Interaction between Warfarin and Linezolid in Patients with Left Ventricular Assist System in Japan

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Abstract

Objective The purpose of this study was to investigate the possible interaction between warfarin and linezolid in patients with a left ventricular assist system (LVAS) for the treatment of severe heart failure.

Methods Patients with LVAS who were treated with linezolid for the treatment of infections from January 2003 to March 2013 were identified from medical records. The impact of linezolid on the clotting function, as well as the dose of warfarin during the first 10 days of linezolid therapy, was investigated. The mean prothrombin time-international normalized ratio (PT-INR) and mean doses of warfarin during 7 days before and 10 days after the initiation of linezolid therapy were calculated for individual patients. The PT-INR per mg of WF dose on the previous day (X) was calculated. The warfarin dose, PT-INR, and warfarin sensitivity index (WSI) value before and after the initiation of linezolid were compared to evaluate the impact of linezolid on the effect of warfarin.

Results Sixteen patients were enrolled in the study. Although the mean PT-INR increased from 3.74 to 4.06, no significant difference was observed (p=0.05). A significant difference was observed in the mean dose of warfarin before and after the initiation of linezolid administration, with a decrease from 3.23 to 2.69 mg/day (p=0.001). In contrast, the mean WSI value significantly increased from 1.37 to 1.82 (p=0.014). After 10 days of linezolid administration, the mean X values increased over the baseline value by 31.7%.

Conclusion These findings suggest that co-administration of linezolid results in increased PT-INR in patients with LVAS treated with warfarin.

Key words: warfarin, linezolid, left ventricular assist system, drug interaction


Introduction

Warfarin is a widely used oral anticoagulant for the prevention of thromboembolic events in patients with chronic atrial fibrillation, prosthetic heart valves, venous thromboembolism, and coronary artery disease (1). Furthermore, warfarin is used for the prevention of pump thrombosis in patients with a left ventricular assist system (LVAS); however, it is characterized by considerable inter- and intra-individual variation in dose requirements. Additionally, the efficacy and safety of warfarin are influenced by changes in concomitant medications, diet, alcohol consumption, acute illness, liver disease, and unknown factors. In particular, interactions with other medications and foods are a major concern associated with warfarin therapy. Therefore, monitoring the prothrombin time-international normalized ratio (PT-INR) and dose adjustments of warfarin are required for desirable safety and efficacy.

Heart transplantation provides considerable survival benefits for patients with end-stage heart failure. However, it is available only for a small fraction of such patients in Japan...
Due to donor shortage, therefore, many heart transplant candidates require long-term support by LVAS while they await transplantation. Despite recent advances in technology, significant complications, such as neurological complications (2), infection (3), and gastrointestinal bleeding, develop during LVAS therapy. Anticoagulant therapy for thrombosis and the infection control of skin lesions at the site of penetration of devices are serious problems in the management of chronic-phase patients with LVAS. In particular, neurological complications, including ischemic stroke and intracranial hemorrhage, are the leading causes of death and are a main reason for transplant ineligibility in patients supported by LVAS. Pump thrombosis is the most common cause of this complication. Therefore, patients with LVAS are treated with both anticoagulant and antiplatelet agents to reduce the risk of cerebrovascular accident. Suboptimal anticoagulation therapy is a significant risk factor for pump thrombosis and may become a critical issue in LVAS therapy (4, 5).

Meanwhile, linezolid is the first oxazolidinone antibiotic agent to be approved from the oxazolidinone class, which has substantial antimicrobial activity against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) (6-9). In clinical practice, linezolid has been used for the treatment of pneumonia, deep skin and soft tissue infections, chronic pyoderma, and various types of infections caused by MRSA and VRE (10-14).

