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ORIGINAL ARTICLE

# Retrospective Study of the Characteristics of Anticoagulant-Type Rodenticide Poisoning in Hong Kong

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## Abstract

**Introduction** Warfarin- and superwarfarin-type anticoagulants are commonly used as rodenticides. Exposure to these agents, especially superwarfarins with long-acting anticoagulant effect, can cause life-threatening coagulopathy in humans. Most superwarfarin poisoning cases had an obvious history of exposure, though occult cases without exposure history have also been reported. The current study aims to examine anticoagulant-type rodenticide poisoning in Hong Kong and to identify the similarities and differences between patients with known exposure history and those whose exposure is recognized only through laboratory testing.

**Methods** The present study was conducted in a tertiary referral clinical toxicology laboratory in Hong Kong. This was a retrospective cohort study of all patients with biochemically confirmed anticoagulant-type rodenticide exposure, from 2010 to 2014.

**Results** Superwarfarin was the most common group of anticoagulant-type rodenticides identified (87.8%), in which bromadiolone and brodifacoum were the most frequently encountered. Among the 41 cases identified, 31 had an obvious exposure history, and 10 were occult poisoning in which the context of exposure remained unidentified. All occult poisoning patients without exposure history presented with bleeding events. These occult poisoning cases often went unrecognized by frontline clinicians, leading to delayed investigation and initiation of treatment. This group of patients was associated with a longer time to diagnose coagulopathy ($p < 0.001$) and confirm rodenticide poisoning ($p < 0.05$), a higher rate of international normalized ratio (INR) rebound after initiation of antidote ($p < 0.001$), and a longer time needed for normalizing INR ($p < 0.05$).

**Conclusion** Occult superwarfarin poisoning is an important yet under-recognized differential cause of unexplained coagulopathy. A high index of clinical suspicion and availability of specialized toxicological test for superwarfarins play a vital role in diagnosis and early initiation of appropriate management. The underlying cause of such poisoning remains obscure and warrants further study.

**Keywords** Bromadiolone · Brodifacoum · Superwarfarins · Rodenticides poisoning · Vitamin K

## Introduction

Superwarfarins are anticoagulant-type rodenticides which act by inhibiting vitamin K epoxide reductase and hence depleting vitamin K-dependent clotting factors. They were developed in 1970s to overcome the resistance against the first-generation warfarin-type anticoagulant rodenticides in rats. The addition of a lipophillic side chain to the 4-hydroxycoumarin skeleton of superwarfarin enhances its affinity for hepatic tissue, and therefore its potency and half-life compared with warfarin [1, 2].

Most of the superwarfarin poisoning cases reported in the literature presented with an obvious history of rodenticide exposure, either accidental (more common in children) or intentional (more common in adults); these patients often did not take a significant amount of rodenticides and had no or minimal clinical signs or symptoms of coagulopathy [3, 4]. Occasionally, some patients had superwarfarin poisoning whose context of exposure remained unidentified, and a number of such occult poisoning cases with significant bleeding events have been reported [5–12]. Though Munchausen syndrome, homicide, and even drugs of abuse laced with

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superwarfarins have been subsequently identified as the cause in a few patients [5, 6], the route and etiology of poisoning remained unidentified in a majority of these cases [7–12]. Early identification of superwarfarin poisoning is important. This allows prompt and effective treatment with high dose of vitamin K1 over a prolonged period. Despite these case reports, a detailed study comparing the clinical characteristics and outcomes between anticoagulant-type rodenticide poisoning in patients with or without exposure history has not been previously described in the literature.

The Hospital Authority Toxicology Reference Laboratory (HATRL), the only tertiary clinical toxicology laboratory in Hong Kong, provides support to all local hospitals in managing patients with complex poisoning problem. We provide specialized toxicology testing for the investigation of anticoagulant-type rodenticide exposures in suspected cases. In the present study, we aim to retrospectively review these poisoning cases to evaluate the clinical characteristics, diagnostic workup, management, and clinical outcomes between the patients with or without exposure history, and to look for similarities and differences of the above parameters in these groups. We hypothesized that the diagnostic workflow and clinical outcomes would be worse in patients with occult poisoning, due to low clinical suspicion of anticoagulant poisoning as a differential diagnosis.

