A Case of Superwarfarin Intoxication without a Definitive History of Brodifacoum Exposure

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Superwarfarin intoxications that induce profound and prolonged coagulopathy are being increasingly reported, to such an extent that it is becoming a comparatively common intoxication. However, there have been few reported cases of superwarfarin intoxication with an inadvertent cause or an unknown origin. A 58-year-old man with recurrent painless hematuria was found to have an acquired deficiency of vitamin K dependent clotting factors, and a large amount of vitamin K was required to correct the coagulopathy. He had no history of warfarin use or any exposure to rodenticides, but brodifacoum was detected in his serum. It is important for physicians to be aware that significant coagulopathy can occur secondary to superwarfarin intoxication, without any known exposure to substances that might induce this. ***(Korean J Hematol 2009;44:53-57.)***

Key Words: Brodifacoum, Coagulopathy, Superwarfarin, Vitamin K

INTRODUCTION

Brodifacoum is a second-generation anticoagulant rodenticide (one of the superwarfarins), which acts like warfarin by inhibiting the gamma carboxylation of vitamin K dependent clotting factors by inhibiting vitamin K 2, 3-epoxide reductase. This inhibition leads to a coagulopathy, which manifests as increased prothrombin time (PT) and activated partial thromboplastin time (aPTT), and deficiencies of vitamin K dependent clotting factors (factor II, VII, IX, X, protein C, protein S, antithrombin III). Superwarfarin rodenticides like brodifacoum are 100-times more potent and have longer serum and tissue half-lives (weeks to months) than warfarin.[1-4)]

The incidence of superwarfarin ingestion has increased over the past several years.[5,6)] The vast majority of superwarfarin intoxications occur in the pediatric population (over 90%), and the intoxications have rarely been reported in adults, except the cases of deliberate ingestion. The main routes of superwarfarin exposure are via oral ingestion (whether intentional or incidental) and inhalation. However, absorption through the skin can occur, and a number of cases with an unknown origin have been encountered.[6-9)] Here, we report a case of brodifacoum intoxication with no identified route, which was confirmed by the detection of brodifacoum in serum.

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CASE REPORT

A 58-year-old man presented with a 3-months history of recurrent painless gross hematuria. He had no relevant previous history of renal disease or bleeding episodes, and no family history of bleeding disorders or malabsorption syndromes. He denied any medications, such as, anticoagulants or illicit drugs, and had no psychiatric problem or suicidal tendency. He had been admitted to the community hospital on July 12th, 2007, where a PT of 156 seconds [international normalized ratio (INR) of 32.3] and an aPTT of 102 seconds were found. Other laboratory test results, including complete blood cell count (CBC) and liver function test were normal. An intravenous pyelography and a cystoscopic examination revealed no abnormalities. Parenteral vitamin K and fresh frozen plasma (FFP) were given and the hematuria was ceased. The patient was discharged on the 9th hospital day (treatment details and laboratory test results are shown in Fig. 1).

On October 21st, 2007, he returned to the outpatient clinic of the community hospital because of the reappearance of gross hematuria for two days. Laboratory tests at that time showed marked PT (165 seconds; INR＞35.19) and aPTT (107 seconds) prolongations and he was transferred to our hospital. Physical examinations revealed numerous ecchymoses in his extremities, and abnormal bleeding at venous puncture sites. Initial laboratory tests at our hospital produced the following results: white blood cell count $6.83\times10^9/\mu$l, hemoglobin 11.8g/dL, platelets $234\times10^9/\mu$l, and PT and aPTT levels off the high end of the scale. Bleeding time was normal (2minutes), and a peripheral blood smear showed no specific findings. Tests for fibrin degradation products (FDP) and D-dimer were negative. Liver and renal function tests showed no abnormalities. Levels of coagulation factor were as follows: factor II 10% of normal; V 99%; VII 10%; VIII 198.3%; IX 7%; X 10%; · 70%; and · 100%. A mixing test was performed, and PT and aPTT were corrected.

