

Exposure to Superwarfarins in Rodenticides: Development of Prolonged Bleeding Defect in an Adolescent

Kemirici Zehirlerindeki Superwarfarine Maruziyet: Bir Ergende Uzun Süreli Kanama Kusuru Gelişmesi

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This case report was presented as a poster in European Association for Haemophilia and Allied Disorders (EAHAD) 2019, 6-8 February 2019, Prague, Czech Republic.

ABSTRACT Superwarfarins which are long-acting, potent anticoagulants are used as rodenticides. Difenacoum is a second generation superwarfarin that inhibits the vitamin K-dependent steps in the synthesis of clotting factors II, VII, IX and X. A 15-year-old adolescent boy presented with persistent nose and gum bleeding. In past medical history there was no event suggesting coagulation defect. Coagulation assays suggested vitamin K dependent factor deficiency. Treatment was started with fresh frozen plasma and 20 mg intravenous vitamin K (phytomenadion). High dose phytomenadion peroral in three divided doses normalized coagulation tests and controlled gum and nose bleeding. When exposure to rodenticide was questioned, such an exposure by inhalation and skin was reported during cleaning the cellar. Duration of the vitamin K dependency was two years. Exposure to superwarfarin containing rodenticides causes severe long-lasting bleeding deficiency. These products must have labels warning about dangers of exposure and they must be sold in pharmacies.

Keywords: Rodenticides; epistaxis;
vitamin K deficiency bleeding

ÖZET Uzun etkili, güçlü antikoagulanlar olan süperwarfarinler kemirici zehiri olarak kullanılırlar. Difenacoum, pıhtılaşma faktörleri II, VII, IX ve X'un sentezindeki vitamin K'ya bağımlı olan basamakları inhibe eden ikinci nesil bir superwarfarindir. On beş yaşında erkek, ergen hasta sebat eden burun ve diş eti kanaması ile getirildi. Tıbbi özgeçmişinde pıhtılaşma kusuru düşündürülecek özellik yoktu. Pıhtılaşma testleri vitamin K'ya bağımlı faktörlerin eksikliğini göstermekteydi. Tedavi taze donmuş plazma ve damar yoluyla 20 mg K vitamini (phytomenadion) ile başlatıldı. Yüksek doz phytomenadion ağız yoluyla günde üç doz halinde kullanılarak pıhtılaşma testleri normale döndü, diş eti ve burun kanaması kontrol altına alındı. Kemirici zehirine maruziyet sorgulandığında fare zehiri atılmış tavan arasını temizleme sırasında cilt ve solunum yoluyla böyle bir maruziyet olduğu anlaşıldı. Vitamin K'ya bağımlılık iki yıl sürdü. Süperwarfarin içeren kemirici zehirlerine maruziyet, ciddi, uzun süreli kanama kusuru yaratır. Bu ürünlerde maruziyetin tehlikeleri konusunda uyarıcı etiketler olmalıdır ve ürünler eczanelerde satılmalıdır.

Anahtar Kelimeler: Rodentisitler; epistaksis;
K vitamini eksikliğine bağlı kanama

Superwarfarins have been in use by mid-1970 throughout the world as anticoagulant rodenticides and pesticides in agricultural and urban rodent control. These anticoagulants include second generation 4-hydroxycoumarins like brodifacoum (BDF) and difenacoum (DFC).^{1,2} They inhibit the synthesis of clotting factors II, VII, IX and X. Superwarfarins were synthesized after development of warfarin re-

sistance among rat populations.² They are more potent than warfarin and they have prolonged anticoagulant effect.³ They have greater affinity for vitamin K(1)-2,3-epoxide reductase, they break this vitamin, accumulate in the liver, have long biological half-lives due to high lipid solubility and enterohepatic circulation. In children and adolescents, exposure may be accidental, secondary (by rat feces), as a re-

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Peer review under responsibility of Türkiye Klinikleri Journal of Pediatrics.