Nipro-Toyobo LVAS® (Nipro, Osaka, Japan) is used as a long-term “bridge-to-transplant” device in the National Cerebral and Cardiovascular Center (NCVC), which is one of the main heart transplant centers in Japan. In some patients treated with Nipro-Toyobo LVAS® and warfarin in the NCVC, a significantly elevated PT-INR was observed when warfarin was concomitantly administered with linezolid. The purpose of the study is to investigate the possible interaction between warfarin and linezolid in patients with Nipro-Toyobo LVAS® for the treatment of serious heart failure.

Materials and Methods

Patients with Nipro-Toyobo LVAS® who were treated with warfarin plus linezolid therapy from January 2003 to March 2013 were identified from medical records. Changes in the warfarin dosage and PT-INR before and after the initiation of linezolid therapy were investigated to assess the impact of linezolid on blood coagulation in patients being treated with warfarin. S-warfarin is approximately 5 times more active compared to R-warfarin and has a half-life of approximately 40 hours. If linezolid alters the pharmacokinetics of S-warfarin, then steady state serum S-warfarin concentrations can be achieved within about 7 days after the initiation of linezolid therapy. Therefore, patients treated with linezolid for less than 7 days were excluded from the study.

It is known that a fever and the food intake affect the efficacy of warfarin. Therefore, patients who developed a fever with temperatures above 38°C within 10 days of linezolid administration or at any time within 7 days prior to linezolid administration were excluded from the study. Patients on liquid diets and total parenteral nutrition (TPN) were also excluded from the study. In addition, patients who had decreased food intake (<50%) during the study period were also excluded.

Data for this retrospective study were retrieved from the patients’ medical records. The demographic data (age, sex, body height, body weight, underlying heart disease), prescription data (warfarin and linezolid doses, dosing period), laboratory data [PT-INR, aspartate transferase (AST), alanine aminotransferase (ALT), serum albumin (ALB), direct bilirubin (D-BIL), blood urea nitrogen (BUN), serum creatinine (CRE), C-reactive protein (CRP), white blood cell count (WBC), neutrophil (NEUT), and platelet count (PLT)] before and after linezolid therapy were extracted. Body temperature, food intake, and concomitant drugs administered during the study period were also retrieved from the medical records. The data obtained 7 days before were compared to that obtained 10 days after the initiation of linezolid therapy. The mean PT-INR and mean doses of warfarin for both these time points were calculated for individual patients, and these values were defined as the pre- and posttreatment values for individual patients, respectively. The PT-INR values per mg of warfarin dose on the previous day (X) were calculated using formula 1, and the warfarin sensitivity index (WSI) was calculated using formula 2 presented in the Supplementary material (15).

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\text{PT-INR}_{\text{after}} - \text{PT-INR}_{\text{before}} = X \times (\text{PT-INR}_{\text{after}} - \text{PT-INR}_{\text{before}})
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\text{WSI} = \frac{\text{PT-INR}_{\text{after}} - \text{PT-INR}_{\text{before}}}{X}
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Data were expressed as the mean ± standard deviation (SD). Data before and after the initiation of linezolid therapy were compared using Student’s t-test; statistical significance was considered to exist at p<0.05. The JMP® 10.0.2 software program (SAS Institute, Cary, USA) was used for all statistical analyses. This study was approved by the Ethics Committees of the NCVC. All patients provided their written informed consent before participating in the study.

Results

There were 80 patients with Nipro-Toyobo LVAS® from January 2003 to March 2013. Of these patients, 32 started linezolid therapy for the treatment of infection. Twelve patients who developed a fever with temperatures above 38°C within 10 days of linezolid administration or at any time within 7 days prior to administration were excluded from the study. Three patients on liquid diets and TPN were also excluded. In addition, one patient who had decreased food intake (<50%) during the study period was excluded. Consequently, 16 patients were enrolled in the study. The characteristics of the study patients are presented in Table 1. During the treatment with linezolid, no patient started or discontinued a co-administered drug that interacted with warfarin.
Linezolid therapies of individual patients are presented in Table 2. All patients were treated with linezolid 1,200 mg/day oral (14 patients) or intravenous (2 patients) for more than 7 days.