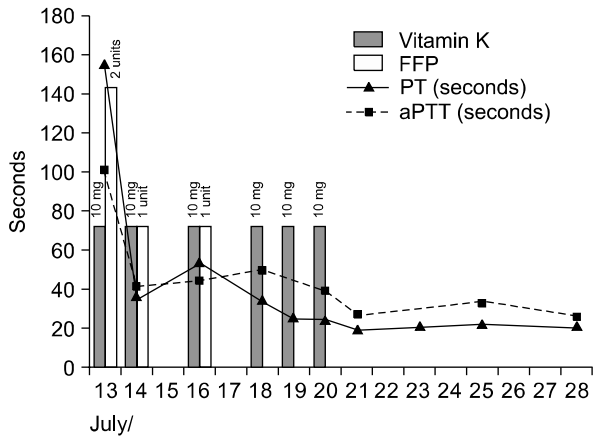

Fig. 1. The details of the treatment and the laboratory tests results obtained at the community hospital. After treatment with parenteral vitamin K and fresh frozen plasma (FFP), prothrombin time (PT) and activated partial thromboplastin time (aPTT) were shortened.

The patient was treated empirically with 20mg of intravenous vitamin K and 15 units of FFP from the 2nd to the 9th hospital days. At that time, hematuria was absent, and laboratory tests were improved (PT 20.9 seconds (INR 1.76), aPTT 31.4 seconds). On the 14th hospital day, PT and aPTT findings were prolonged again (PT 36 seconds (INR 3.05), aPTT 46.5 seconds), and coagulation factor assay results were; factor II 13%, V 85%, VII 24%, VIII 167.8%, IX 35%, X 13%, XL 71%, and XII 105%. Specimens of blood were sent to a reference laboratory to check the serum levels of vitamin K, warfarin, brodifacoum, and difenacoum, and at the same time, we started oral vitamin K (5mg once daily). After the 20th hospital day, PT and aPTT were much improved (18.5 and 29.5 seconds, respectively), and he was discharged (details of treatment and laboratory test results at our hospital are shown in Fig. 2). After discharge, the patient continued to take oral vitamin K (5mg daily) and PT and aPTT were maintained within the normal range. At his last follow-up visit at 2 months after discharge, he was well and had experienced no further bleeding or

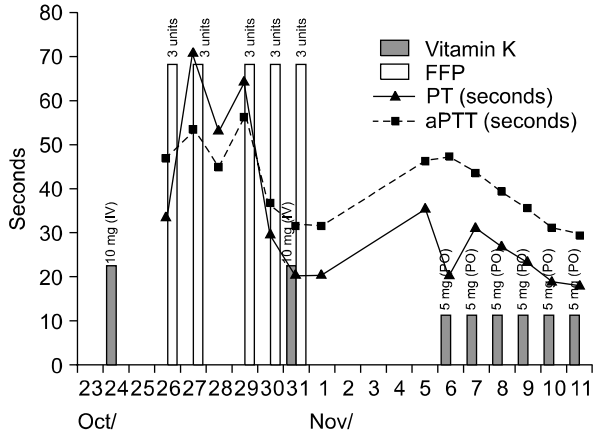

Fig. 2. The details of the treatment and the laboratory tests results at our hospital. Note that prothrombin time (PT) and activated partial thromboplastin time (aPTT) were off-scale from October 23 to 25. However, after the administration of intravenous vitamin K and multiple units of fresh frozen plasma (FFP), PT and aPTT were shortened. Furthermore, PT and aPTT were prolonged after these treatments were stopped.

clotting problems.

After all, his serum vitamin K1 and K2 levels were 0.26ng/mL (normal 0.15～1.25ng/mL) and <0.05ng/mL (normal≤0.10ng/mL), respectively (this specimen was obtained after administrating 15 units of FFP and 20mg of intravenous vitamin K). Significantly, his serum brodifacoum level was 48ng/mL (a positive result for brodifacoum poisoning), whereas findings for warfarin and difenacoum were negative. Accordingly, he was diagnosed to be suffering from a vitamin K-dependent coagulation factor deficiency due to accidental exposure to brodifacoum.

