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Short Communication

Combined superwarfarin poisoning with extremely high levels of bromadiolone

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ABSTRACT

Long-acting anticoagulant rodenticides are responsible for many human poisonings around the world. This communication reports a self-poisoning of a 40 year-old woman with an anticoagulant rodenticide with more than fifteen times the maximum allowed concentration for commercial rodenticides. Bromadiolone and brodifacoum were identified in the patient's serum. Serum bromadiolone levels exceeded 30 µg/L. The high concentration reached by bromadiolone, the fact that two superwarfarins were found in the patient's serum, as well as the good prognosis and evolution of the case represent the highlights of this communication. The rapid onset of vitamin K_1 therapy, together with the potential presence of resistance-related factors, could have led to the favorable outcome of the case.

KEYWORDS: bromadiolone, brodifacoum, human poisoning, massive intake.

INTRODUCTION

Bromadiolone and brodifacoum are long-acting anticoagulant rodenticides. They are known as superwarfarins because they are structurally related to warfarin, though much more potent [1]. They cause a prolonged anticoagulant effect through the inhibition of the enzyme vitamin K 2,3-oxide reductase (VKOR), resulting in vitamin K-dependent clotting factor deficiency [1]. The clinical presentation may include reduced prothrombin activity (PA) values, prolonged activated partial thromboplastin time (aPTT), hematuria, gingival bleeding, epistaxis, gastrointestinal bleeding and/ or life-threatening intracranial hemorrhages [2]. Management of the poisoned patient requires administration of vitamin K_1. For patients actively bleeding or at high risk of bleeding, whole blood transfusions, fresh frozen plasma, recombinant Factor VIIa or prothrombin complex administration may be needed [3].

We present the case of a massive self-poisoning with superwarfarins, which had a good prognosis and a favorable evolution.

CASE STUDY

A 40 year-old woman, brought in by her parents, was admitted into the Emergency Unit, with suspected self-poisoning. During the ensuing medical interrogation, she admitted having taken, 15 hours earlier, an unknown amount of a liquid rodenticide in a suicide attempt.

The patient (weight 60 kg, height 158 cm) had no history of smoking or alcohol consumption. Her medical record showed she had been treated for depression with anti-depressants (escitalopram),

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antipsychotics (sertindole) and benzodiazepines (clonazepam). Even though the woman was asymptomatic, she had an altered PA value, which is the reason why she was admitted at the Intensive Therapy Unit and treated with vitamin K_1.

Laboratory tests revealed a hematocrit of 41%, leucocyte count of 4.70 x 1000/mm^3 and platelet count of 246 x 1000/mm^3. The PA was 34% (normal range: 70-120%) and the aPTT was 33 s (normal range: 23-44 s). On the same day two more PA results were obtained, 26% and 15%, a few hours later. The other common laboratory parameters were normal.

The abdominal ultrasound, Doppler echocardiogram and electrocardiogram results were normal and did not show signs of internal bleeding.

Based on the results of the PA, although no signs of bleeding were observed, the patient was treated with vitamin K_1 according to the guideline of diagnosis and treatment of poisonings [4]. The treatment started at a dose of 120 mg/day (slow intravenous infusion to avoid anaphylactoid reactions) on the first day after admission, followed by 80 mg/day for the next six days and continued gradually decreasing to 30 mg/day, for 21 more days. On day one, a blood sample was remitted to the Laboratory of Analytical Toxicology of the University of Buenos Aires for the investigation and quantitation of warfarin and superwarfarins.

The investigation of warfarin and superwarfarins (bromadiolone, difenacoum and brodifacoum) in serum was performed by liquid chromatography.

Two superwarfarins, brodifacoum and bromadiolone were detected in the patient's serum. Brodifacoum concentration was 0.98 µg/mL and bromadiolone concentration was extremely high (more than 30 µg/mL). Additional serum samples for the determination of superwarfarins were obtained on days 6, 15, 21, 27 and 37 after admission. Serum levels of brodifacoum and bromadiolone are shown in Table 1.

Both, brodifacoum and bromadiolone concentrations, decreased as a function of time, but they did not seem to have the same elimination pattern, in fact, not even similar patterns. While bromadiolone levels dropped quickly between days 1 and 15 and then slowly till day 27 at which point they became non-detectable, brodifacoum levels decreased constantly but slower than bromadiolone levels and remained detectable until day 37.

Coagulation parameters were monitored daily. PA showed great improvement as a result of vitamin K_1 therapy (Figure 1), and also as brodifacoum and bromadiolone serum levels decreased (Table 1). The abrupt fall in PA values (from 81% to 40%) observed between days 16 and 17 was in response to the erroneous administration of menadione (vitamin K_3) instead of phytomenadione (vitamin K_1) on day 15.