The laboratory data, prescription data, and food intake before and after the initiation of linezolid therapy are presented in Table 3. A significantly increased CRE level was observed after linezolid therapy. However, it was within the normal range for men in our hospital (0.60-1.10 mg/dL). There were no significant differences in any other laboratory data between before and after the initiation of linezolid therapy. Additionally, no significant difference was observed in the food intake between before and after the initiation of linezolid therapy.

The mean PT-INR, warfarin dose, and mean WSI value before and after the initiation of linezolid therapy are presented in Fig. 1. Although the mean PT-INR increased from 3.74 to 4.06, the increase was not significant (p=0.05). A significant reduction from 3.23 to 2.69 mg/day was observed in the mean dose of warfarin from 7 days before to 10 days after the initiation of linezolid therapy (p=0.001). In contrast, the mean WSI value significantly increased from 1.37 to 1.82 (p=0.014). The mean X value increased from 1.39 at baseline to 1.83 on the tenth day after the initiation of linezolid therapy (Fig. 2). After 10 days of administration, the mean X value increased over the baseline value by 31.7%.

Discussion

The present study showed that administering linezolid to patients treated with warfarin and Nipro-Toyobo LVAS® may enhance the effects of warfarin therapy. After the initiation of linezolid therapy, a dose reduction of warfarin was needed to maintain a PT-INR of 3 to 4, which is the target PT-INR range for patients treated with Nipro-Toyobo LVAS®; however, an increased PT-INR was frequently observed. The mean X value on each day after linezolid therapy exceeded the baseline value. An X value 31.7% higher than the baseline value was observed on the tenth day after the initiation of linezolid therapy. Although it has been believed that linezolid does not have potential drug interactions with warfarin, our findings suggest that the interaction with linezolid increased the effect of warfarin.

The common factors contributing to the change in the effect of warfarin are the liver function, renal function, thyroid function, a fever, clinical condition, drug-drug interaction, food-drug interaction, supplement-drug interaction, and vitamin K intake during the same time period (16). Although the mean CRE level was significantly increased after the initiation of linezolid therapy, this clinical laboratory data is within the normal range. There were no significant differences in any other laboratory data between before and after the initiation of linezolid therapy. Warfarin has numerous pharmacodynamic and pharmacokinetic drug-drug and food-drug interactions, thereby a number of drugs, foods, and supplements affect blood coagulation in patients treated with warfarin (17, 18). Consequently, significant differences in the PT-INR before and after the initiation of linezolid therapy may be attributable to the interaction of warfarin with linezolid.

Possible mechanisms of interaction with warfarin involve metabolic inhibition and induction, vitamin K intake, and changes in plasma protein binding. However, the protein binding rate of linezolid is relatively low (31%) (19). In the present study, no significant difference was observed in the albumin level between before and after the initiation of linezolid therapy. Therefore, linezolid may not affect the protein binding capacity of warfarin. Warfarin is a racemic mixture of the R and S stereoisomers of the drug. S-warfarin is primarily metabolized by cytochrome P-450 (CYP) 2C9 isozyme, whereas R-warfarin is metabolized by CYP1A2 and 3A4 (20, 21). However, several animal and human studies revealed that linezolid is not detectably metabolized by CYP (22), and it did not induce or inhibit the activities of clinically significant human CYP isoforms, including CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 (20, 23). In addition, linezolid metabolism is by non-enzymatic oxidation, and therefore, drug interactions based on CYP inhibition or induction are not expected. It is speculated that there is no pharmacokinetic interaction when linezolid is co-administered with warfarin.

