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Report

Interaction Between Piperacillin/Tazobactam and Warfarin: a Single-Center Retrospective Single-Arm Cohort Study

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Antibiotics influence the anticoagulation effect of warfarin and increase the bleeding risk in patients who are receiving warfarin. Piperacillin/tazobactam (PIPC/TAZ) is commonly used to treat infections such as healthcare-associated infection. However, there have been few reports about the interaction between warfarin and PIPC/TAZ. In this study, we investigated the influence of PIPC/TAZ on the anticoagulation effect of warfarin in hospitalized patients. The primary outcome was elevation of prothrombin time international normalized ratio (PT-INR) after PIPC/TAZ administration. Secondary outcomes were the proportion of patients with supratherapeutic levels of PT-INR, discontinuation of administration or reduction in the dose of warfarin, bleeding, transfusion, and vitamin-K rescue. Fifteen patients were enrolled in this study. PT-INR elevation occurred in 11 (73.3%) of the 15 patients. The median value of PT-INR after administration of PIPC/TAZ was significantly higher than the value before administration: 2.22 (interquartile range (IQR), 2.05-2.76) and 1.90 (IQR, 1.36-2.45), respectively (p = 0.024). Three (20%) of the 15 patients had PT-INR over 4, and discontinuation of administration or reduction in the dose of warfarin was needed in 6 (40%) of the 15 patients. Bleeding occurred in one patient, transfusion was performed in one patient and vitamin-K rescue was performed in one patient. This study showed that PIPC/TAZ induced elevation of PT-INR in patients receiving warfarin and that discontinuation or reduction in the dose of warfarin was needed in 40% of the patients. Therefore, we recommend to close monitoring of PT-INR in patients treated with warfarin during PIPC/TAZ administration.

Key words warfarin, drug-drug interaction, antibiotics, piperacillin/tazobactam, prothrombin time international normalized ratio

INTRODUCTION

Adverse drug events are an important issue because they often increase the risk of hospitalization, and the incidence of bleeding induced by anticoagulants has been increasing in recent years.[1)] Warfarin, one of the oral anticoagulants, induces an anticoagulation effect by blocking the activity of vitamin K epoxide reductase. Warfarin is inexpensive and widely used, but it has some clinical problems including a narrow therapeutic window of prothrombin time international normalized ratio (PT-INR) and various drug-drug interactions. Therefore, PT-INR needs to be monitored closely and the dose of warfarin needs to be adjusted according to the PT-INR level.

Adverse events induced by antimicrobial agents have also been reported in hospitalized patients.[2)] Most antibiotics including sulfamethoxazole, fluoroquinolones and metronidazole influence the anticoagulation effect of warfarin and increase the risk of bleeding in elderly patients receiving warfarin.[3)] Piperacillin/tazobactam (PIPC/TAZ), an antipseudomonal beta-lactam antimicrobial, is commonly used in high-risk patients with resistant bacterial infections such as healthcare-associated pneumonia[4)] and intra-abdominal infection.[5)] Amoxicillin/clavulanate (AMPC/CVA), another beta-lactam antimicrobial with a beta-lactamase inhibitor, has been reported to cause bleeding and elevation of PT-INR in some cases during anticoagulation therapy with warfarin.[6)] Although the interaction between piperacillin/tazobactam and warfarin have been written in each package insert, there have been few reports on whether PIPC/TAZ affects the anticoagulation effect of warfarin in patients.

The aim of this study was to determine the influence of PIPC/TAZ on the anticoagulation effect of warfarin in patients.

MATERIALS AND METHODS

Patients This study was a single-center retrospective single-arm cohort study conducted in a 276-bed secondary-care hospital in Japan. Patients were recruited between January 1, 2012 and July 30, 2016. Patients who were hospitalized and continuously prescribed warfarin and in whom PT-INR was determined before and after PIPC/TAZ administration were included in this study. We excluded patients who died during

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the therapeutic period, patients who were under 18 years of age, patients for whom administration of warfarin was stopped before PIPC/TAZ administration, patients for whom anticoagulation therapy with warfarin was initiated during PIPC/TAZ administration, patients for whom oral administration was impossible and patients for whom PT-INR was not checked and concomitant use of contraindicated drugs which enhance the anticoagulation effect of warfarin.

