A long road to recovery after a superwarfarin 

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Background

Anticoagulant rodenticides are poisons targeted at rats, mice and rabbits. Warfarin was a rodenticide, until the 1970’s when superwarfarins were developed to overcome a rapidly developing warfarin resistance in rats. The most common active ingredient in commercially available superwarfarin rodenticides is brodifacoum.1,2 As brodifacoum is readily available in unregulated quantities, it toxicity presents a serious public health concern.3,4

Superwarfarins are readily absorbed through the skin, however most poisonings occur by ingestion or inhalation.5 Human exposures are usually accidental, however, may be suicide or homicidal attempts or used for ‘lacing’ drugs of abuse.6,7

Brodifacoum is extremely potent: the lethal dose for the average population is described to be 15mg.8 It is highly lipophilic and is slowly eliminated via zero-order kinetics at high concentrations, and first order kinetics at lower concentrations.9,10 Its half-life in humans is 243-1656 hours; warfarin’s is only 17-37 hours.11 Superwarfarins are about 100-fold more potent than warfarin.12

Case Report

- 20yo female with left calf pain and bruising to her arms and trunk.
- No medical history, non-smoker, no illicit drug use, social alcohol.
- Left leg ultrasound revealed a plantaris muscle rupture.

- Elevated coagulant studies on admission (see table 1).
- Prolonged Echis clotting time (14) indicating vitamin K deficiency.
- She had reduced factor VII (0.02) and factor X levels (<0.01).

- Positive brodifacoum level of 590 microg/L
- Patient admitted to ingesting rodenticide 3 days prior to presentation
- Diagnosis: brodifacoum toxicity
- Commenced on IV vitamin K

- Prothrombinex 300mg IV and vitamin K 10mg IV STAT given.
- Cause was unclear:
- Differential diagnosis: vitamin K deficiency, acquired coagulant factor deficiency or toxin ingestion

- Haematology and toxicology consulted
- Dose of vitamin K was increased daily to show reversibility of INR and to stabilise a dose.
- Dose was stabilised at 300mg daily with plan for 3-6 months’ treatment

- Discharged with weekly GP reviews for INR and PT monitoring and for a brodifacoum level in 3 months.
- Four months after discharge vitamin K was ceased. (No blood results from this point are available)

Day 1 1 (2hr post) 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
INR >10 >10 >10 1.9 3.0 2.6 3.2 1.8 1.7 1.8 1.5 1.5 1.4 - 1.3 1.2 1.1 1.1
PT >100 >100 >100 101 21 32 25 35 35 18 19 18 20 17 16 15 - 14 13 12 12
APTT 126 134 131 31 33 36 36 35 - - - - - - - - - - -
Total FFP 10ml IV 10 10 10 10 10mg IV 40 40 40 20mg PO 40 40 40 mg mg mg PO PO PO PO PO PO PO PO PO PO PO PO PO PO
Vit K Dose

Table 1: Patients INR results and corresponding daily vitamin K doses

Discussion

Overdoses of warfarin and superwarfarins will present clinically similarly (with bleeding, prolonged PT and increased INR). The effect of treatment on coagulation profile can help differentiate between the two toxicities due to the difference in their half-lives. Warfarin anticoagulation is rapidly corrected with fresh frozen plasma (FFP) and vitamin K, but superwarfarin toxicity will result in repeatedly increased PT and INRs after FFP and vitamin K, even if levels were initially corrected.11 Measuring brodifacoum levels can confirm superwarfarin toxicity, however, few laboratories in Australia are able to perform this.12

Blood, FFP, and factor transfusions can be used as urgent treatment options for bleeding, though effects are short lived due to the long half-life of brodifacoum.13 The initial dose of vitamin K depends on the INR.14 The oral route is preferred due to risk of haematomata with the parenteral route.15 The maintenance dose is decided by titration against daily INRs. The long half-life of superwarfarins means that treatment with vitamin K is continued at high doses (15-800mg/day) for months after the poisoning.16,17

Periodic withdrawal of treatment with careful INR monitoring is used to assess treatment duration. Close INR monitoring is recommended for 2 weeks after stopping treatment.18 Gunja et al. suggest that vitamin K cessation can safely occur once brodifacoum levels have fallen below 10 microg/L.19

The pharmacists role is depicted in figure 2. Non-compliance was a concern with this patient due to her mental health issues and as she required 30 (10mg) capsules a day. The cost outweighed the ease of compounding the dose. The pharmacist recommended splitting the dose across the day and counselled the patient on the ability of opening capsules.

Conclusion

Treatment for superwarfarin toxicity includes months of high-dose vitamin K. The role of the pharmacist is important to maximise compliance and adherence for the length of treatment.

References

5 Therapeutic Guidelines: Toxicology: long-acting anticoagulants (superwarfarins). Published 9/7/2012.