CASE REPORT

Superwarfarin poisoning and its management

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SUMMARY

Difenacoum is a long-acting superwarfarin-type anticoagulant that exerts its effect through inhibiting vitamin K 2,3-epoxide reductase. Inhibition of this enzyme leads to reduced bioavailability of the metabolically active form of vitamin K resulting in decreased production of vitamin K-dependent proteins including coagulation factors II, VII, IX and X. A 45-year-old woman with psychiatric illness presented with haematuria. Laboratory test results indicated she had been exposed to a vitamin K antagonist which was subsequently identified as difenacoum. She was initially treated with phytomenadione, red cell suspension and octaplex. She was discharged on 30 mg phytomenadione daily but monitoring of vitamin K markers indicated that compliance was poor, and 152 days post-admission she presented with haemoptysis. Difenacoum and other superwarfarin rodenticides are freely available for purchase by the public. Cases such as this continue to raise issues about their availability and regulation.

BACKGROUND

The discovery of vitamin K antagonists has its origins in poisoning. Fatal haemorrhagic disease in cattle following the ingestion of spoiled sweet clover was first described during the 1920s.¹ This was later linked to impaired prothrombin function² and subsequently a 4-hydroxycoumarin compound, named dicoumarol was identified as the agent responsible.³ Synthesis of dicoumarol analogues led to the synthesis of warfarin,⁴ which was successfully deployed as an anticoagulant rodenticide alongside other first generation vitamin K antagonists including coumarins such as coumachlor, coumatetralyl; and indandiones including diphacinone. In response to the appearance of resistance among rat populations,^{5 6} long-acting warfarin derivatives; superwarfarins such as brodifacoum, bromodialone and difenacoum, were synthesised. In parallel to these developments warfarin was introduced as a therapeutic anticoagulant in humans used for prophylactic treatment of thromboembolic disease.

Vitamin K antagonists elicit their anticoagulant effect by inhibiting the action of vitamin K 2,3-epoxide reductase (VKOR), which is responsible for the conversion of the inactive vitamin K epoxide to the active hydroquinone form, which is then available as a cofactor for the γ -carboxylation of vitamin K-dependent proteins by the enzyme vitamin K-dependent carboxylase. As a result of inhibition of this process, γ -carboxylation of the hepatic vitamin K-dependent clotting factors II, VII, IX, X, is impaired, leading to inhibition of coagulation.⁶ Vitamin K antagonists are also known to elicit a procoagulant effect and cases have been

reported where patients exposed to superwarfarins present with thrombosis as well as bleeding,⁷ which is likely to be related to the inhibition of the vitamin K-dependent anticoagulant proteins C and S. Although the majority of cases reported in the literature indicate bleeding is the most common complication of superwarfarin poisoning clinicians should be aware of this less common presentation.

Superwarfarins are highly potent, long-acting, vitamin K antagonists. The enhanced potency of superwarfarins is due to their greatly extended tissue half-lives, their lipophilic nature causing them to reside for long periods in the liver.⁸ Exposure to these commonly available rodenticides can result in potentially fatal haemorrhage and less commonly thrombosis.^{7 9 10} Acute life-threatening complications can be prevented with timely intervention. Immediate administration of fresh frozen plasma,⁸ four factor prothrombin complex concentrate and/or phytomenadione (vitamin K₁) can successfully reverse the anticoagulant effects of the antagonist.¹¹ With tissue half-lives estimated at between 16 and 220 days, reversal of superwarfarin toxicity is a long-term issue^{11–13} therefore long-term daily treatment with phytomenadione is necessary. Phytomenadione (also known as phylloquinone or vitamin K₁) is more effective at reversing anticoagulation than menadione (vitamin K₃). In vivo menadione occurs only as an intermediate in the conversion of vitamin K₁ to menaquinone-4 (MK-4), which is then transported to tissues.^{14 15} Menadione is not directly active as a coenzyme for vitamin K carboxylase and therefore any activity of menadione is conferred by the action of MK-4 post-conversion. Since hospital pharmacies often believe that different forms of vitamin K are equipotent, administration of menadione presents a potential pitfall in treatment, leading to delayed recovery and increased risk of complications.

