

## CASE REPORT

# A Pragmatic Approach to Superwarfarin Intoxication in a Resource Constraint Setting; a Case Report

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## Abstract

**Introduction:** Superwarfarins are highly lethal rodenticides which are much more potent than the warfarin owing to various structural changes in the parent compound that confers high half-life and increase affinity to vitamin K epoxide.

**Case Presentation:** We report a case of a 19 years old female who presented bleeding prolonged PT and APTT. Factor assay showed significantly lower levels vitamin K dependent coagulation factors. She was given conventional doses of FFP and vitamin K for two consecutive days, although she responded clinically but her coagulation profile failed to show any improvement. Hence superwarfarin poisoning was considered. Based on this assumption patient was cross questioned repeatedly, and subsequently she admitted that she had ingested rodenticide with the suicidal intent. Hence she was given higher doses of vitamin K and FFP for several days after which her PT and APTT shortened significantly.

**Discussion:** Superwarfarin toxicity clinically presents with bleeding and deranged coagulation profile. Differentiating it from other causes is challenging but very crucial, as it does not responds to usual doses of vitamin K and plasma.

**Conclusion:** This case highlights the importance of maintaining high index of suspicion of superwarfarin toxicity in coagulopathy of unknown etiology that fails to respond to conventional doses of treatment. Detailed history with interrogation of leading questions in such cases is of integral importance.

**Keywords:** FFP; Superwarfarin; Toxicity

How to cite this article: Ali M, Mansouri H, Asad Ali S. A Pragmatic Approach to Superwarfarin Intoxication in a Resource Constraint Setting; a Case Report. *Asia Pac J Med Toxicol* 2018;7(2):49-51.

## INTRODUCTION

Vitamin K antagonists are commonly prescribed oral anticoagulants in clinical practice for

thromboprophylaxis and management of thromboembolism complications (1). However, they are also routinely used for pest control worldwide (2). These rodenticides called superwarfarin, were introduced first in 1970 preceding emerging resistance to warfarin by rodents (3). These compounds act by blocking vitamin K epoxide reductase enzyme (4) and in contrast to warfarin they have increased half-lives and increased affinity for the primary enzyme (5). Hence they are several times more potent and some of them have half-life which may vary from 20-62 days (6). Brodifacoum, most commonly used superwarfarin is a 4-hydroxy coumarin with a 4-bromo side chain, possess its own hazards; when kept at home for pest control as it may result in accidental or intentional ingestion with substantial outcomes in terms of morbidity and mortality (7).

Reported cases of superwarfarin intoxication are usually accidental and often seen in children; however it has been used for suicide, homicide and surreptitious administrations as well (8). Some accidental cases with per-cutaneous

absorption have also been reported and possess a risk if protective measures like gloves are not worn while applying rodenticides (9). If ingested, clinical spectrum of presentation can range from as minor as mucosal bleeding to life threatening events such as intra-cerebral bleeding (9-11). It is an important differential which should be kept in mind in any patient who presents with vitamin K dependent coagulopathy (12). We describe a case of young female who ingested rodenticide with suicidal intent and presented with consequential bleeding symptoms.

## CASE HISTORY

A 19-year old female from rural area was referred to Emergency by a local GP with one day history of profuse gum bleed, epistaxis and hematuria; which was sudden in onset. Her family and past history of significant bleeding was unremarkable. There was no fever, abdominal pain, vomiting or diarrhea. General physical examination revealed small bruises on arms and thighs and a soaked nasal packing along with active gum bleed. Rest of the systemic examination was unremarkable. Drug history provided by patient was also negative. Work up of laboratory investigation was sent. Complete blood count showed hemoglobin (Hb) of 10.2 gm/dL,

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Received 06 April 2018, Accepted 13 May 2018

hematocrit 35.1%, mean corpuscular volume 87.5 fL, mean corpuscular hemoglobin 28.4 pg, white cell count was  $7.0 \times 10^9/L$  and platelet count of  $179 \times 10^9/L$ . Peripheral film revealed anisocytosis and normochromic red cell. White blood cell and platelets were normal on film. Initial coagulation workup showed prothrombin time (PT) of greater than 120 seconds and activated partial prothrombin time (APTT) of 129 seconds. Haematology consult was sought. Mixing studies showed correction of both PT and APTT with normal plasma which ruled out the presence of coagulation factor inhibitors. Her fibrinogen and d-dimer levels were within normal limits (280mg/dL and 0.1 mg/L respectively) ruling out disseminated intravascular coagulation (DIC). Factor Assay was performed which exhibited low levels of factor II (2.5%), VII (0.6%), IX (0.9%) and X (0.1%).