It is known that warfarin interacts with several antibiotics. Hypoprothrombinemia has been reported to occur as a result of antibiotic administration. It has been reported that several antibiotics cause vitamin K deficiency by reducing the number of enteric bacteria which synthesize vitamin K in the intestines (21, 22). The suppression of bacterial flora by antibiotics may be a possible mechanism for the interaction of warfarin and antibiotics (21, 22). Recently, Sakai et al. reported that the PT-INR increased following concomitant linezolid treatment in five of six patients who were recovering from heart-related surgery (24). They suggested that these results were attributable to the possible drug interaction between warfarin and linezolid. Furthermore, they hypothesized that linezolid might potentiate the effects of warfarin by lowering the level of vitamin K. Our results from the study are consistent with their findings, thereby supporting the hypothesis that linezolid may influence the effect of warfarin.

In the present study, we demonstrated the possibility for
Figure 1. The PT-INR value (a), warfarin dose (b), and WSI value (c) before and after linezolid therapy. Although the warfarin dose is reduced significantly, PT-INR is elevated after linezolid therapy initiation. WSI is elevated significantly after the initiation of linezolid therapy. Vertical bars represent the standard deviation. PT-INR: Prothrombin time-international normalized ratio, WF: Warfarin, WSI: Warfarin sensitivity index
an interaction between warfarin and linezolid in patients with LVAS; however, there are some limitations associated with the present study. First, the available sample size in our study was small, and the study subjects were limited to patients with LVAS. Warfarin was used for the prevention of pump thrombosis in patients with LVAS. Linezolid is likely used for the treatment of MRSA infections for patients with LVAS, because linezolid has good tissue penetration and should be effective in treating tissue infection (25). However, warfarin is generally used for the prevention of thromboembolic events in patients with chronic atrial fibrillation, prosthetic heart valves, venous thromboembolism, and coronary artery disease. Although administering linezolid to patients treated with warfarin and LVAS enhanced the effects of warfarin therapy, it was uncertain whether these effects are applicable to other patient populations. Sakai et al. have reported that the PT-INR values significantly increased from 1.62 before concomitant linezolid administration to 3.00 on day 4 or 5 of concomitant therapy in patients who were recovering from heart-related surgery. For patients with Nipro-Toyobo LVAS®, a PT-INR of 3 to 4 is desirable, which is higher than that for other clinical settings of warfarin therapy. Therefore, patients with LVAS may be at high risk of linezolid-induced interaction with warfarin, and this drug interaction may be a crucial concern in these patients. Although we have specifically targeted patients with LVAS in the present study, linezolid-induced interactions with warfarin should be evaluated in other patients. Second, the mechanism of this interaction remains unclear. We hypothesize that linezolid might potentiate the effects of warfarin by lowering the level of vitamin K; however, the vitamin K level was not investigated in this study. Further studies are required to examine the effects of linezolid therapy on the level of vitamin K. Third, the serum concentration of linezolid was not determined in the present study. Because the relationships between the serum concentration of linezolid and clinical efficacy and safety are unclear, the serum concentration of linezolid is not commonly determined in clinical practice. However, the serum linezolid concentration may impact the PT-INR in patients treated with warfarin. Therefore, the impact of the serum linezolid concentration on the PT-INR in patients treated with warfarin should be investigated in future studies.

In conclusion, the present study suggested that co-administration of linezolid and warfarin results in an increased PT-INR in patients with LVAS. For patients with LVAS, severe anticoagulant therapy with warfarin is required to maintain an optimum therapeutic effect. Although it has been believed that linezolid does not have potential drug interactions with warfarin, our data strongly suggested that linezolid may influence the effect of warfarin. The mechanism of the interaction between warfarin and linezolid is unclear; however, the PT-INR should be frequently checked for the prevention of thromboembolic events, including pump thrombosis, in patients with LVAS. In addition, the PT-INR should be closely monitored to maintain appropriate anticoagulation therapy for all patients treated with warfarin and linezolid. Further studies are required to confirm our findings and to clarify the mechanism of interaction between these two drugs.

The authors state that they have no Conflict of Interest (COI).

References