In this article we describe a case of a vulnerable adult who became exposed to difenacoum, the diagnosis and the issues surrounding the long-term treatment of the patient.

CASE PRESENTATION

A 45-year-old woman attended the accident and emergency department with a 2-day history of suprapubic pain and discomfort. This was associated with a 1-day history of frank haematuria. She denied any illicit drug use and had no access to warfarin. She had a history of psychiatric illness and was on both quetiapine and fluoxetine. A corroborative history from family members suggested she was found at home eating soil and plant debris. On examination, the patient was vacant and avoided eye contact. There was mild tenderness in

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the suprapubic region and frank haematuria was noted.

Initial laboratory investigations gave the following results: haemoglobin=65 g/L, white cell count= 7.7×10^9 /L, neutrophils= 4.5×10^9 /L, platelets= 354×10^9 /L. The blood film showed normochromic, normocytic anaemia with no evidence of microangiopathic haemolytic anaemia. Renal and liver function tests were normal and a toxicology screen was negative. Clotting studies were abnormal with a prothrombin time (PT) >200 s, an international normalised ratio (INR)>10 and activated partial thromboplastin time (APPT) of 114 s. A 50:50 mix was performed and showed normalisation of clotting factors (APTT=26.3 s and PT=13 s). Clotting factor studies gave the following results: FVIII=159%, FIX=3%, FVII=<5%, Factor II=<5%, FX=<5%, FV=132% and fibrinogen=4.65 g/L. A kidney, ureter and bladder X-ray and ultrasound scan of the bladder and pelvis appeared normal.

On admission to accident and emergency (prior to diagnosis of superwarfarin exposure) the patient was given 10 mg intravenous phytomenadione. She was then transfused with four units of red cell suspension, octaplex was not given as per local protocol as there was no history of warfarin use. A repeat PT and INR 4 h after administration of intravenous phytomenadione showed INR>10 and PT>200 s. In view of the persistent haematuria and deranged clotting studies octaplex (3000 units) was administered 6 h after admission to hospital and she was started on oral phytomenadione (10 mg thrice daily). After administration of octaplex the haematuria resolved, however gross haematuria reappeared on day 5 post exposure and she was again given octaplex (3000 units). A subsequent cystoscopy showed no evidence of bladder cancer but did indicate mucosal haemorrhage. Diagnosis of superwarfarin exposure was not confirmed until 3 days post-admission after the patient's coagulation had normalised. She was then prescribed phytomenadione (30 mg daily) and discharged from hospital.

The patient was monitored regularly (figure 1) but in January 2014 she admitted to intermittent compliance to the phytomenadione treatment. In February 2014 she was admitted with an episode of haemoptysis (152 days post-admission), which was treated with intravenous phytomenadione (10 mg). Her haemoptysis and INR resolved and she was again discharged on phytomenadione (30 mg daily).

INVESTIGATIONS

Screening for superwarfarins and determination of plasma difenacoum concentration was by normal-phase HPLC with diode array detection (DAD). Vitamin K₁ and vitamin K₁ 2,3-epoxide were determined by reversed-phase HPLC with post column derivatisation and fluorescence detection. Undercarboxylated prothrombin (PIVKA-II) was determined by ELISA.

Difenacoum was detected in the patient's plasma in a sample taken 1 day postexposure. The identity of the antagonist was confirmed by matching the retention time and ultraviolet (UV) spectrum to that of a pure standard. PIVKA-II was estimated at >100 AU/L while vitamin K₁ was 0.1 µg/L (0.15–1.55 µg/L) and vitamin K₁ 2,3-epoxide was undetectable (<0.12 µg/L). In a subsequent sample (35 days post exposure) difenacoum had become undetectable, PIVKA-II had fallen to 48.6 AU/L, vitamin K₁ was 0.53 µg/L and vitamin K₁ 2,3-epoxide was 1.51 µg/L.