## Methods

We performed a retrospective cohort study to review all cases referred to the HATRL that were biochemically confirmed to have anticoagulant-type rodenticide exposure from January 2010 to December 2014. A preliminary review of charts was completed to identify all cases of anticoagulant rodenticides testing requests referred to the HATRL via the laboratory database as well as the patients' electronic medical records. Cases with negative anticoagulant rodenticide test results and confirmed cases of coagulopathy due to overdose of warfarin therapy were excluded from the study. The charts of patients who met inclusion criteria were reviewed as described by Gilbert et al. [13]. Study variables were defined and included the following: demographic characteristics, clinical presentation, medical and drug history, laboratory investigations, toxicology findings including serum levels of superwarfarins, time of each relevant tests requested, and treatment administrated with reference to time of first presentation, as well as toxicological effects, clinical effects, laboratory abnormalities, and medical interventions of each patients. Data were abstracted to a standardized data collection form in Microsoft Excel® (Microsoft Corporation, USA), with standardization of listed descriptions of elements to be imported in each cell, definition of important variables, and units of measurement and abbreviations to be used. One of the authors performed data abstraction for the 15 cases in 2014, while another author performed data abstraction for all the 41 cases over the 5-year study period. Percentage of agreement between the overlapping data sets was calculated. Any discrepancies in results was reviewed and discussed jointly for clarification, with a third independent author to arbitrate any discordances. The above parameters in the group of patients with an initially disclosed history of rodenticide exposure were compared with the patients whose route of exposure and etiology of poisoning remained unidentified after detailed questioning on social, medical, occupational, dietary, and drug history.

Treatment outcomes included rebound of international normalized ratio (INR) after initiation of treatment, the time needed to achieve normal INR, and coagulopathy-related morbidity and mortality. In this study, rebound of INR is defined as INR increase of more than 20% compared with previous result after an initial drop, taking into account of reference change value calculated with the within-subject coefficient of variation ($CV_{WB}$) and analytical coefficient of variation ($CV_A$) of INR [14, 15]. The timing of test requests, treatment initiation, and outcome measures in this study were all expressed relative to the time of first presentation to the Emergency Department.

Coagulopathy is defined as INR > 1.5, with mild derangement defined as INR between > 1.5 and ≤ 2.5 and significant coagulation disturbance defined as INR > 2.5 [16]. Expanding upon an established poisoning severity score (PSS) [17], the severity of the cases in this study was classified as follows: no coagulopathy with peak INR ≤ 1.5 (grade 0), mild coagulation disturbances with peak INR > 1.5 and ≤ 2.5 (grade 1; minor), significant coagulation disturbances with peak INR > 2.5 but no bleeding events (grade 2; moderate), significant coagulation disturbances with peak INR > 2.5 together with bleeding events (grade 3; severe), and fatal poisoning (grade 4). In the present study, vitamin K1 treatment is deemed to be indicated in patients with poisoning severity of grade 1 or above. The initial dosing of vitamin K1 is generally considered adequate if more than 30 mg is given per day in divided doses based on local experience and data from previous studies [2, 4, 18].

Qualitative analysis of warfarin- and superwarfarin-type agents in serum specimens was performed by liquid chromatography tandem mass spectrometry (LC-MS/MS) using multiple reaction monitoring mode. This qualitative analytical method covered both superwarfarin-type agents (including brodifacoum, bromadiolone, difenacoum, flocoumafen, and difethialone) and warfarin-type agents (including warfarin, coumatetralyl, coumachlor, coumafuryl, pindone, chlorophacinone, and diphacinone). Serum quantitative analysis was performed for the two most frequently encountered superwarfarins, brodifacoum, and bromadiolone, using LC-MS/MS.

Statistical analyses on demographic, clinical, and laboratory data are performed with R (The R Project, an international

collaboration), Microsoft Excel® (Microsoft Corporation, USA), KyPlot (KyensLabInc, Tokyo, Japan), and MedCalc (MedCalc software bvba, Belgium). The null hypothesis would be that groups with or without exposure history to rodenticides have no significant differences in aforementioned indices. Testing of normality is done by Andersen-Darling test. Where normality is accepted, descriptive statistics are obtained as mean and standard deviation, and comparison of means are done via independent sample *t* test; where normality is rejected, descriptive statistics are obtained as median and interquartile range (IQR), and comparison of median is done by performing Mann-Whitney *U* test. Demographic data and categorical variable comparison are done by comparison of two proportions. For group comparison, a *p* value of less than 0.05 is taken as statistically significant.

