less days. 'Max-INR' was the maximum value of INR during this treatment status, and a 'post-INR' was done 3 days after stopping ciprofloxacin.

3. Statistical analysis

Because it was difficult to confirm a normal distribution for the continuous variables due to the small sample size, we first conducted a normality test. We conducted an independent two-sample t-test for the variables satisfying the normality test and the Mann-Whitney U test for the others. We conducted a chi-square test for the categorized variables. All statistical analyses were performed with the SAS 9.1.3 (Institute Inc., Cary, NC, USA).

RESULTS

Nine cases and 19 control subjects were included in this study. The mean age was 65.7 years, with seven patients (25.00%) younger than 60 years and six patients (21.43%) older than 80 years. Seventeen of the 28 patients (60.71%) were female. Twelve patients (42.86%) had two or three comorbidities and two patients (7.14%) had more than six comorbidities. Previous bleeding history including GI bleeding was reported by seven patients (25.00%). Eleven patients (39.29 %) used ciprofloxacin for UTI and nine patients (32.14%) used ciprofloxacin for pneumonia. Eight patients (28.57%) were prescribed ciprofloxacin for other infections. The patients in this study took an average of 10 drugs (10.04±3.64, data are not shown), and these drugs were categorized into an average of six classes (6.00±2.00). Other characteristics of cases and control subjects are summarized in Table 1.

According to the normality testing, maximum INR, length of hospitalization, and ADL were not normally distributed in the cases. ADL, warfarin dosage, and length of hospitalization did not satisfy the normality testing in the control subjects (data are not shown). Statistical analysis shows that the total number of drug category ($p=0.041$), maximun INR ($p<0.001$), and ADL ($p<0.001$) were significantly different between the two groups. A statistical difference in maximum INR reflects that cases and control subjects are properly divided. In the categorized variables, no variables were statistically different between the groups (Table 1). Assessed drugs including acetaminophen, corticosteroids, GI protective drugs, selective serotonin reuptake inhibitor, and cytochrome P450 inducer or inhibitor did not induce INR prolongation (data are not shown). Body mass index, pressure sores, and duration of treatment or hospitalization were not associated with INR prolongation (data are not shown).

The case group included nine patients. The most common reason for taking ciprofloxacin was UTI (5 patients). Other indications included pneumonia, acute gastroenteritis, cellulitis, and empirical use due to fever. The case patients had three to five comorbidities. The duration of hospitalization varied from six days to 375 days. The mean pre-INR was 2.33 and the maximum INR varied from 5.21 to 14.68 (mean maximum INR, 7.11). The INRs decreased to the desired value (mean INR, 2.06) after ciprofloxacin cessation (Fig. 2) (Tables 2, 3).

There were no significant complications resulting from INR prolongation. After treatment with ciprofloxacin, most patients reported a spontaneous return to the desired INR range, though some patients were required to hold their warfarin temporarily. One patient experienced a severe INR prolongation of 14.68, and she was admitted to the intensive care unit for worsened general condition. She was transfused with

Table 1. Basic characteristics of cases and control subjects (n=28)

