

CASE REPORT

Potential drug-drug interaction between tolvaptan and warfarin in a geriatric patient with heart failure

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Abstract

Tolvaptan is a key drug for patients with heart failure. Here, we present a 92-year-old woman, whose PT-INR/dose increased from 1.74 to 3.30 after warfarin and tolvaptan co-administration, and resulted in a large cerebral infarction after warfarin dose down. Therefore, the interaction between these two drugs may be clinically significant.

KEYWORDS

cerebral infarction, drug-drug interaction, heart failure, tolvaptan, warfarin

1 | INTRODUCTION

Tolvaptan is a selective vasopressin receptor antagonist that is used for the treatment of congestive heart failure, cirrhosis, and hyponatremia resulting from inappropriate antidiuretic hormone secretion syndrome. It is also used for the suppression of worsening renal function in patients with autosomal dominant polycystic kidney disease. Further, warfarin is a vitamin K antagonist and anticoagulant that is used for the treatment of conditions, such as thromboembolism resulting from atrial fibrillation. Saito et al. reported potential temporary drug-drug interactions between tolvaptan (at doses above 7.5 mg/d) and warfarin.^{1,2} Based on the results of their in vitro study, they concluded that the mechanism involves free warfarin via protein-binding substitution.² To the best of our knowledge, no clinically difficult treatment resulting from the

interaction between tolvaptan and warfarin has been reported. Here, we present a case in which the interaction between tolvaptan and warfarin made appropriate anticoagulant therapy difficult 2 months after tolvaptan administration was dosed up to 15 mg/d, resulting in ischemic stroke in a patient with chronic heart failure.

2 | CASE PRESENTATION

The patient was a 92-year-old woman (height, 147 cm; body weight, 50.6 kg) with chronic heart failure, atrial fibrillation (AF), chronic kidney disease (CKD; estimated glomerular filtration rate (eGFR), 23.5; serum creatinine level, 1.60 mg/dl), hypertension, dyslipidemia, and sleep apnea syndrome. In January 2019, she was admitted to Showa University Hospital owing to worsening heart

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failure symptoms resulting from increased pleural effusion and leg edema. On the day of admission, the patient was started on carperitide 0.0125 $\mu\text{g}/\text{min}/\text{kg}$ (iv) and furosemide 40 mg/d (iv) to improve the congestive state. Given that this treatment resulted in sufficient fluid reduction, the patient experienced weight loss (approximately 4 kg); thus, transvenous treatment was stopped on day 9. Further, given that a sufficient urine volume was not obtained and that some pleural effusion remained, her tolvaptan dose was increased from 7.5 to 15 mg/d on day 13. Thereafter, spironolactone 25 mg/d (po) was initiated, while azosemide was dosed up from 30 to 60 mg/d during hospitalization. The comprehensive treatment for heart failure resulted in decreased pleural effusion and also lowered limb edema. The patient was then discharged given that she reached the target body weight. By day 25, the symptoms of heart failure had improved completely (Figure 1).

In March 2019, follow-up laboratory data revealed that her prothrombin time international normalized ratio (PT-INR) had increased from 1.74 to 2.23 during hospitalization to 3.30. Thus, to avoid bleeding, the warfarin dose was decreased from 1 to 0.5 mg/d. A month after this dose reduction, her PT-INR decreased to 1.15, and the low-dose warfarin treatment was continued given her age. In October 2019, 6 months after the reduction of the warfarin dose, the patient was re-hospitalized due to worsening heart failure. Her PT-INR at readmission was 1.20, and on day 5 day of rehospitalization, the patient suddenly developed consciousness disturbance and left hemiplegia, and

brain magnetic resonance imaging revealed a large cerebral infarction in her right cerebral artery region. Therefore, urgent endovascular thrombectomy was performed, and the anticoagulant therapy was changed to continuous intravenous infusion of heparin during the perioperative period. Finally, we titrated 7.5 mg/d of tolvaptan and 1 mg/d of warfarin and under these conditions, we could control heart failure and achieve the appropriate PT-INR value to prevent further cerebral infarction. Additionally, after the dose titration, her PT-INR increased to 1.95, and ischemic stroke recurrence was not observed until July 2020. Specifically, the PT-INR/dose for warfarin decreased from 3.30 to 1.74 before and after changing the dose of tolvaptan from 15 to 7.5 mg/d, even though related laboratory data related to liver and renal function and concomitant drugs that affect the warfarin effect did not change.

3 | DISCUSSION

Tolvaptan is primarily metabolized by cytochrome P450 (CYP)3A4, a drug-metabolizing enzyme that is present in the gut and liver. Further, has been reported that blood tolvaptan concentration could increase 5.4-fold when ketoconazole, a potent CYP3A4 inhibitor, is administered.³ Furthermore, it is known that S-warfarin and R-warfarin are metabolized via CYP2C9 and CYP3A4 (or CYP1A2), respectively,⁴ and it has also been reported that the anticoagulant activity of warfarin is primarily exerted by S-warfarin, whose renal excretion is less than 1% of the