This study was approved by the Hong Kong Hospital Authority Kowloon West Cluster Research Ethics Committee (approval number KW/EX-14-215). For all the patients' data presented in the case series, we obtained a waiver of consent for publication from the above institutional review board as this study presents minimal risk, if any, to the patients and personal information about an identifiable patient is minimal.

## Results

Our laboratory received 76 requests for anticoagulant-type rodenticide testing in the present study period from 2010 to 2014. Forty-one cases were tested positive and were included in the study. Double data abstraction was performed on 15 of these cases (36.6%), and the two authors showed excellent inter-rater reliability with percentage of agreement over 93% for all studied parameters. All patients were Chinese aged 1 to 90 years. Thirty-one patients (75.6%) reported a history of exposure, whereas the remaining 10 patients (24.4%) did not. Demographics, clinical, biochemical, and treatment data of these patients were listed in Table 1. All patients without exposure history were males while those with exposure history showed a mere male predominance. The demographics and the clinical presentation of these patients were compared and summarized in Table 2.

Superwarfarin was the most commonly encountered group of anticoagulant-type rodenticides ($n = 36$). Bromadiolone was the most common superwarfarin encountered ($n = 33$), followed by brodifacoum ($n = 9$). They were used either as a single agent or in combination with other anticoagulant(s). Bromadiolone was detected in 23 out of 31 patients with exposure history (74.2%) and in all 10 patients without exposure history (100%). Isolated use of warfarin-type anticoagulants, such as chlorophacinone, coumatetralyl, and warfarin, were detected in only a minority of patients with exposure history ($n = 5$). The types of rodenticides detected in the patients' blood specimens were compared and summarized in Table 3.

For the 31 patients with exposure history, with the exception of one pediatric patient who had accidental exposure to rodenticide, all others were adult patients with intentional ingestion of rodenticides due to deliberate self-harm. Concerning the types of rodendicide use, 28 patients took rat bait in solid form, and the remaining 3 patients reported a history of superwarfarin stock solution intake. Amid this group with bromadiolone or brodifacoum exposure, the peak serum superwarfarin levels in the three patients taking superwarfarin stock solution (3720, 6206 and 33,100 ng/mL respectively) were significantly higher than those consuming the solid rat bait (median, 67 ng/mL; IQR, 8−154 ng/mL). On the other hand, the ten patients without exposure history had a median peak serum superwarfarin level of 337 ng/mL (IQR, 87−562 ng/mL). Peak serum superwarfarin levels measured for individual patients were summarized in Table 1, and comparison of superwarfarin levels in the two groups of patients was listed in Table 3.

All patients with known exposure history presented within 48 h of rodenticide exposure (median, 8.5 h; IQR, 2.6−15.9 h), and none had coagulopathy at presentation. During the hospital stay, 20 patients (64.5%) remained asymptomatic with normal INR (PSS grade 0). The remaining 11 patients (35.5%) developed coagulopathy without clinical bleeding. Of these, five had PSS grade 1 poisoning with INR > 1.5 and ≤ 2.5, and the other six had PSS grade 2 poisoning with median INR of 5.52 (IQR, 4.78−6.80). All the patients with PSS grade 0 took a few pieces to a small pack of solid bait. The five patients with PSS grade 1 took one to two packs of solid bait. Three of the six patients with PSS grade 2 took more than two packs of solid bait, while the other three took stock solution of various amount. On the other hand, all patients without exposure history presented with bleeding events, including mucocutaneous bleeding (e.g., epistaxis, oral mucosal bleeding, hematuria, and gastrointestinal bleeding), ecchymoses, hematoma over limbs, and hemoperitoneum. They all had grossly increased INR above the upper reporting limit (> 6.0), and therefore classified as PSS grade 3 poisoning. No coagulopathy-related mortality was noted in the present study.