Characteristic	Cases*	Control subjects†	p-value
Age (yr)	69.89±9.52	66.37±16.64	0.562
<60	1 (11.11)	6 (31.58)	0.410
60-69	4 (44.44)	3 (15.79)	
70-79	2 (22.22)	6 (31.58)	
≥80	2 (22.22)	4 (21.05)	
Sex			1.0
Male	3 (33.33)	8 (42.11)	
Female	6 (66.67)	11 (57.89)	
No. of comorbidities			1.0
2-3	4 (44.44)	8 (42.11)	
4-5	5 (55.56)	9 (47.37)	
6-7	0 (0)	2 (10.53)	
Previous bleeding history			1.0
No	7 (77.78)	14 (73.68)	
Yes	2 (22.22)	5 (26.32)	
Previous admission history‡			1.0
No	3 (33.33)	7 (36.84)	
Yes	6 (66.67)	12 (63.16)	
Activities of daily living§	18 (6-18)	6 (6-18)	<0.001
6	1 (11.11)	15 (78.95)	0.001
9-14	3 (33.33)	3 (15.79)	
18	5 (55.56)	1 (5.26)	
Body mass index (kg/m^2)			0.771
<19	1 (11.11)	5 (26.32)	
19-24	4 (44.44)	8 (42.11)	
≥25	4 (44.44)	6 (31.58)	
Pressure sore			0.290
No	6 (66.67)	17 (89.47)	
Yes	3 (33.33)	2 (10.53)	
Aspirin use			0.352
No	6 (66.67)	16 (84.21)	
Yes	3 (33.33)	3 (15.79)	
Other antiplatelet agents			1.0
No	7 (77.78)	13 (68.42)	
Yes	2 (22.22)	6 (31.58)	
Ciprofloxacin indication			0.271
Pneumonia	1 (11.11)	8 (42.11)	
Urinary tract infection	5 (55.56)	6 (31.58)	
Others‖	3 (33.33)	5 (26.32)	
Total no. of drug category¶	7.11±2.32	5.47±1.65	0.041
Duration of treatment**	4.67±2.50	7.47±4.15	0.074
Duration of hospitalization	35 (6-375)	21 (3-137)	0.431
Mortality			0.321
No	8 (88.89)	19 (100)	
Yes	1 (11.11)	0 (0)	
Warfarin dosage	2.5 (2-5)	2.5 (1-5)	0.376
Pre-INR††	2.23 (1.20-4.60)	1.70 (1.19-2.62)	0.052
Maximum INR	6.44 (5.21-14.68)	2.22 (1.21-3.44)	<0.001

The values for continuous variables including age, total numbers of drug category, and duration of treatment followed normal distribution. These values are expressed as mean±standard deviation, and p-values were calculated by independent two sample t-test. ADL, warfarin dosage, pre-INR, maximum INR, and duration of hospitalization do not satisfy the normality test and are expressed as median values (minimum value-maximum value), and p-values were obtained by the Mann-Whitney U test. However, age and ADL can be expressed as categorized variables, shown above as total frequency (%). Other categorized variables are shown as total frequency (%), and p-values were calculated by the chi-square test (Fisher's exact test). ADL, activities of daily living; INR, international normalized ratio.

*Cases were chronic anticoagulated patients whose INR increased to >5.0 at any point during the treatment with concurrent use of warfarin and ciprofloxacin without increase in the warfarin dose. †Control subjects were enrolled patients whose INR did not increase beyond 3.5 with concurrent use of ciprofloxacin and warfarin. ‡History of gastrointestinal bleeding which included cerebral hemorrhage. §Activities of daily living represents patients' performance status. Higher scores reflect greater dependent trends in daily life. ‖Any inflam- matory disease excluding pneumonia and UTI. ¶No. of classes of medications taken by patients. **Length of concurrent use of ciprofloxacin and warfarin. ††INR measured 3 days before concurrent use of ciprofloxacin and warfarin.

Table 2. Baseline medical history of case group before initiation of ciprofloxacin (n=9)

Case	Sex	Age (yr)	Indications	Cormobidities	Bleeding*	ADL
1	F	68	UTI	HTN, DM, VHD, A-fib	No	12
2	F	70	Pneumonia	CVA, CHF, VHD, A-fib, Asthma	Yes	18
3	F	89	UTI	DM, HTN, CVA	No	18
4	F	69	FUO (empirical use), Fibrous dysplasia	HTN, DM, VHD, A-fib, Hyperthyroidism	No	6
5	F	86	UTI	DVT, CVA, Osteoporosis, HTN	No	18
6	M	58	Cellulitis	DM, ESRD, Osteomyelitis	No	9
7	M	72	AGE	AGC, Meningioma, A-fib	No	13
8	F	63	UTI	DM, CAOD, VHD, Colon cancer	Yes	18
9	M	72	UTI	CKD, CVA, C-cord injury	No	18

ADL, activities of daily living; UTI, urinary tract infection; HTN, hypertension; DM, diabetes mellitus; A-fib, atrial fibrillation; CVA, cerebrovascular disease; CHF, congestive heart failure; VHD, valvular heart disease; FUO, fever unknown origin; DVT, deep vein thrombosis; ESRD, end stage renal disease; AGC, advanced gastric cancer; CAOD, coronary artery occlusive disease; CKD, chronic kidney disease; C-cord injury, cervical cord injury.
*Previous history of bleeding-associated complications due to warfarin use.

