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รายงานผู้ป่วย *Case report*

Drug-Drug Interaction between Warfarin and Alendronate Sodium in Elderly Patient: a Case Report

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Abstract While alendronate sodium is prescribed to mitigate the risk of bone fractures in older adults, it is crucial to be cognizant of its potential adverse effects. This is particularly important for elderly patients who have a history of one or more venous thromboembolism (VTE) events. The medication's benefits must be carefully weighed against its risks in this vulnerable population. A 77-year-old female with a history of deep vein thrombosis (DVT), currently on warfarin, presented with spontaneous ecchymosis and was seen in the out-patient department. This patient had a prior hip fracture. She was diagnosed using the FRAX score, which indicated a 10-year probability of 35% for a major osteoporotic fracture and 23% for a hip fracture. The patient had been on long-term warfarin therapy due to her history of DVT. Alendronate sodium was prescribed to the patient at 70 mg once a week. Within one month, the patient experienced a provoked increase in inter-national normalized ratio (INR) to 7.76, followed by a gradual decrease to 1.55 after the medication was stopped. The patient also developed spontaneous ecchymoses on the skin. In elderly female patients with osteoporosis and a history of DVT who are on warfarin therapy, alendronate sodium can cause significant increase in INR by over 50% and lead to spontaneous skin bruising. Healthcare providers should be caution when prescribing alendronate sodium to older adults already taking warfarin. It is crucial to be vigilant about the increased risk of bleeding complications that may arise from this drug interaction.

***Keywords*:** **elderly patient; alendronate sodium; deep vein thrombosis; osteoporosis; warfarin; venous thromboembolism**

Introduction

Warfarin treatment regimens are notably complex to manage. In addition to being a drug with a narrow therapeutic index, it does not follow the typical dose-response pattern and has characteristics that predispose it to interactions. These characteristics include a high binding rate to plasma proteins and metabolization by cytochrome P450 enzymes.

Furthermore, warfarin acts in the complex processes of blood coagulation, platelet activation, and inflammation. For these reasons, warfarin has great potential for interactions with other drugs, foods, and herbal medicines[1].

Bisphosphonates (BPs) are recommended as the first-line medication for elderly osteoporosis patients, especially for postmenopausal women with osteoporosis. They provide antiresorptive effects by binding to the calcium hydroxyapatite crystals in bone, specifically combining with the bone surface where active bone remodeling occurs. Their effects include inhibiting osteoclast activity, reducing the risk of bone fractures in the spine, hip, and other parts of the skeleton, and accelerating osteoclast apoptosis. BPs can increase bone mineral density (BMD) and decrease fracture risk[2,3].

In a recent case, we observed not only an increase in the international normalized ratio (INR) of blood coagulation but also the occurrence of unexplained skin bruising after administering alendronate sodium to an elderly female patient with deep vein thrombosis (DVT) who was being treated with the anticoagulant warfarin. The adverse reaction we observed with alendronate sodium appears to be extremely uncommon, with minimal prior reporting in clinical studies. Although the patient had been anonymized, the study has received the approval of the ethics review board of Sisaket Hospital (REC COA No.013/2566), and written consent was obtained from the patient to publish the case report.

Case report

A 77-year-old female was seen in the outpatient department. Typical estimated glumerulo filtration rate (eGFR) measurements range from 50 to 70 mL/min/1.73m² (Figure 1). She was diagnosed with a FRAX score indicating a 10-year probability of 35% for a major osteoporotic fracture and 23% for a hip fracture. Her medical history included: thyrotoxicosis with diffuse goiter for over 10 years, avascular necrosis of the hip resulting in hip replacement 9 years ago, a prior hip fracture detected as a radiographic observation alone, and DVT for 8 years. The INR values had been within the target range consistently (Figure 2). Four days before her visit, she suffered a

Figure 1 Estimated glomerular filtration rate (eGFR) trends for the patient from 2014 to 2024

