


# Ischemic Stroke Symptoms After Warfarin Reversal With 4-Factor Prothrombin Complex Concentrate Case Report

Hospital Pharmacy  
2020, Vol. 55(1) 69–71  
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DOI: 10.1177/0018578718823739  
journals.sagepub.com/home/hpx  


Laura Carson<sup>1</sup> and John E. Price II<sup>1</sup>

## Abstract

**Objective:** An 83-year-old woman with atrial fibrillation on chronic warfarin therapy was given 4-factor prothrombin complex concentrate to reverse her warfarin for surgery. She had fallen off a step stool at home and fractured her left wrist which initially the surgeon was going to repair surgically. **Method:** The day after she received 4-factor prothrombin complex concentrate, she developed stroke-like symptoms, National Institutes of Health Stroke Scale (NIHSS) was 14, and met criteria for tissue plasminogen activator (tPA) administration. Tissue plasminogen activator was administered and she was transferred to the intensive care unit (ICU), per hospital protocol. **Results:** She remained in the ICU for 24 hours for follow-up and monitoring. Her warfarin was restarted and bridged with enoxaparin. She was not a candidate for antiplatelet therapy due to her history of a gastrointestinal (GI) bleed. **Conclusion:** At discharge, she had no residual effects from her stroke-like symptoms and a magnetic resonance imaging (MRI) of her brain was negative for an acute cerebrovascular accident (CVA).

## Keywords

adverse drug reactions, anticoagulants, blood products, critical care, CQI, medication safety, physician prescribing

## Introduction

With the introduction of anticoagulation reversal agents, the risk of losing hemostatic stability leading to uncontrollable bleeding and possible exsanguination has been reduced.<sup>1,2</sup> Of the possible causes of hemostatic instability, falls account for more than 700 000 hospitalizations and are one of the most common causes of traumatic brain injuries.<sup>3,4</sup> The benefit of prothrombin complex concentrate and idarucizumab comes with a recognized thromboembolic risk that must be weighed against the hemodynamic instability. During the clinical trials for prothrombin complex concentrate, patients with a recent history of a thromboembolism were not included. Prothrombin complex concentrate holds a black box warning for both fatal and nonfatal thromboembolic complications.<sup>5,6</sup> It is noted that providers are constrained by time and resources, which can further complicate traumatic injuries with delayed, missed, and incorrect diagnoses with subsequent treatments in up to 20% of cases.<sup>7,8</sup>

included atrial fibrillation, hyperlipidemia, hypertension, history of a transient ischemic attack, and history of a gastrointestinal (GI) bleed. For her atrial fibrillation, she was maintained on warfarin with a goal international normalized ratio (INR) of 2 to 3. Her family history does not include a history of stroke.

At admission to the ED, her INR was supratherapeutic at 3.41. Emergent surgery was planned for the open repair of her wrist and therefore her warfarin was reversed with 4-factor prothrombin complex concentrate, dose 1500 units intravenous (IV) once (patient weight: 63 kg, dose: 25 units/kg), as well as vitamin K 10 mg IV once. The follow-up INR 30 minutes after 4-factor prothrombin complex concentrate administration was 1.22.

After the INR was reversed, the general surgeon consulted the specialist, and the orthopedic surgeon decided to delay the surgery until the following morning. In addition, the specialist decided the best option would be a closed

## Case Presentation

An 83-year-old woman presented to the emergency department (ED) with a deformity to her left wrist after falling off a step stool at home. The patient's past medical history

<sup>1</sup>Stormont-Vail Healthcare, Topeka, KS, USA

### Corresponding Author:

John E. Price II, Stormont-Vail Healthcare, 1500 SW 10 Ave., Pharmacy ED Satellite, Topeka, KS 66604-1353, USA.  
Email: jiiprice@gmail.com

reduction of her left wrist instead of an open reduction. Propofol was used for sedation and the patient experienced no immediate adverse reactions. About 12 hours after surgery, the patient became lethargic and developed symptoms of a stroke, including slight left facial droop, confusion, and inappropriately answering questions. She had weakness in both lower extremities and her left upper extremity was not as strong as her right upper extremity. The hospitalist diagnosed the patient with a stroke. A stat computed tomography (CT) was ordered which did not reveal a bleed, National Institutes of Health Stroke Scale (NIHSS) was 14, and the patient was evaluated for tissue plasminogen activator (tPA). The patient's blood glucose was 107 mg/dL, blood pressure 157/72 mm Hg, INR 1.06, prothrombin time 14.2 seconds, and platelets  $170 \times 103/\mu\text{L}$ . It was determined the patient was a candidate for tPA and the bolus and drip were started promptly. As follow-up after tPA administration, a CT angiogram of her head and neck were done with normal results. The morning after receiving tPA, the patient was alert, able to speak, and without stroke symptoms. Later in the day, a magnetic resonance imaging of her brain and a magnetic resonance angiogram of her neck were done, which were both normal and did not show any signs of an acute or old infarct.

Twenty-four hours after tPA administration, her warfarin was restarted and she was bridged with enoxaparin therapy. She was not a candidate for antiplatelet therapy because she had a history of a GI bleed and therefore aspirin was not started. She had no residual stroke symptoms and was discharged to a skilled nursing facility.

## Discussion

In the ED, the principle goal is to identify and address the issue. However, without proper communication among the health care teams, one group may commence to resolve a benign problem by administration of unnecessary, expensive medications and a different, more specialized team can change the patient's care plan based on the situation. This patient's status was identified as a medical emergency, by the general surgeon, which would require prompt anticoagulation reversal and open surgery. After the INR had returned to baseline, the surgery was postponed by the specialist until the following day and proceeded with a closed reduction negating the need for reversal when the general surgeon contacted the specialist. The major difference between closed and open reduction is the external manipulation of bone fragments and surgical incision with dissection of the different tissues that would result in higher blood loss from blood vessels with need for reversal of anticoagulation. This delay and reversal would widen the hypercoagulable window increasing the risk of clot and ultimately of stroke. Restarting anticoagulation can be equally crucial to the prevention of thrombosis among high-risk patients.<sup>9,10</sup> For high-risk procedures and depending upon the drug, anticoagulation is

resumed with hemostasis and within 24 hours of surgery or tPA.<sup>10,11</sup> According to the Naranjo algorithm, the likelihood of 4-factor prothrombin complex concentrate causing the adverse drug reaction is probable with a total score of 7.<sup>12</sup> The patient did not receive a placebo, no serum factor levels were drawn, dose was completed prior to the reaction, and has no history of or need for further anticoagulation reversal. Future complications to consider are the surgeon(s) is not available, all operating rooms are full, reassessment of initial insult downgrades the trauma/severity, changes in type of surgery, delays for surgery, drug availability, and so on. To prevent future incidents, the ED satellite pharmacists, trained to provide reversal of the anticoagulant, should be involved in the communication of the surgical decision. The pharmacist can recommend for or against anticoagulation reversal depending on the patient's care plan.

## Conclusion

This patient's case illustrates the importance of understanding the risk and benefits of inducing a hypercoagulable state. With the reversal of the patient's anticoagulation therapy, the patient was subjected to an increased risk of stroke from restored cofactors in the presence of atrial fibrillation. The irregular contractions in the heart's left atrial appendage would lead to blood pooling which could form a clot and after dislodging, become emboli obstructing the arteries of the brain blood flow. Her CHADS-VAS score was 6, which correlated to a 9.7% risk of stroke per year. This case report adds to a limited body of literature available for giving tPA to patients who develop stroke-like symptoms shortly after warfarin reversal with 4-factor prothrombin complex concentrate.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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