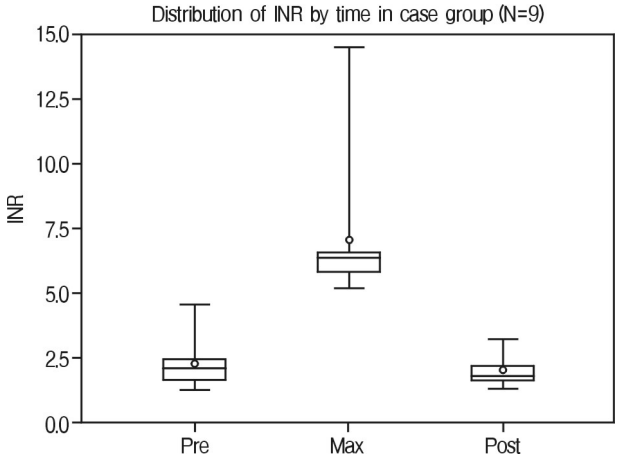

Fig. 2. International normalized ratio (INR) distributions to show drug interaction between ciprofloxacin and warfarin for the case group (nine subjects). Pre-INRs were measured at admission or 3 days before initiation of ciprofloxacin and post-INRs were checked 3 days after stopping ciprofloxacin. Max-INR was the highest INR measured during treatment.

fresh frozen plasma and received vitamin K injections to normalize the INR. Five patients (55%) had ADL scores of 18, suggesting a poor general condition compared with control subjects. No patients died due to INR prolongation; however, a patient died because of progression of stomach cancer combined with sepsis (Table 3).

DISCUSSION

There have been many reports of patients on warfarin experiencing INR prolongation due to enhanced anticoagulation effect induced by the concurrent use of antibiotics and other drugs. However, most reports were case reports, retrospective observations, or studies performed in healthy volunteers; and they failed to show statistically significant evidence between drug interaction and INR prolongation in acutely ill patients[8,21]. These results support other factors may be at play in the INR prolongation.

We analyzed several factors that were suspected and found that patients who had experienced high INR levels had high ADL scores and took multiple medications compared to patients who had not. We could assume that patient condition induces coagulopathy because patients who had poor general condition tended to have high ADL scores and were generally taking many drugs.

Ahmed et al.[17] reported that an average of 16% dose reduction of warfarin before starting trimethoprim-sulfamethoxazole was helpful in maintaining INR values <4.0 and preventing development of coagulopathy. However, it was also reported that dose reduction of warfarin was not helpful for levofloxacin users to maintain target INRs. There is little evidence of coagulopathy related to warfarin and levofloxacin interaction, and research data has not been able to show guidelines for dose reduction before use of antibiotics. Because that report was not a randomized study, selection bias and other factors may have contributed to the findings.

Schelleman et al.[20] reported that cotrimoxazole and fluconazole induced INR prolongation and demonstrated this statistically. However, they reported that infection and its sequale also induced INR prolongation. This result implied that drug

Table 3. Progress of case group after treatment with ciprofloxacin (n=9)

Case	Hospitalization (day)	Pre-INR*	Max-INR†	Post-INR‡	Cx	Time§ (day)	Outcome‖
1	11	2.38	6.44	1.62	None	3	Healed
2	35	1.92	6.44	1.55	None	3	Healed
3	36	2.44	5.38	2.16	None	2	Healed
4	81	2.11	5.84	1.66	None	2	Healed
5¶	13	1.20	6.80	3.18	None	2	Expired
6	55	4.6	6.55	3.20	None	2	Healed
7	6	1.63	5.21	1.25	None	2	Healed
8	27	1.45	14.68	1.80	None	1	Healed
9	375	2.37	6.66	2.12	None	2	Healed

Cx, complications; INR, international normalized ratio.
*Patient's INR 3 days before concurrent use of ciprofloxacin and warfarin. †Patient's maximum INR during use of ciprofloxacin and warfarin concurrently. ‡Patient's INR 3 days after stopping ciprofloxacin. §Duration of decrease of INR to controlled value. ‖Patient's status after treatment. ¶Case 5: death due to progression of stomach cancer combined with sepsis.

interactions between antibiotics and warfarin were not the only factors affecting INR measures.