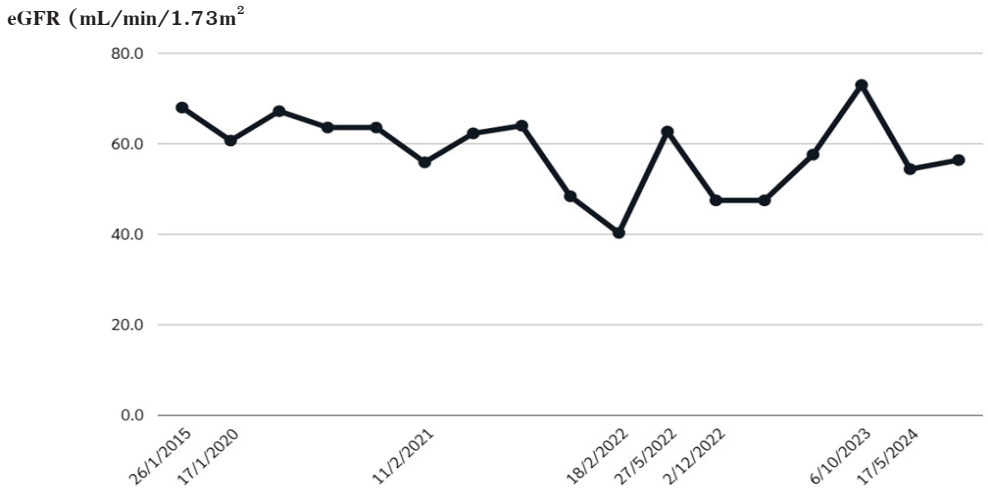
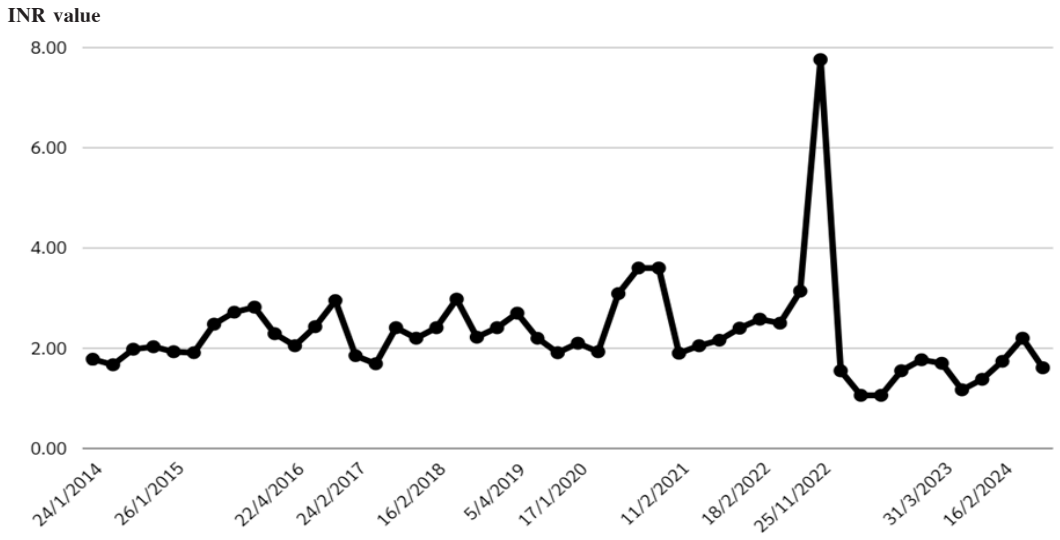


Figure 2 INR values of the case report from early 2014 to 2024



sudden fall and experienced pain near the front of the hip. From then on, she started taking an alendronate tablet (produced by Cadila Healthcare in India) at a dose of 70 mg per week. The patient's INR was 2.14 when she was discharged. Warfarin tablets (produced by Sriprasit Pharma) were prescribed to the patient at a dose of 2 mg once a day. Surprisingly, at the next follow-up after 1 month, the patient's serum INR had increased from 2.14 to 7.76. The oral administration of alendronate sodium tablets was stopped immediately, and the patient was given phytonadione 5 mg orally. Then the patient's serum INR fell to 1.55 within 7 days. Meanwhile, she experienced spontaneous ecchymoses on her skin. Fortunately, the ecchymoses stopped progressing by the seventh day. The patient denied taking any medications other than warfarin sodium and alendronate sodium tablets. She also denied any significant changes in her diet.