Received: 08 Dec 2019

Received in revised form: 02 Mar 2020

Accepted: 15 Mar 2020

Available online: 20 Apt 2020

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sult of suicide attempt or due to Munchausen syndrome by proxy. Toxicity is by oral, skin and respiratory exposure and exposure causes mucosal bleeding (gingiva, nose, rectum, upper gastrointestinal, vaginal), widespread bruising, haematomas, haematuria with flank pain, haemoperitoneum, bleeding into any organ including brain, anemia, hypovolemia and even coma.¹ Because of the inhibition of the vitamin K-dependent anticoagulant proteins (protein C and protein S), patients also can present with thrombosis as a less common presentation.⁴ Superwarfarin poisoning can lead to life-threatening complications.

In this article, we describe an adolescent who presented with severe mucosal hemorrhage after accidental exposure to rodenticide containing difenacoum and required vitamin K prophylaxis for two years.

CASE REPORT

A fifteen-year-old adolescent boy presented with nose and gum bleeding beginning three weeks ago. Otherwise he seemed quite healthy. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged. He had history of circumcision, an operation for finger contracture and tooth extraction without any bleeding complication. Also there was no bleeding history in the family. Full blood count, liver and kidney functions were within normal limits. PT 52.6 sec, INR 6.1, aPTT 44.3 sec, trombin time 15 sec, fibrinogen 224 mg/dl, in vitro bleeding time (collagen/ADP aggregation 92 sec, collagen/epinephrine aggregation 153 sec) and mixing tests were within normal limits. Laboratory results suggested vitamin K dependent factor deficiency (FV 94%, FVII 3%, FVIII 107%, vWF Ag 22%, FIX 23%, FX 18.7%, protein C 11%, protein S 14%, antithrombin 107%). After 20 mg intravenous Konakion® (phytomenadione) and 10 ml/kg fresh frozen plasma infusion, there was temporary improvement in coagulation tests. Exposure to rodenticides was suspected. Family remembered that the boy cleaned the cellar and garret and exposed to rodenticide three weeks ago. Rodenticide was poured to the cellar about one year ago. They were unaware of toxic potential and their son performed cleaning without protective mask,

gloves and suit, and exposed to rodenticide by inhalation and skin. Exposed rodenticide contained difenacoum (Bad Cat pelet®, Licence Unichem/ Slovenia, manufacturer Dual Chemistry, İstanbul).

Konakion® ampuls 60 mg/day in three divided doses were used orally for three weeks. This dose maintained normal INR. But then he presented with nose bleeding and INR increased to five-fold. Vitamin K dose was escalated to 90 mg/day in three divided doses and he required another six weeks of vitamin K. Vitamin K dose was decreased gradually with PT and aPTT monitorization. When patient withdraw Konakion ampuls due to poor compliance to treatment, nose bleed recurred. Duration of coagulation defect was about two years.

DISCUSSION

An adolescent boy presenting with mucosal bleeding and abnormalities in coagulation tests in the absence of bleeding history even during surgical interventions, can be challenging to the hematologists. Medical history excluded any congenital coagulation defect. The boy seemed quite healthy and there was no abnormalities in other functions of the liver. Patient and family reported no accidental ingestion of any drug or attempt for suicide. There was no suspicion for Munchausen syndrome or drug abuse.⁵ There was no history of chronic diarrhea that will cause vitamin K deficiency. Rodenticide exposure was questioned and family remembered cleaning the cellar and pouring rodenticide to the cellar about one year ago. Unfortunately superwarfarins are persistent in the environment. Not only rodents but even other animals feeding with contaminated grass and humans exposed to rodenticide contaminated rat feces may be affected. American Association of Poison Control Centers reported 10413 superwarfarin exposures annually with 2750 patients treated. In epidemiologic data of 1987-2012, nearly 90% of the exposures were among children. Fortunately only 2% of the exposures result in morbidity and mortality.⁶

When both PT and aPTT are prolonged, diagnosis must be confirmed by measuring vitamin K dependent factors such as prothrombin, factor VII, factor IX, factor X, as well as antithrombotic protein