The diagnosis of anticoagulant-type rodenticide poisoning was made in all patients with known history of exposure at first presentation. However, in the group of patients without exposure history, the underlying coagulopathy as the cause of the bleeding events was not identified in 60% of them at first consultation. Three of them were diagnosed as minor bleeding events (such as epistaxis, gum bleeding, and hematuria) and were discharged at the emergency department without further workup on first presentation. The diagnoses were only made after they were re-admitted with more severe bleeding. For the remaining three patients, their initial presentations were classified as surgical or orthopedic complaints, including

**Table 1** Demographics, clinical, biochemical, and treatment data of the 41 patients with biochemically confirmed anticoagulant-type rodenticide poisoning

| | Patient | | Clinical presentation | Form of rat bait taken | Peak INR | Time of peak INR post-exposure (h) | Agents detected in serum, and peak/highest bromadiolone/brodifacoum level(s) measured | Time of serum sample taken post-exposure (h) | Vitamin K1 regimen | FFP used |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (year) | Sex | | | | | | | | |
| Patients with exposure history | | | | | | | | | | |
| 1 | 44 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Liquid | > 6.0 | 51.8 | Bromadiolone 33,100 ng/mL | 33.5 | 30 mg PO 4 times a day for 5 days, 40 mg 4 times a day for 54 days, 20 mg 2 times a day for 42 days | No |
| 2 | 79 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Liquid | > 6.0 | 97.2 | Bromadiolone 6260 ng/mL | 44.7 | 25 mg PO 4 times a day for 12 days, 25 mg PO 2 times a day for 17 days | No |
| 3 | 37 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Liquid | 4.8 | 59.5 | Bromadiolone 3720 ng/mL | 46.0 | 30 mg IV for 1 dose, 30 mg PO 3 times a day for 1 day, 50 mg PO 4 times a day for 1 day, 40 mg PO 3 times a day for 22 days, 30 mg PO 3 times a day for 15 days | No |
| 4 | 25 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 5.8 | 51.0 | Bromadiolone 137 ng/L[#], brodifacoum 335 ng/L[#] | 70[#] | 30 mg PO 3 times a day for 13 days, 10 mg PO 3 times a day for 68 days | No |
| 5 | 23 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 2.2 | 32.4 | Bromadiolone 115 ng/mL, brodifacoum 300 ng/mL | 25.2 | 10 mg PO daily for 7 days, 10 mg PO 4 times a day for 58 days, 10 mg PO daily for 26 days | No |
| 5 | 34 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 2.1 | 33.7 | Bromadiolone 239 ng/mL, warfarin | 3.3 | 20 mg PO 3 times a day for 5 days, 10 mg PO daily for 5 days, 5 mg PO daily for 5 days | No |
| 7 | 65 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 1.7 | 48.1 | Bromadiolone 259 ng/mL | 24.3 | 10 mg PO daily for 8 days, 15 mg PO 2 times a day for 6 days, 10 mg PO 2 times a day for 21 days | No |
| 8 | 90 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 1.9 | 35.1 | Bromadiolone 103 ng/mL[#] | 33.0[#] | 10 mg IV 3 times for 7 days (then died of hospital acquired pneumonia) | No |
| 9 | 79 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 2.2 | 20.4 | Brodifacoum 56 ng/mL[#] | 109[#] | 10 mg IV 3 times a day for 8 days | No |
| 10 | 60 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 5.2 | 65.3 | Coumatetralyl | – | 15 mg PO 2 times a day for 9 days | No |
| 11 | 69 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | 3.2 | 24.8 | Coumatetralyl | – | 10 mg PO daily for 2 days, 15 mg PO 2 times a day for 2 days, 10 mg PO daily for 3 days | No |
| 12 | 47 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 396 ng/mL, coumatetralyl | 7.5 | Not given (INR monitored every 1–2 days for 14 days and remained normal) | No |
| 13 | 53 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 228 ng/mL | 42.0 | Not given (INR monitored for 29 days and remained normal) | No |
| 14 | 53 | Female | | Solid | < 1.5 | N/A | Bromadiolone 188 ng/mL | 7.2 | | No |