Data Collection Data obtained from medical records were reviewed and analyzed. We collected data for age, sex, laboratory examinations, comorbidities including hypertension, histories of stroke, heart failure, malignancy, history of bleeding, abnormal liver function, and chronic kidney disease (CKD) (defined as estimated glomerular filtration rate of less than 60 mL/min/1.73m^2 using serum creatinine levels before PIPC/TAZ administration), daily dosage of warfarin, reason for anticoagulant therapy, concomitant medications, infectious diseases, daily dosage of PIPC/TAZ, pretreatment with other antibiotics before PIPC/TAZ, and PT-INR value before PIPC/TAZ administration (current data) and that after PIPC/TAZ administration (within 7 d after the completion of PIPC/TAZ administration).

Outcomes The primary outcome was elevation of PT-INR after PIPC/TAZ administration. Secondary outcomes were the proportion of patients with supratherapeutic levels of PT-INR, discontinuation of administration or reduction in the dose of warfarin, vitamin K rescue, hemorrhage, and red cell transfusion during the therapeutic period. The grades of "increase in INR" have been defined by Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 was defined as an elevated value by 1-1.5 times, grade 2 was defined as an elevated value by 1.5-2.5 times, and grade 3 was defined as an elevated value by 2.5 times and more.

Statistical Analysis Fisher's exact test was used to compare the differences in descriptive and categorical variables, and the Wilcoxon's signed-rank test was used to compare differences in continuous variables. Two-sided p-values less than 0.05 were defined as indicating statistical significance. EZR (Easy R) v1.32 was used for data processing and statistical analyses.[7)]

Ethics This study was approved by the institutional review board of Sapporo Hokushin Hospital.

RESULTS

Patient Characteristics We enrolled 15 patients in this study (Fig. 1). Table 1 shows the characteristics of the patients. The mean age of the patients in this study was about 80 years. The proportion of women was about 25%. CKD was the most frequent comorbidity in the patients. Antiplatelets were the most frequently administered concomitant medications. The reason for initiating anticoagulant therapy was atrial fibrillation in two-thirds of the patients. Pneumonia and urinary tract infections were the most frequent infectious diseases. More than two-thirds of the patients were administered other antibiotics as pretreatment. There were no patients for whom prescribed medications, including metronidazole, rifampicin, carbamazepine, phenytoin, and anti-thyroid drugs, have been reported to interact with warfarin.

Outcomes The values of PT-INR in the patients before and after treatment with PIPC/TAZ are shown in Fig. 2. The median PT-INR after PIPC/TAZ administration was significantly higher than that before PIPC/TAZ administration (2.22 and 1.90, respectively). The outcomes in the patients in this study are shown in Table 2. PT-INR elevation was observed in about three-quarters of the patients in this study, and 20% of the patients had supratherapeutic PT-INR. Administration of warfarin was stopped or the dose was reduced in 40% of the patients who received PIPC/TAZ. Bleeding occurred in one patient, transfusion was performed in one patient and administration of a reversal agent to warfarin was performed in one patient. The ratios of PT-INR/dose of warfarin were not significantly different before and after administration of PIPC/TAZ (median (IQR): 1.16 (0.64-1.56) and 1.27 (0.96-2.18), respectively, p = 0.07, Wilcoxon's signed-rank test) (Fig. 3). A summary of 3 cases with supratherapeutic values of PT-INR is shown in Table 3. The three patients were 65 years of age or older and had a history of CKD. Moreover, they were prescribed medications including amiodarone, allopurinol, glimepiride, heparin and indomethacin that have been reported to show interactions with warfarin.

DISCUSSION

Our study suggested that PIPC/TAZ induces PT-INR elevation in patients receiving warfarin. To our knowledge, this is