Discussion

Deep venous thrombosis (DVT) is a common complication after hip arthroplasty, with an incidence rate of 40-60%[4]. Therefore, long-term anticoagulation therapy using warfarin to maintain an INR of 2-3 has been a common method for these patients to prevent a serious condition in which a blood clot develops in a vein deep within the body. After a fall, an elderly female patient's estimated FRAX score would significantly change. The 10-year probability of major osteoporotic fracture is 35%, and for hip fracture, it is 23%.

This case study suggests that alendronate sodium may potentially enhance the anticoagulant properties of warfarin, leading to a significant increase in INR values—by over 50%—within a month of administration. Warfarin, which has a fundamental structure based on 4-hydroxycoumarin, is known for its high plasma protein binding capacity, exceeding 99% post-absorption. However, it is important to note that the effectiveness of warfarin's anticoagulant action can be significantly altered by various external factors, including concurrent medications and dietary choices[5].

The mechanism by which alendronate sodium may enhance the anticoagulant effect of warfarin could be

as follows: One potential explanation lies in their competitive interaction with plasma proteins. Alendronate sodium may displace warfarin from its protein-bound state, leading to an elevated concentration of unbound warfarin in the bloodstream. This increase in free warfarin could potentially amplify its anticoagulant action. This competitive binding mechanism offers a plausible hypothesis for the observed interaction between these two medications[6].

Alendronate sodium functions as a potent suppressor of osteoclast activity. Upon ingestion, it can cause a transient reduction in blood calcium levels. This temporary hypocalcemia can influence the blood coagulation cascade, resulting in an extended prothrombin time. Consequently, this leads to a short-term elevation in the INR. The impact on calcium levels and subsequent effects on coagulation provide another possible explanation for the observed interaction between alendronate and anticoagulant medications[7].

The effects of bisphosphonate drugs on bone tissue may reduce the amount of trabecular bone and bleeding. Inhibition of farnesyl pyrophosphate synthase enzyme and reduction of prenylation of various plasma proteins, including methylenetetrahydrofolate reductase, may lead to changes in blood coagulation processes[8]. Additionally, the liver processes warfarin using two key enzymes: cytochrome P450-2C9 (CYP2C9) and vitamin K epoxide reductase (VKORC1). Alendronate sodium and its breakdown products have the potential to interfere with these enzymes' activities. By inhibiting CYP2C9 and VKORC1, alendronate sodium may slow down the body's ability to metabolize warfarin[9].

Even though the elevated INR may return to lower levels within a short period after being stopped, and the spontaneous skin bruising that occurs after taking alendronate sodium may resolve, it is crucial to remain vigilant about the potential bleeding risks associated with this medication. Healthcare providers and patients alike should maintain a high level of awareness regarding the possibility of bleeding complications throughout the course of treatment with alendronate sodium, especially in patients with other risk factors for bleeding.

To reduce these potential risks for elderly female patients with DVT who are taking warfarin and need to take alendronate sodium as well, the following suggestions could be beneficial:

1. When initiating alendronate sodium treatment in patients who have well-controlled and stable INR levels, it is advisable to make appropriate reductions in their warfarin dosage.

2. It is crucial to closely monitor any fluctuations in INR values.

3. Patients should be observed for the development of any bruising or subcutaneous hemorrhages, as these could be indicators of increased bleeding risk.

4. Before administering alendronate sodium, the patient's INR should be rechecked. If the INR level is detected above the normal range or shows significant fluctuations, oral alendronate tablets should be withheld.

5. Opting for novel anticoagulants as a substitute for warfarin offers several benefits. These newer medications have the advantage of requiring less frequent INR monitoring, which can be more convenient for patients. Additionally, they tend to have a lower likelihood of interacting with other drugs, potentially reducing complications from medication interactions. This class of anticoagulants may provide

a more manageable treatment option for some patients. However, other factors must also be considered, such as cost, approved indications, and suitability for individual patients[10].