DISCUSSION

Ingestion of difenacoum was confirmed using three independent assays. Measurement by HPLC with DAD and UV spectrophotometry confirmed the identity of the antagonist. Measurement of PIVKA-II and vitamin K₁ 2,3-epoxide (relative to the vitamin K₁ concentrations) provided supporting evidence for the presence of an antagonist, indicating the degree of inhibition of carbonylation and provided evidence of the continuing presence of the antagonist in the patient's body. The vitamin K₁ concentration from the sample taken one day post exposure was below the lower limit of the reference range (<0.15 µg/L) indicating possible low tissue stores of vitamin K prior to exposure. The vitamin K₁ level in the sample taken 35 days postexposure was within the reference range and consistent with the poor compliance to the phytomenadione treatment reported by the clinician.

Difenacoum is long-acting superwarfarin type anticoagulant rodenticide. In addition to difenacoum, other superwarfarin compounds are also commonly available in the UK including bromodiolone and brodifacoum. They are widely used and freely available for purchase by the public in general. There is no standardised regimen for treatment of superwarfarin exposure, but treatment should initially be focused on the management of bleeding and complications thereof through transfusions, blood derivatives and phytomenadione (either

Figure 1 Monitoring of the patient's coagulation (international normalised ratio, INR). Solid line denotes a normal INR, dotted line denotes a typical upper limit of target range for stable anticoagulation. (I) Patient presented with deranged coagulation and haematuria, was given 10 mg intravenous phytomenadione and transfused with four units of red cell suspension, 4 h later the INR was >10 and prothrombin time >200 s and so octaplex (3000 units) was administered. (II) Haematuria resolved and oral phytomenadione (10 mg thrice daily) was initiated. (III) Gross haematuria reappeared and she was again given octaplex (3000 units). (IV) Readmitted with an episode of haemoptysis 152 days postadmission, treated with intravenous phytomenadione (10 mg).

intravenously or orally). For long-term treatment, daily phytonadione is required to ensure coagulation is maintained while the toxin remains in the liver. In this case, due to compliance issues, maintenance of normal coagulation was not achieved, which led to a second episode of bleeding 152 days post exposure.

Inhibition of VKOR, responsible for recycling of vitamin K 2,3-epoxide back to the metabolically active hydroquinone form, results in inhibition of γ -carboxylation. Therefore in cases of potent VKOR inhibition such as this, a continuous supply of vitamin K₁ is required to maintain the vitamin K requirements of the carboxylase enzyme for synthesis of vitamin K dependent proteins. The extrahepatic vitamin K dependent proteins (eg, osteocalcin, matrix gla protein etc) are likely to be effected also, however it is not known to what extent.

Difenacoum was first introduced in Britain in the 1970s.¹⁶ It has approximate plasma and tissue (liver) half lives of 20.4 and 61.8 days respectively (animal models).¹⁷ There are many reports of similar cases in the literature, which indicate common causes of poisoning are accidental ingestion, suicide attempts and Munchausen syndrome.⁹ Less common are surreptitious administration¹⁸ and by mixing with recreational drugs.¹⁹ Although potentially lethal, reports of death due to superwarfarin poisoning are rare compared to cases treated successfully. Treatment and regular monitoring is likely to be required for many months¹⁰ and is likely to be compromised if there are compliance issues as in this case.

The cost of this patient's treatment was estimated at £11 000. Superwarfarins are widely employed rodenticides and are freely accessible for purchase by the public. The continued occurrence of superwarfarin poisoning indicates that this is an ongoing public health issue, impacting on patients and their families and contributing to healthcare costs.

Learning points

- ▶ Superwarfarin poisoning is potentially fatal and rapid correction of the coagulation abnormality at presentation is essential.
- ▶ Diagnosis may be confirmed and monitored by measurement of vitamin K markers and by direct measurement of the antagonist.
- ▶ Continued treatment with phytonadione is essential to maintain coagulation and may be required for many months post exposure, poor compliance with the phytonadione treatment may result in a reoccurrence of bleeding.

Contributors Details of the case were provided by SF. The laboratory analysis was carried out by DJC and KD while DJH provided advice on the laboratory work and writing of the article. The article was written primarily by DJC with assistance from the other authors.

Competing interests None.

Patient consent Obtained.

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