The patient evolved satisfactorily. She continued receiving vitamin K_1 therapy (10 mg/day, orally) until day 42, and was discharged after 50 days of hospitalisation. Three months after discharge, during a follow-up medical check-up, she signed the informed consent form for the publication of her case.

The analysis of the liquid rodenticide showed a bromadiolone concentration of 979 µg/mL. No trace of brodifacoum was detected.

DISCUSSION

Several characteristics made this case unusual. In the first place, two superwarfarins were identified in the serum, but only one was found in the liquid rodenticide. This fact could mean that she could

Table 1. Serum levels of brodifacoum and bromadiolone.

Day	**1**	**6**	**15**	**21**	**27**	**37**
Brodifacoum (ng/mL)	985	837	431	140	< 43*	< 43*
Bromadiolone (ng/mL)	33669	4984	319	107	ND**	ND**

*Brodifacoum, limit of quantification: 43 ng/mL.
**Bromadiolone, limit of detection: 30 ng/mL.
ND: non-detectable.

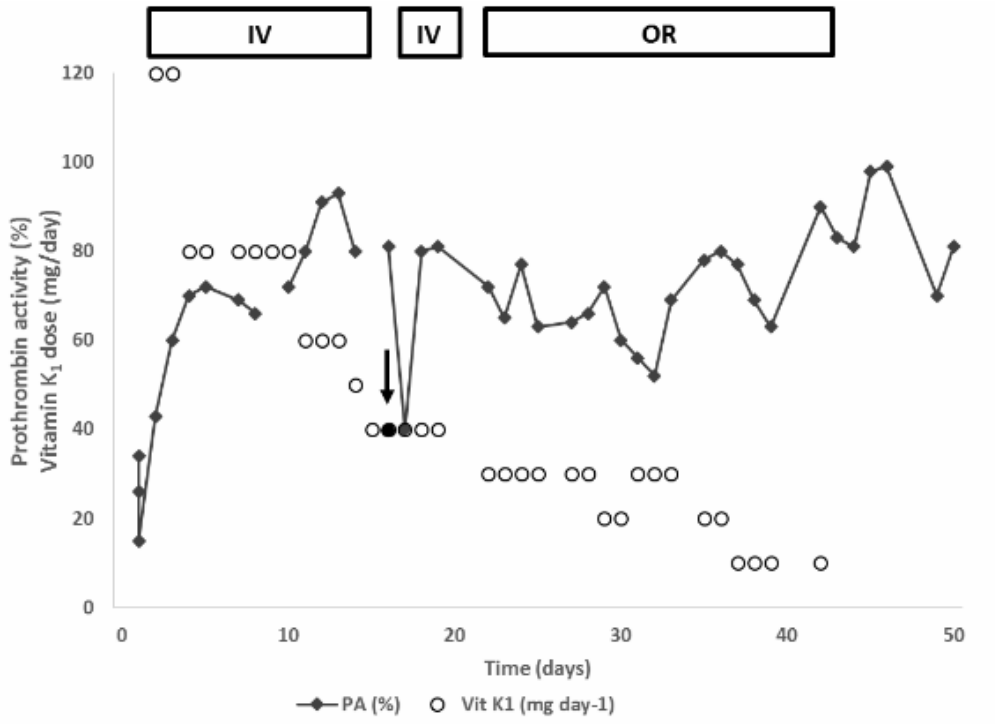

Figure 1. Evolution of prothrombin activity (PA) and vitamin K_1 (Vit K_1) as a function of time (days). IV: intravenous route, OR: oral route. Arrow points the day vitamin K_3 was administered. Left scale (0-120) represents % and mg/day.

have had at least one previous attempt to self-harm by ingesting rodenticides, even though she never admitted it.

The concentration of bromadiolone found in the serum (33.7 µg/mL) was much higher than a previously reported case [5].

The extremely high concentration found in the serum of our patient on day one, could not only be explained by the concentration found in the liquid, but had to be associated with a high intake. The intake was estimated from the remaining volume in the container and, accordingly, it could have been of about 200 mL.

Surprisingly, and despite the extremely high level of serum bromadiolone, she did not show major clinical manifestations, neither on admission nor during her hospitalisation. Coagulation parameters were abnormal during the first day after admission, but they quickly reached normal values after starting the therapy with vitamin K_1. The progressive decrease of PA activity on day one was consistent with the fact that she had been recently exposed to at least one superwarfarin. Therapy with vitamin K_1 reached doses of 120 mg/day and seemed to restore coagulation parameters. In the literature, there are few reported cases of poisoning with bromadiolone and there is even less data on doses of vitamin K_1 administered. Two cases of suspected bromadiolone poisoning received 20 mg/day of vitamin K_1 for more than two months [6]. Higher doses of vitamin K_1 (from 100 to 600 mg/day) have been described for brodifacoum-poisoned patients [7, 8]. Brodifacoum is more potent than bromadiolone; therefore, it is expected to cause more severe effects and require higher doses of vitamin K_1. However, two situations have to be considered here: firstly, due to the serum concentration of bromadiolone found in this case, stronger symptomatology would be expected; and secondly, a high concentration of brodifacoum (0.985 µg/mL) was also found in the serum.