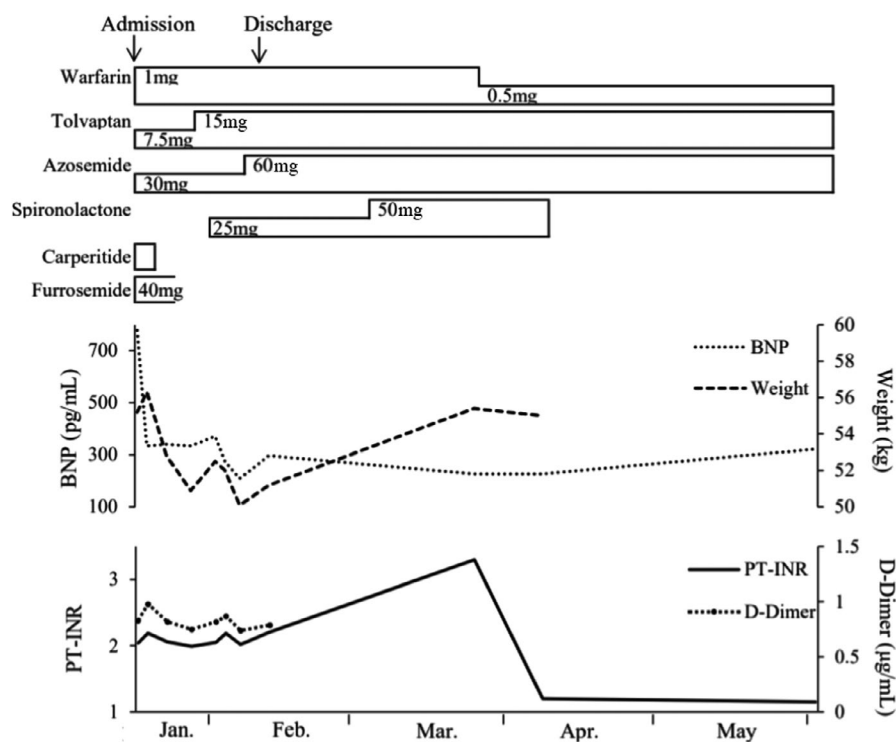


FIGURE 1 Clinical course of the present case

total amount administered.⁵ However, warfarin can enhance PT-INR when it is co-administered with CYP3A4 inhibitors, such as voriconazole.⁶ Further, based on a study involving healthy volunteers, that is, young healthy men and women aged 18–45 years, Shoaf et al.⁷ reported that tolvaptan does not affect warfarin pharmacokinetics via CYP3A4 inhibition. Conversely, our patient was an elderly woman, aged 92 years. Generally, CYP3A4 activity is high in young women, but low in geriatric individuals.^{8,9} Our patient had a complex condition in terms of CYP3A4 activity; however, in addition to CYP activity, the above-mentioned first and second hypotheses may partially explain the pharmacokinetic drug-drug interaction between tolvaptan and warfarin.

Saito et al. reported that interactions between tolvaptan (at doses higher than 7.5 mg/d) and warfarin alters the PT-INR of patients; however, they noted that these interactions are temporary given that the altered free warfarin concentrations recovered within 2 weeks.^{1,2} For our patient, the timing of the increase in PT-INR and the increase in the tolvaptan dose rationally matched; no change in PT-INR was observed when the tolvaptan dose was 7.5 mg/d. Further, the PT-INR of our patient was monitored frequently after her discharge. Higher PT-INR, although temporarily, was noted just after discharge; however, the higher PT-INR observed 2 months after the co-administration of warfarin and tolvaptan could not be easily explained. Thus, we hypothesized that first, our patient had severe renal dysfunction associated with grade 4–5 CKD, and reportedly, tolvaptan causes only 1%–5% renal dysfunction after administration.¹⁰ Notably, our patient already had severe CKD; therefore, the renal impairment effect of the tolvaptan treatment might not have induced the increase in the PT-INR of the patient. Rather, it possibly resulted in the decreased renal clearance of warfarin. Second, PT-INR is reportedly associated with warfarin concentration in the liver.¹¹ Additionally, most cases of liver hypoxia are caused by heart failure, respiratory failure, or sepsis, and specifically, liver hypoxia in heart failure is triggered by pulmonary edema or arrhythmia.^{12,13} Therefore, heart failure that induces liver hypoxia may also result in total body hypoxia, including liver hypoxia.¹⁴ Therefore, warfarin metabolism does not depend on the amount of liver blood flow. Nevertheless, heart failure-induced liver hypoxia may result in the low metabolic clearance of warfarin via cytochrome (CYP) P450 2C9, 1A2, or 3A4.

Recently, in Japan, autosomal dominant polycystic kidney disease and inappropriate antidiuretic hormone secretion syndrome were added as indications for the use of tolvaptan at doses of up to 120 mg/d (March 2014) and 60 mg/d (June 2020), which are far higher than that recommended for heart failure (up to 15 mg/d).

Additionally, a wide range of daily tolvaptan doses (up to eightfold compared with the daily dose for heart failure) may affect the occurrence of clinically relevant drug-drug interactions.

In conclusion, patients treated with tolvaptan at doses higher than 7.5 mg/d and warfarin may show potential pharmacodynamic, physical condition-based, or unknown mechanism-based drug-drug interactions. Nonetheless, we emphasize that this possible drug-drug interaction needs to be further investigated.

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None.

CONFLICT OF INTEREST

YM received honorarium from Otsuka. TS received honorarium from Otsuka, Eisai, TOWA, NIPRO, and Fuji Pharma. The other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All the authors satisfy the four ICMJE recommended criteria for authorship. Satomi Nimura and Kenji Momo drafted the manuscript. Kanayuki Kitahara, Kazuyo Ueshima, Yasuhide Mochizuki, and Toshiro Shinke interpreted the data. Tadanori Sasaki interpreted the data and approved the final publication.

CONSENT

We obtained informed consent and publication consent verbally from the patient, in accordance with the Act on the Protection of Personal Information and its guideline in Japan, which consider verbal consent from patients as ethically appropriate. We have uploaded this verbal informed consent to the electronic medical record of our hospital. In addition, according to journal policy, we obtained written informed consent from her family because she died.

DATA AVAILABILITY STATEMENT

Data sharing: Not applicable—no new data were generated.

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