This report details a potential and possibly significant drug interaction between warfarin and bisphosphonates, which required a 40% to 50% reduction in warfarin dosage. The maximal effect of this interaction appears to be delayed, which is consistent with previous studies[11,12]. When beginning or ending bisphosphonate therapy for osteoporosis, we advise vigilant monitoring of INR levels and adjustment of warfarin dosages. To fully understand this drug interaction and establish proper guidelines for managing anticoagulation in patients using both medications, more extensive research involving larger patient groups is essential. Such studies would help validate our observations and offer much-needed direction on appropriate monitoring protocols for this specific patient population.

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การเพิ่มขึ้นของระดับ International Normalized Ratio (INR) และความเสี่ยงของการเกิดเลือดออกหลังได้รับ Alendronate Sodium ร่วมกับ Warfarin ในผู้ป่วยสูงอายุ: กรณีศึกษา

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บทคัดย่อ: แม้ว่ายาอะเลนโดรเนตโซเดียมจะนิยมใช้เพื่อลดความเสี่ยงของกระดูกหักในผู้สูงอายุ แต่มีความจำเป็นต้องตระหนักถึงผลข้างเคียงที่อาจเกิดขึ้น โดยเฉพาะในผู้ป่วยสูงอายุที่มีประวัติเกิดลิ่มเลือดอุดตันในหลอดเลือดดำ การพิจารณาใช้ยาควรประเมินความเสี่ยงเมื่อเทียบกับประโยชน์อย่างรอบคอบในกลุ่มประชากรนี้ มีรายงานกรณีศึกษาเป็นผู้ป่วยหญิงอายุ 77 ปีที่มีประวัติลิ่มเลือดอุดตันในหลอดเลือดดำส่วนลึก (deep vain thrombosis; DVT) ได้รับการรักษาด้วยยาวาร์ฟารินในระยะยาว มาพบแพทย์ที่แผนกผู้ป่วยนอกด้วยอาการเลือดออกใต้ผิวหนังโดยไม่ทราบสาเหตุ ซึ่งเดิมมีประวัติกระดูกสะโพกหัก ได้รับการวินิจฉัยโดยใช้คะแนน FRAX และได้รับการประเมินด้วยคะแนน FRAX ซึ่งพบว่ามีความเสี่ยงร้อยละ 35 ที่จะเกิดกระดูกหักจากภาวะกระดูกพรุนในระยะเวลา 10 ปี และเสี่ยงร้อยละ 23 สำหรับการเกิดกระดูกสะโพกหัก หลังจากนั้นแพทย์ได้สั่งใช้อะเลนโดรเนตโซเดียมขนาด 70 มก. สัปดาห์ละครั้ง ภายในระยะเวลาหนึ่งเดือนผู้ป่วยมีค่า INR เพิ่มขึ้นเป็น 7.76 และลดลงเหลือ 1.55 ในวันที่เจ็ดหลังจากหยุดยาวาร์ฟาริน แต่ยังคงมีจ้ำเลือดใต้ผิวหนัง ดังนั้น ในผู้ป่วยหญิงสูงอายุที่มีภาวะกระดูกพรุนร่วมกับประวัติ DVT ซึ่งได้รับยาวาร์ฟาริน การใช้ยาอะเลนโดรเนตโซเดียมร่วมด้วยอาจทำให้ค่า international normalized ratio (INR) เพิ่มขึ้นมากกว่าร้อยละ 50 และอาจนำไปสู่การเกิดจ้ำเลือดที่ผิวหนัง บุคลากรทางการแพทย์ควรใช้ความระมัดระวังในการสั่งยาอะเลนโดรเนตโซเดียมให้กับผู้สูงอายุที่กำลังใช้ยาวาร์ฟารินอยู่ สิ่งสำคัญคือต้องเฝ้าระวังความเสี่ยงที่เพิ่มขึ้นของภาวะแทรกซ้อนจากเลือดออกที่อาจเกิดขึ้นจากปฏิกิริยาระหว่างยานี้

คำสำคัญ: **ผู้ป่วยสูงอายุ; อะเลนโดรเนตโซเดียม; ลิ่มเลือดอุดตันในหลอดเลือดดำส่วนลึก; โรคกระดูกพรุน; วาร์ฟาริน; ลิ่มเลือดอุดตันในหลอดเลือดดำ**