A possible explanation for the absence of severe symptomatology and for the vitamin K_1 requirements could be related to the presence of resistance to the action of this type of compounds.

Studies on resistance to anticoagulant therapy in humans involve the investigation of the influence of genetic and non-genetic factors. Researches on genetic factors are focused on the presence of polymorphism in genes related to 4-hydroxycoumarin kinetics and dynamics [9-11]. *VKORC1* and *CYP2C9* are the most studied genes in that aspect. Unfortunately, the presence of any gene polymorphism could not be investigated in our patient, which is why only a hypothesis can be considered. Among non-genetic factors influencing the response to anticoagulant therapy, literature mentions age, gender, weight, height, diet and medication [12-14]. The influence of such factors, which alone would not be significant, could become significant in association with genetic factors. As far as we are aware, the patient had a standard diet, and the reported therapeutic use of escitalopram and sertindole has been described as not affecting warfarin requirements [13, 15]. No information on the interaction between clonazepam and warfarin was found.

Finally, the complete elimination of bromadiolone from blood occurred within 27 days. Despite the high initial bromadiolone concentration, the period of elimination turned out to be similar to those previously reported [16, 17]. Brodifacoum continued being detectable until day 37, the day when the last serum sample was remitted for analysis. The literature reports the complete elimination of brodifacoum from the blood in periods up to seven months [18], but in this case, as the exact moment of exposure was unknown, no comparison was possible.

CONCLUSION

To our knowledge, this case presents the highest bromadiolone serum concentration reported in the literature. It also showed the blood elimination pattern of bromadiolone and brodifacoum in a single person. These two facts, together with the good evolution of the case, represent the highlights of this communication.

Despite all the information supporting the resistance to warfarin and related compounds, nothing appears to fully explain this particular case. The most likely explanation could be the confluence of genetic and non-genetic resistance-related factors, which together with the rapid onset of vitamin K_1 therapy led to the favorable outcome of the patient.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Watt, B. E., Proudfoot, A. T., Bradberry, S. M. and Vale, J. A. 2005, Toxicol. Rev., 24(4), 259.
2. King, N. and Tran, M. H. 2015, Transfus. Med. Rev., 29(4), 250.
3. Haesloop, O., Tiilick, A. and Strote, J. 2016, Am. J. Emerg. Med., 34(1), 116.e1.
4. Talamoni, M. A., Crapanzano, G. A. and Greco, V. 2014, Guía de diagnóstico y tratamiento en toxicología. Second Edition. Eudeba Eds. Spanish.
5. Vindenes, V., Karinen, R., Hasvold, I., Bernard, J. P., Mørland, J. G. and Christophersen, A. S. 2008, J. Forensic. Sci., 53(4), 993.
6. Greeff, M. C., Mashile, O. and MacDougall, L. G. 1987, Lancet, 2(8570), 1269.
7. Lipton, R. A. and Klass, E. M. 1984, JAMA, 252(21), 3004.
8. Pavlu, J., Harrington, D. J., Voong, K., Savidge, G. F., Jan-Mohamed, R. and Kaczmarski, R. 2005, Lancet, 365(9459), 628.
9. Wadelius, M. and Pirmohamed, M. 2007, Pharmacogenomics J., 7(2), 99.
10. Au, N. and Rettie, A. E. 2008, Drug Metab. Rev., 40(2), 355.
11. Hirai, K., Yamada, Y., Hayashi, H., Tanaka, M., Izumiya, K., Suzuki, M., Yoshizawa, M., Moriwaki, H., Akimoto, T., Tsuji, D., Inoue, K. and Itoh, K. 2015, Thromb. Res., 135(5), 861.
12. Garcia, D., Regan, S., Crowther, M., Hughes, R. A. and Hylek, E. M. 2005, Chest, 127(6), 2049.
13. Allen, S. N., John, S., Shannon, J. and Ferrara, J. 2013, US Pharm., 38(11), 23.

14. Khoury, G. and Sheikh-Taha, M. 2014, Clin. Pharmacol., 6, 103.
15. Haduch, A., Ogórka, T., Boksa, J. and Daniel, W. A. 2005, Pharmacol. Rep., 57(6), 872.
16. Grobosch, T., Angelow, B., Schönberg, L. and Lampe, D. 2006, J. Anal. Toxicol., 30(4), 281.
17. López, C. M. and Olmos, V. 2006, Intoxicación con rodenticidas superwarfarínicos desde el laboratorio toxicológico. [On line]. 2006, Revista de Toxicología en línea (ReTEL).
18. Olmos, V. and Lopez, C. M. 2007, Clin. Toxicol. (Phila.), 45(5), 487.