C and protein S. Acquired inhibitors, although rare in young age must be excluded by mixing studies. Disseminated intravascular coagulation (DIC) screening (fibrinogen, D-dimer, complete blood count) must be performed. But there was no infection, trauma or other factors that will trigger DIC. To control and prevent bleeding, vitamin K replacement is required. Optimal daily dose is found with PT and aPTT monitoring and dose escalation. Fresh frozen plasma 15 ml per kg body weight must be used in the first day to control hemorrhage. In the absence of bleeding, a prolonged PT is not an indication for fresh frozen plasma infusion.⁷

In rats, after a single oral dose of 1.2 mg/kg difenacoum, 1.5% of the dose was found in the rat liver after 24 hours. There was a biphasic elimination. During the first phase of elimination, half-life was 3 days and slower phase was 118 days. Oral lethal dose 50 for DFC was 1.8 mg/kg.⁸ If patients present within one hour after ingestion of >1 mg superwarfarin, activated charcoal administration is recommended.

There is no standardized treatment regimen after difenacoum exposure but fresh frozen plasma and vitamin K should be started at once. Daily vitamin K treatment is required for several months due to long half-life. In animal models half-life in plasma and tissue (liver) was 20.4 and 61.8 days respectively.⁹ Due to fat solubility, hemostatic failure can proceed beyond a year after ingestion.¹⁰

There is no clear consensus on the starting dose for vitamin K; reported dosing strategies ranged from 0.1 to 0.3 mg per kg body weight daily, divided into 3 or 4 doses. In the maintenance treatment, vitamin K is administered 15 to 600 mg daily and the most common dosage was 100 mg daily.⁶ Vitamin K treatment can not be stopped until PT is in normal range without any treatment. This period may extend from 3 months to more than a year.⁷ Early tapering or discontinuation of vitamin K can lead to reoccurrence of bleeding symptoms. In the present patient, initial daily dose was 20 mg phytomenadione intravenously then dose was increased to 60 mg daily in three divided dose. After recurrence of nose bleeding oral dose was increased to 90 mg daily. The patient was followed as outpatient after the first week. Vitamin

K tablet was not available in the country; ampuls were administered by oral route.

Oral, skin and respiratory exposure to superwarfarin containing rodenticides must be avoided. Complete suit protection and adequate ventilation is necessary for clean-up procedures.¹¹ Dead rodents should be burned. After skin exposure, all areas should be thoroughly washed with soap and water.¹² In Turkey, these rodenticides are easily available for purchase and they are quite cheap. In 2008, the Environment Protection Agency (EPA) concluded that superwarfarin should be restricted to use by certified pesticide applicators only and be off-limits to the consumer market. Regulations were passed to limit children's exposure and bait products be limited to bait stations. According to EPA regulations, bait formulation should not contain more than 0.005% superwarfarin (50 mg/kg).¹³

As a conclusion, exposure to superwarfarins like difenacoum causes severe long-lasting coagulation defect. Maintenance treatment with vitamin K is essential for several months. Health authorities must alarm the public for potential dangers of rodenticides. They must not be easily available. They must be sold in pharmacies and warning labels and clear documents about avoidance of exposure must be available. Bait formulations should be controlled by government authorities before release to the market. Bait stations should be used to prevent reach of children and domestic animals. Rodenticide contamination to water supplies and food should be prevented.

Written informed consent of the family was obtained for publication of the case report.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Sema Aylan Gelen, Nazan Sarper; **Design:** Emine Zengin; **Control/Supervision:** Nazan Sarper; **Data Collection and/or Processing:** Sema Aylan Gelen, Emine Zengin, Nazan

Sarper; Analysis and/or Interpretation: Sema Aylan Gelen, Nazan Sarper; **Literature Review:** Sema Aylan Gelen; **Writing the Article:** Nazan Sarper; **Critical Review:** Nazan Sarper; **Materials:** Emine Zengin.

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