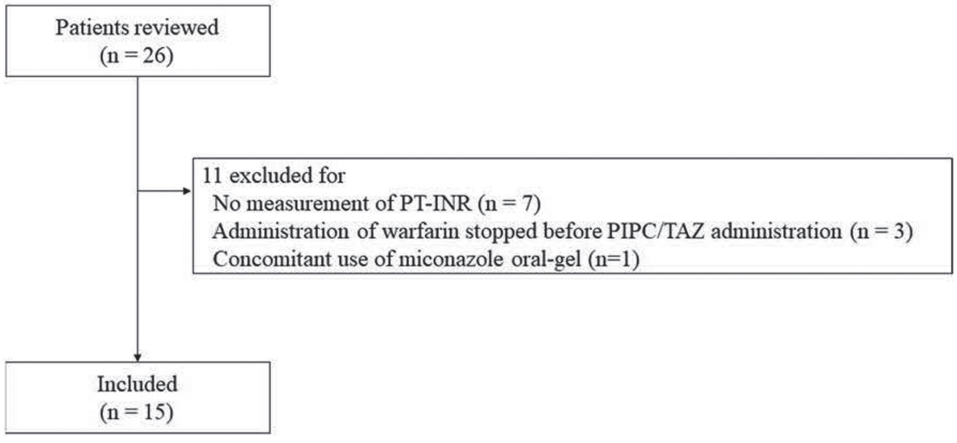

Fig. 1. Diagram for Selection of Patients

PT-INR, prothrombin time international normalized ratio; PIPC/TAZ, piperacillin/tazobactam.

Table 1. Characteristics of Patients Who Received Warfarin and PIPC/TAZ

Characteristic	Patients (n = 15)
Age (years), median [min-max]	82 [65-89]
Female, n (%)	4(26.7)
Comorbidity	
Hypertension, n (%)	11 (73.3)
Chronic kidney disease, n (%)	13 (86.7)
Heart failure, n (%)	10 (66.7)
Malignancy, n (%)	3 (20)
Stroke history, n (%)	2 (13.3)
Bleeding history, n (%)	1 (6.7)
Abnormal liver function, n (%)	1 (6.7)
Serum albumin (mg/dL), median [IQR]	3.30 [2.95-3.50]
Hypoalbuminemia (<3 mg/dL), n (%)	4 (26.7)
Daily dosage of warfarin (mg), median [min-max]	1.8 [0.5-3.5]
Prescribed medication, median [min-max]	13 [0-18]
Polypharmacy, n (%)	13 (86.7)
Concomitant	
Antiplatelets, n (%)	7 (46.7)
Amiodarone, n (%)	3 (20)
NSAID	1 (6.7)
Reason for anticoagulation therapy	
Atrial fibrillation, n (%)	11 (73.3)
Valve replacement, n (%)	2 (13.3)
Intraventricular thrombus, n (%)	1 (6.7)
Post coronary artery graft bypass, n (%)	1 (6.7)
Infectious diseases	
Pneumonia, n (%)	8 (53.3)
Urinary tract infection, n (%)	4 (26.7)
Sepsis, n (%)	1 (6.7)
Surgical site infection, n (%)	1 (6.7)
Febrile neutropenia, n (%)	1 (6.7)
Hospital days (day), median [IQR]	30 [21-35]
Daily dosage of PIPC/TAZ	
4.5 g, n (%)	1 (6.7)
9.0 g, n (%)	4 (26.7)
13.5 g, n (%)	10 (66.7)
Duration of PIPC/TAZ therapy, median [IQR]	8 [5-10]
Pretreatment with antibiotics, n (%)	11 (73.3)
Ampicillin/sulbactam, n (%)	3 (20)
Cephalosporins, n (%)	2 (13.3)
Macrolides, n (%)	2 (13.3)
Carbapenems, n (%)	2 (13.3)
Fluoroquinolones, n (%)	1 (6.7)
Clindamycin, n (%)	1 (6.7)
Sulfamethoxazole/trimethoprim, n (%)	1 (6.7)

PIPC/TAZ, piperacillin/tazobactam; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drugs

Table 2. Outcomes in Patients Treated with a Combination of Warfarin and PIPC/TAZ

Outcomes	Patients (n = 15)
Elevation of PT-INR, n (%)	11 (73.3)
Grade 1, n (%)	5 (33.3)
Grade 2, n (%)	5 (33.3)
Grade 3, n (%)	1 (6.7)
PT-INR > 4, n (%)	3 (20)
Stopping or dose reduction of warfarin, n (%)	6 (40)
Hemorrhage, n (%)	1 (6.7)
Blood transfusion, n (%)	1 (6.7)
Vitamin K rescue, n (%)	1 (6.7)

PIPC/TAZ, piperacillin/tazobactam; IQR, interquartile range; PT-INR, prothrombin time international normalized ratio