DISCUSSION

In the described case, coagulopathy was acquired rather than congenital, given the absence of a personal and familial history of bleeding diathesis. Because laboratory data showed PT and aPTT prolongation corrected in mixing test, normal CBC (including a peripheral blood examination), normal blood chemistry, and the absence of FDP and D-dimer, the following conditions could be excluded; liver disease, disseminated intravascular coagulopathy, and the presence of coagulation factor inhibitor. Coagulation factor assays performed during the diagnostic period showed low levels of vitamin K dependent coagulation factors and normal values for non-vitamin K dependent coagulation factors, indicating an acquired deficiency of vitamin K dependent coagulation factors. Treatment with 15 units of FFP and 20mg of intravenous vitamin K could stop bleeding and shorten PT and aPTT, although could not be normalized. Recurrent hematuria after stopping treatment and a persistent vitamin K dependant coagulation factor deficiency suggest the presence of a long-lasting vitamin K inhibitor. The patient had not ingested warfarin or any other medication, and denied exposure to superwarfarin, but his serum brodifacoum finding was positive, and thus, he was diagnosed to have a deficiency of vitamin K dependent coagulation factors due to accidental exposure to brodifacoum. Superwarfarin intoxication via oral ingestion is well known and its incidence is increasing, but how serum infiltration occurs in patients without a history of oral ingestion is unclear, although some cases have been reported in which poisoning occurred by inhalation or direct skin contact.[10,11] The patient had worked in a landfill for five years, in a recycling center for three years, and currently works as a ragman. Thus, we suspect that he was exposed to superwarfarin at work, and it had been absorbed through skin into the systemic circulation.

Diagnosing a patient with superwarfarin-induced coagulopathy can be difficult. There may not be a history of superwarfarin exposure, and the initial clinical presentation is not always obvious. In a case with a definite history of superwarfarin ingestion, PT and aPTT are the best screening tests. However, in patients presenting with a vitamin K dependent coagulation factor deficiency of unknown cause, vitamin K epoxide/vitamin K ratio and serum superwarfarin (brodifacoum, difenacoum, etc.) tests can confirm superwarfarin intoxication. On the other hand, if superwarfarin

intoxication is suspected, and these tests are not readily available, high-dose vitamin K could be administered empirically.

Various means of treating superwarfain toxicity are described in the literature,[12,13] but no consensus has been reached other than that actions to restore normal PT, aPTT, and coagulation factor levels. Patients with active life-threatening bleeding should be administered FFP, coagulation factor concentrates and vitamin K, whereas patients not demonstrating active bleeding but with prolonged PT and aPTT should be administered high dose vitamin K to normalize coagulopathies. Because superwarfarin is 100-times more potent and has a much longer half-life than warfarin, the duration of the coagulopathy is more extended and treatment is more protracted, and requires much higher doses of vitamin K. Treatment periods and vitamin K doses required vary, due to; the different amount of superwarfarin consumed, deliberate or unintentional noncompliance with vitamin K therapy, continued exposure to superwarfarin, and different superwarfarin metabolic rates. Vitamin K doses ranging between 15mg/day and 800mg/day have been reported, although in some reports showed continuous coagulopathy after being administration of 15～50mg/day of vitamin K.[14,15] In our patient, the coagulopathy responded to 5mg/day of vitamin K for a month. Treatment is usually necessary for many months, and vitamin K dosages should target the maintenance of a normal PT. It should be noted that due to the risk of an anaphylactoid reaction, intravenous administration of vitamin K is commonly avoided; the oral, intramuscular and subcutaneous routes are preferred.

In conclusion, this case report showed a possibility for the superwarfarin intoxication causing significant coagulopathy, even when the cause of exposure is unknown. When a patient presents with hemorrhagic coagulopathy and prolonged PT and aPTT values of unknown cause, testing for superwarfarin intoxication should be considered. Awareness and suspicion for this problem and the prompt initiation of high dose vitamin K therapy can be life-saving in cases of superwarfarin intoxication.

요 약

브로디파코움은 정도가 심하고 장기간 지속되는 응고장애를 유발하는 2세대 항응고 살서제이다. 살서제 중독은 비교적 흔한 중독으로 알려져 있으나, 우연에 의한 중독이나 원인이 밝혀지지 않은 중독은 드물게 보고되고 있는 실정이다. 본 증례에서는 재발성의 무통성 혈뇨를 주소로 내원한 58세 남자 환자가 후천성 비타민 K 의존성 혈액 응고 인자의 결핍을 보였으며 이 혈액 응고 장애를 교정하는데 매우 많은 양의 비타민 K가 필요하였고 치료 중단시 다시 악화되었다. 이 환자는 와파린이나 살서제의 복용력이 없었으나 혈청에서 브로디파코움이 측정되어, 브로디파코움 중독에 의한 응고장애로 진단되었다. 본 례에서와 같이 임상적으로 유의한 응고장애를 보이는 환자에서 노출 병력이나 경로가 분명치 않은 살서제 중독도 한가지 원인으로써 고려되어야 한다.

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