Fixed dose 4-factor prothrombin complex concentrate for bleeding caused by long acting anticoagulant rodenticides

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Title Page

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(2) 4-factor PCC in LAAR overdose

Introduction

Medication-related poisonings are becoming an increasingly common occurrence in emergency departments (ED), accounting for over 400,000 ED visits across the United States in 2014 [1]. Of the over 400,000 ED visits in 2014, 1766 visits were related to prescription warfarin poisonings [2]. Warfarin was first discovered and marketed as a rodenticide due to its mechanism of action—inhibition of vitamin K epoxide reductase thereby depleting active vitamin k reserves, which in turn reduces the synthesis of active clotting factors and leading to hemorrhaging of rodents. However, in the 1960s some rodents became resistant to warfarin through gene transmission [3]. To combat resistance in rodents, scientists developed a "superwarfarin" or a long-acting anticoagulant rodenticide (LAAR) [4]. Previous reports describe hematemesis, hematuria, hematomas, epistaxis, melena, vaginal bleeding, and hemoptysis from alveolar hemorrhage leading to death in some cases of human ingestion [5-14]. Here, we report a case of life threatening bleeding caused by LAAR and treatment with fixed-dose 4-factor prothrombin complex concentrate (PCC).

Case

A 65-year-old male with a past medical history including hypertension, diverticulosis, partial nephrectomy after trauma presented to the ED complaining of gross hematuria. The patient reported using synthetic marijuana two days prior to arrival. On initial evaluation, the patient stated that he noticed blood in his urine yesterday along with bright red blood with a bowel movement the morning of his arrival to the ED. The patient also reported blood-tinged sputum, diffuse increasing headache, and severe abdominal pain. On initial exam the patient was afebrile, blood pressure 144/80 mmHg, respirations 18, and saturating 98% on room air. The patient's pulse was 131, but sinus rhythm. Other significant physical exam findings included the patient in mild distress and diffuse abdominal pain with voluntary guarding in all four quadrants. Initial labs showed a hemoglobin of 13.3 g/dL, platelets of 195 $x10^9$/L and an initial INR that was greater than 20. Computed tomography (CT) of the head did not show any intracranial hemorrhage; however, a CT of the chest showed pulmonary hemorrhage.

Given presentation of severe coagulopathy, increasing headache, severe abdominal pain with a history of abdominal surgeries, the patient was given IV vitamin K 10 mg, Kcentra® 2000 units, and 4 units fresh frozen plasma. The patient was admitted to the intensive care unit for close monitoring. His INR dropped from over 20 to 1.42, thirty minutes after the 15-minute fixed dose PCC infusion. Hemoglobin never dropped to a level requiring transfusion and the heart rate did improve with pain control and fluids. The anticoagulant poisoning panel was positive for difenacoum and brodifacoum.

Discussion

Our case describes a patient presenting with hematuria, hematochezia and hemoptysis, in the setting of pulmonary hemorrhage, from an overdose of synthetic marijuana laced with LAAR. In 2013, Kcentra® was approved for the urgent reversal of acquired coagulation deficiency induced by vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with acute major bleeding. Kcentra® contains heparin, Factors II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin. Its labeling indicates weight-based dosing centered on pre-treatment INR results, with a max dose of 50 units/kg (not to exceed 5000 units) for a pre-treatment INR >6 [15]. Previous case reports have demonstrated the success of using PCC in the management of acute bleeding caused by LAAR using weight-based dosing between 25 and 50 units/kg. [16,17].

Fixed dose PCC was first introduced by Yasaka et al. in 2005 [18] and repeated studies by different investigators have shown similar efficacy of INR reversal, in patients on warfarin, when comparing weight-based and fixed-dose strategies [19-25]. Risk of thrombosis increases with corresponding dose increases as well, leading one to consider an alternate dosing strategy that alleviates this risk.

Although a fixed dose strategy has not been reported for LAAR overdoses until now, we used results from patients in previous studies, about PCC for warfarin reversal, to help determine the optimal dose of 2000 units for this case. In a 2015 study from Klein et al., a retrospective chart review reveled 39 patients on chronic warfarin therapy who received a fixed dose of 1500 units of Kcentra® for urgent reversal of their INR. Post hoc analysis revealed that 11 patients failed to have their INRs fully reversed to less than 1.5. Of these patients, 27.3% had an initial INR >10 and their median weight were 95.3kg—both variables showing

trends toward an increased risk of treatment failure [22]. Our patient had an acute exposure to a VKA (i.e. LAAR) and had an initial INR reported as "INR > 20" along with alveolar hemorrhage. This case report further augments the findings from Klein et al. demonstrating that a fixed-dose of 2000 units of 4-factor PCC may be the optimal dose for patients with an INR over 10, even in the setting of a LAAR poisoning. This dose may lead to a rapid reversal of the INR to less than 1.5, while avoiding any excessive increased risk of thrombosis in most patients. The optimal dose of Kcentra® is not yet known because the Food and Drug Administration did not require dose-finding studies as part of the approval of the drug [26]. The lower total dose can help lead to decreased thromboembolic complications for the patient as well as a lower cost, while maintaining efficacy. This case highlights the need to consider the use of PCC in the setting of life threatening bleeding caused by LAAR poisoning. This case further emphasizes the value of a fixed-dose approach of PCCs, which can be used in chronic or acute exposure to vitamin K antagonists.

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