The biochemical work-up displayed normal liver function tests and since test for vitamin K epoxide reductase is not available in our set-up, it was taken as indirect evidence of normal hepatic synthetic function and its ability to metabolize vitamin K. Renal profile was also within normal limits. Based on above mentioned findings diagnosis of vitamin K-dependent clotting factor deficiency was considered. She was initially given 4 units of Fresh frozen plasma (FFP) (at 15ml/kg) along with 10mg of intravenous vitamin K to control her bleeding. The same dose was repeated the next day which controlled her bleeding symptoms; however her coagulation profile remained deranged despite of repeated plasma infusions. Keeping in mind the overall results and absence of response to usual doses of plasma and vitamin K, the possibility of vitamin K inhibitors was considered. As precise tests were not available, patient and her family were asked leading questions about ingestion of warfarin like drugs. Although denied initially, but later on persistent re-questioning the patient admitted ingestion of rodenticides with suicidal intent due to some family matters.

Subsequent to her confession, she was given twice daily infusion of FFP along with 100 mg parenteral vitamin K and after three days of her hospital stay. Her PT shortened to 42.3 seconds, INR 3.9 and APTT 64 sec. There was no active bleeding during hospital stay. Psychiatric evaluation was also taken. After observation of 72 hours, she was discharged on oral vitamin K of 40mg twice daily. Acknowledging the long half-life of superwarfarin she was counseled to report back to emergency in case of bleeding and follow in clinic after 1 week. Vitamin K was tapered off over the course of 3 months on her visits in clinic.

## DISCUSSION

Vitamin K dependent coagulation factors (II, VII, IX, X, protein C and protein S) are synthesized in liver in an inactive state. Their activation requires presence of carboxylase enzyme which converts amino-terminus glutamic acid to gamma-carboxyglutamic acid. This gamma carboxylation is dependent on the active form of vitamin K which during this process gets converted to an inactive form known as vitamin K epoxide. The re-conversion of inactive vitamin K epoxide to active vitamin K is done through the action of 2,3 vitamin K epoxide reductase. Warfarin and superwarfarin blocks the action of 2,3 vitamin K epoxide reductase, inhibiting the

conversion of vitamin K epoxide into its active form and causing vitamin K dependent clotting factor deficiency.

In places like ours where it is not possible to measure the toxin levels, a good drug history is all one can rely upon. Psychiatric evaluation plays a very important role in the evaluation of nature of ingestion and ruling out self-administration as these poisons are easily accessible at homes and stores. Involvement of law enforcing agencies must be considered if homicidal poisoning is suspected (11).

This case emphasizes to consider superwarfarin toxicity in a patient who presents with active bleeding of unknown etiology with profound and prolonged elevation of PT and APTT along with depletion of vitamin K related coagulation factors; not responding to standard doses of FFP and vitamin K. Although, for super warfarin intoxication the standard of practice is confirmation by affirmative history followed by chemical analyses of urine and serum samples (13); this approach is practical in a setting where levels of brodifacoum are not available. An affirmative history of rodenticide ingestion by inquiring leading question is of prime importance in such cases. It should be noted that hematuria is the most common clinical manifestation of superwarfarin intoxication.

In hospital settings, PT can be used to monitor the response of the patient to treatment; where facility of measuring serum level of brodifacoum is not available. Treatment options range from FFPs, intravenous/oral vitamin K depending upon the nature or risk of bleeding and patients usually require several months of vitamin K supplementation either in the oral or parenteral form (11, 14, 15).

Zupancić-Salek S et al considered giving recombinant FVII as a safe and effective option for acute bleeding secondary to superwarfarin toxicity (10). Haesloop O et al suggests that prothrombin complex concentrates can also be very useful for the risk for serious bleeds considering the severe and persistent coagulopathy (16). Though for the developing countries it still remains as a costly option and the availability of the product is also questionable sometimes.

## CONCLUSION

This case highlights the importance to consider rodenticide exposure in an otherwise normal patient who presents with vitamin K dependant coagulopathy of unknown etiology. Exposure to rodenticides must be inquired while taking history as the management requires prolonged and profound doses of vitamin K. A good history and routine investigations pertinent to coagulopathy are important measures to reach the diagnosis particularly in our setting where commercial tests to measure levels of brodifacoum and vitamin K epoxide reductase are not reachable.

**Conflict of interest:** None to be declared.

**Funding and support:** None.

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