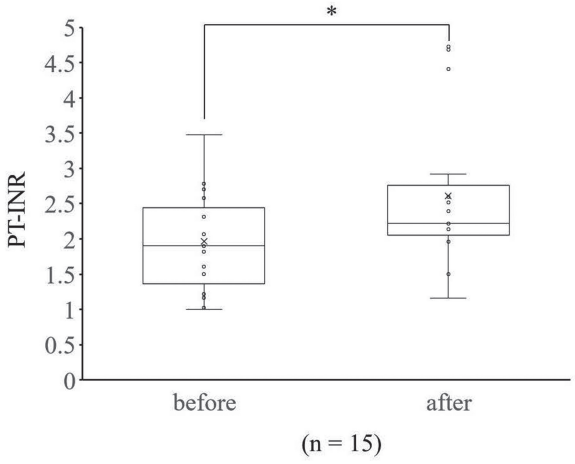

Fig. 2. Prothrombin Time International Normalized Ratios Before and After Treatment with PIPC/TAZ in Patients Who Received Warfarin

PT-INR, prothrombin time international normalized ratio; PIPC/TAZ, piperacillin/tazobactam. *Wilcoxon's signed-rank test, *p = 0.024.

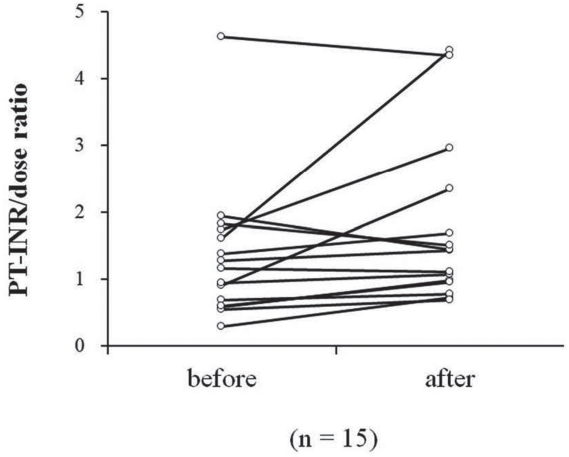

Fig. 3. Ratios of PT-INR/Dose of Warfarin Before and After Treatment with PIPC/TAZ in Patients Who Received Warfarin

PT-INR, prothrombin time international normalized ratio; PIPC/TAZ, piperacillin/tazobactam.

the first report on the influence of PIPC/TAZ on the anticoagulation effect of warfarin in a clinical setting.

Renal dysfunction is common in elderly people. Most of the patients in our study were elderly patients with CKD. Renal impairment is a risk factor for bleeding that is included in the HAS-BLED score.[8] Since most of the patients in this study had CKD, the study population might be a high-risk population for bleeding. Moreover, it has been reported that patients with CKD stage G3a or higher have a risk of hospitalization with severe infections such as kidney and urinary tract infections and bloodstream infections.[9] Therefore, broad-spectrum antibiotics such as PIPC/TAZ have frequently been used for treating infections in elderly patients with CKD.

Polypharmacy can lead to an increase in the risk of drug-drug interaction. Most of the patients in this study were prescribed 5 or more medications including medications that increase the risk of bleeding such as antiplatelets. Furthermore, three patients who were prescribed amiodarone, which is strong inhibitor of cytochrome P450 2C9, and/or indomethacin, which is an albumin binding inhibitor, showed supratherapeutic values of PT-INR after PIPC/TAZ administration. Since elderly people often have multiple comorbidities, they are prescribed many medications. The bleeding risk in elderly patients is therefore likely to be higher than that in younger patients.

In our study, administration of PIPC/TAZ resulted in a significant increase in PT-INR in patients receiving warfarin. Moreover, 40% of the patients had supratherapeutic levels of PT-INR. According to the Japan Cardiology Society,

Table 3. Summary of Cases Showing Observed Over-Anticoagulation After PIPC/TAZ Administration

		Case 1	Case 2	Case 3
Age (years)		85	65	70
Sex		female	male	male
Infectious diseases		SSI	pneumonia	UTI
Comorbidity		heart failure hypertension CKD	heart failure hypertension CKD	heart failure stroke CKD
Concomitant		calcitriol candesartan cibenzoline indomethacin lansoprazole levodopa/carbidopa mosapride nifedipine polaprezinc senna sofalcone triazolam	ambroxol amiodarone carvedilol mexiletine nicorandil sotalol ursodeoxycholate furosemide (iv) dopamine (iv) L-cysteine (iv) canrenoate (iv) dobutamine (iv) vancomycin (iv) heparin (iv) famotidine (iv) TPN (iv)	allopurinol amiodarone aprindine carvedilol docarpamine furosemide glimepiride lansoprazole metformin nicorandil pimobendan senna sitagliptin spironolactone
Indication for anticoagulant therapy		atrial fibrillation	cardiac intraventricular thrombus	atrial fibrillation
PT-INR	(before)	1.61	2.70	2.78
	(after)	4.41	4.68	4.73
INR/dose	(before)	1.61	0.90	1.74
	(after)	4.41	2.34	2.96
Days after PIPC/TAZ administration		4	5	12