Although several reports have been published to show drug-drug interactions between warfarin and ciprofloxacin, this relationship has not yet been proved. What research has demonstrated is a trend of INR prolongation with concurrent warfarin and ciprofloxacin use. Therefore, it is recommended that INR should be carefully monitored during therapy with ciprofloxacin[4,6-13,17-20].

We compared patients who had and who did not have INR prolongation during concurrent use of warfarin and ciprofloxacin to evaluate additional factors triggering INR prolongation. We showed that there was a statistical difference between the groups for ADL and the total number of classes of medications taken. We adjusted ADL for the items on the Katz ADL index, including bathing, dressing, going to toilet, feeding, continence, and transferring[22,23]. Patient performance on each item was evaluated. Although each item was classified by Katz et al.[23] into two categories, dependent and independent, we classified them into three categories, independent, partially dependent, and fully dependent. For each category, we assigned 1, 2, and 3 points, respectively. The total score for ADL ranged from six to 18. We observed that patients with high scores tended to suffer INR prolongation and that total classes of pills taken by patients had a positive correlation with coagulopathy.

Although previous studies reported that poor general condition induced INR prolongation, most results were not quantified. In our study, we quantified the general condition through the ADL score and presented the correlation between ADL score and INR prolongation. We also showed that the total classes of drugs taken correlated positively with INR prolongation. Because patients who had poor conditioning tended to be taking more drugs than others, we assumed the total classes of drugs could represent a poor general condition. Therefore, we are able to use the number of classes of drugs as a variable to reflect a patient's general condition. We expected to be reducing the warfarin dose quantitatively according to the ADL score as an objective indicator of general conditioning.

On the other hand, previous reports suggested that INR prolongation might develop due only to fever and infection. However, both our cases and controls were admitted because of infection and fever. Furthermore, we showed that length of hospitalization was not statistically related between the two groups. Therefore, we thought that INR prolongation developed due to acute illness was controlled between the groups.

In addition, the samples of previous studies were mostly young healthy volunteers. However, we identified cases and controls of elderly hospitalized patients who took multiple drugs to control variable diseases. Consequently, we expect that our results will be clinically valuable for hospitalized patients taking several medications with several underlying medical problems. No severe complications occurred throughout this study, and we thought the study progressed safely.

There were some limitations in this study. Our study was neither a multicenter study nor a randomized study. Therefore, selection bias was possible. Second, our study is too small to be generalized, with a sample size of nine cases and 19 control subjects. Although this sample size could possibly show a one to one relationship between variables, we could not statisti-

cally prove one to multiple relationships. Therefore, large population studies should be done. Third, our hospitalized study sample consumed general diets with the foods being different for each individual. Thus, we did not know the amount of vitamin K intake by each person nor did we have a system to control or quantify it. Generally, patients who were in a poor general condition tended to have decreased appetite, which might have compromised their nutritional status. We cannot ensure that the uncontrolled intake of vitamin K and poor nutritional status are independent of our results. Finally, we identified cases whose INRs were elevated >5.0 and control subjects whose INRs were <3.5. As there were no objective guidelines to define INR prolongation, we used INR range of 2.5-3.5 for postoperative patients with mechanical valves and 2.0-3.0 for others. Thus, we attempted to achieve an INR value of 2.5 to avoid unexpected hemorrhage and to maintain efficacy. An INR >5.0 is not an ordinary course of fluctuation and can cause GI bleeding or intracranial hemorrhage. We also identified two other groups based on the INR value, the <4.0 group and the <5.0 group (data not shown). Comparing these two groups with the control group, we got the same results as the group with INRs >5.0 (data not shown). However, we were uncertain as to whether an INR increase to 4.0-5.0 represented INR prolongation or individual fluctuation. Therefore, we limited and identified the control group as INR <3.5.

Despite these study limitations, we set an objective index for the general conditioning of patients as a triggering factor of INR prolongation, with demonstrated statistical significance. If we can overcome the above limitations, we expect to be able to present objective guidelines for warfarin dose reduction in chronically anticoagulated patients prior to starting antibiotics.

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