PIPC/TAZ, piperacillin/tazobactam; SSI, surgical site infection; UTI, urinary tract infection; CKD, chronic kidney disease; TPN, total parental nutrition; PT-INR, prothrombin time international normalized ratio; PIPC/TAZ, piperacillin/tazobactam

the appropriate range of PT-INRs is 1.6 to 3.0 and bleeding risk increases at a PT-INR of 3 or higher.[10,11] Thus, we consider that the concomitant use of warfarin with PIPC/TAZ may increase the bleeding risk. In contrast, the INR/dose ratios before and after administration of PIPC/TAZ were not significantly different in our patients. However, in about 80% of our patients, the PT-INR/dose ratio after administration of PIPC/TAZ was higher than that before administration of PIPC/TAZ. Therefore, PIPC/TAZ might influence the anticoagulation effect of warfarin.

AMPC/CVA is a beta-lactam antibiotic/beta-lactamase inhibitor combined agent (BLBLI), as is PIPC/TAZ, and it has been reported that it causes elevation of PT-INR and hemorrhage in patients receiving warfarin.[6,12–14] Elevated supratherapeutic levels of PT-INR were also observed in some cases without hemorrhage. Therefore, a lack of PT-INR monitoring in patients who have received warfarin during PIPC/TAZ administration may result in a delay in finding hemorrhage and managing the bleeding. In this study, PT-INR was not monitored in about one-third of the patients who received warfarin in the antimicrobial therapy period. Pharmacists and physicians should closely monitor PT-INR during PIPC/TAZ administration in patients who are treated with warfarin.

Our study has several limitations. First, our study was a single-center retrospective observational study. Therefore, there might be unknown confounding factors. Our results might be difficult to extrapolate to young adults because all of the patients in this study were elderly patients. The proportions of elderly patients with comorbidities and elderly patients receiving multiple medications are high, and those proportions were also high in our study. It has been reported that polypharmacy is related to bleeding risk in elderly patients with venous thromboembolism.[15] In our study, most of the patients were prescribed 5 and more medications. However, PIPC/TAZ is frequently used for treatment of high-risk patients, such as elderly patients, who have bacterial infection with antimicrobial resistance. Hence, it is assumed that our patients were appropriate patients for this study. Second, there were both patients with elevated PT-INR and patients without elevated PT-INR. Zhang and colleagues conducted a prospective study and reported that AMPC/CVA did not induce an increase in PT-INR.[16] However, our study population was different from their study population because only stable cases were selected for their study. In contrast, it was reported that BLBLIs as well as ceftriaxone for urinary tract infection induced increases in PT-INR in elderly patients receiving warfarin.[17] PIPC/TAZ is commonly used for treatment of severe infections such as sepsis, pneumonia, and pyelonephritis. Moreover, it was reported that the degree of PT-INR elevation in patients administered high doses of AMPC/CVA was significantly larger than that in patients administered standard doses of AMPC/CVA.[18] The usual dose of PIPC (12-16 g per day) in PIPC/TAZ is larger than the doses of other beta-lactam antibiotics. Therefore, our results might be associated with the patients' status and/or the doses of PIPC/TAZ. Third, approximately two-thirds (11/15) of the patients in our study received other antibacterials before PIPC/TAZ administration. Therefore, pretreatment with each drug might have influence the anticoagulation effect in our patients. However, PT-INR elevation in those patients was observed after PIPC/TAZ administration. Finally, it could not be concluded from the results of our study whether PIPC/TAZ is a higher risk than other antimicrobials for over-anticoagulation. Further research is needed.

In conclusion, our study suggested that PIPC/TAZ influences the anticoagulation effect of warfarin and increases the bleeding risk in patients receiving warfarin. The results of coagulation tests should be closely monitored to prevent an unexpected elevation of PT-INR and/or serious hemorrhage in

patients who receive warfarin during PIPC/TAZ therapy.

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Conflict of interest The authors declare no conflict of interest.

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