**Table 1** (continued)

| | Patient | | Clinical presentation | Form of rat bait taken | Peak INR | Time of peak INR post-exposure (h) | Agents detected in serum, and peak/highest bromadiolone/brodifacoum level(s) measured | Time of serum sample taken post-exposure (h) | Vitamin K1 regimen | FFP used |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (year) | Sex | | | | | | | | |
| | | | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | | | | | | Not given (INR monitored > 48 h and remained normal) | |
| 15 | 54 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 154 ng/mL[#] | 151.8[#] | 10 mg PO 4 times a day for 9 days (as prophylactic treatment for increasing trend of INR in the first 48 h), 10 mg PO 4 times a day for 27 days (in view of high serum superwarfarin level) | No |
| 16 | 40 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 148 ng/mL[#] | 69.5[#] | Not given (INR monitored for 26 days and remained normal) | No |
| 17 | 43 | Male | Suicidal attempt with rodenticide ingestion, jumped from height with polytrauma | Solid | < 1.5 | N/A | Bromadiolone 75 ng/mL | 22.0 | 10 mg IV daily for 8 days, 10 mg PO daily for 24 days* | Yes* |
| 18 | 47 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 58 ng/mL | 12.0 | 10 mg IV daily for 2 days | No |
| 19 | 40 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 22 ng/mL | 3.5 | Not given | No |
| 20 | 49 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 12 ng/mL | 18.8 | Not given | No |
| 21 | 55 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 5 ng/mL | 32.5 | Not given | No |
| 22 | 18 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Brodifacoum 9 ng/mL | 24.0 | Not given | No |
| 23 | 1 | Female | Accidental exposure to rodenticides, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 7 ng/mL | 28.5 | Not given | No |
| 24 | 18 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 7 ng/mL | 24.5 | Not given | No |
| 25 | 30 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 8 ng/mL, warfarin | 32.0 | 10 mg PO daily for 2 days | No |
| 26 | 63 | Male | | Solid | < 1.5 | N/A | Bromadiolone 8 ng/mL | 5.5 | Not given | No |

**Table 1** (continued)

| | Patient | | Clinical presentation | Form of rat bait taken | Peak INR | Time of peak INR post-exposure (h) | Agents detected in serum, and peak/highest bromadiolone/brodifacoum level(s) measured | Time of serum sample taken post-exposure (h) | Vitamin K1 regimen | FFP used |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age (year) | Sex | | | | | | | | |
| | | | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | | | | | | | |
| 27 | 63 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Bromadiolone 7 ng/mL | 36.0 | Not given | No |
| 28 | 75 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Coumatetralyl | N/A | Not given | No |
| 29 | 35 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Coumatetralyl | N/A | Not given | No |
| 30 | 34 | Female | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Flocoumafen | N/A | Not given | No |
| 31 | 51 | Male | Suicidal attempt with rodenticide ingestion, clinically asymptomatic | Solid | < 1.5 | N/A | Warfarin | N/A | Not given | No |
| Patients without exposure history | | | | | | | | | | |
| 32 | 72 | Male | Initially presented with blood stained saliva and gum bleeding; re-admitted with gastrointestinal bleeding | Unknown | > 6.0 | Unknown | Bromadiolone 66 ng/mL | Unknown | 10 mg IV daily for 5 days, 10 mg PO daily for 57 days | No |
| 33 | 79 | Male | Bruises over limbs | Unknown | > 6.0 | Unknown | Bromadiolone 42 ng/mL, brodifacoum 16 ng/mL | Unknown | 10 mg IV daily for 7 days | Yes |
| 34 | 54 | Male | Right arm hematoma | Unknown | > 6.0 | Unknown | Bromadiolone 222 ng/mL | Unknown | 10 mg IV daily for 10 days, 20 mg PO 3 times a day for 63 days | Yes |
| 35 | 70 | Male | Hemoperitoneum | Unknown | > 6.0 | Unknown | Bromadiolone 452 ng/mL, brodifacoum 15 ng/mL | Unknown | 10 mg IV daily for 21 days, 10 mg PO 3 times a day for 5 days, 5 mg PO 3 times a day for 26 days | No |
| 36 | 61 | Male | Gross hematuria | Unknown | > 6.0 | Unknown | Bromadiolone 534 ng/mL | Unknown | 10 mg PO daily for 15 days, 10 mg PO 3 times a day for 80 days | No |
| 37 | 81 | Male | Gum bleeding | Unknown | > 6.0 | Unknown | Bromadiolone 579 ng/mL | Unknown | 10 mg IV daily for 2 days, 20 mg PO 2 times a day for 14 days, 20 mg PO 4 times a day for 69 days | Yes |
| 38 | 60 | Male | Initially presented with epistaxis; re-admitted with hematoma over limbs | Unknown | > 6.0 | Unknown | Bromadiolone 87 ng/mL, chlorophacinone | Unknown | 10 mg IV daily for 7 days, 10 mg PO 6 times a day for 2 days, 20 mg PO 6 times a day for 57 days | Yes |
| 39 | 61 | Male | Gross hematuria, gum bleeding | Unknown | > 6.0 | Unknown | Bromadiolone 879 ng/mL, brodifacoum 29 ng/mL | Unknown | | Yes |

**Table 1** (continued)

| Patient | | Clinical presentation | Form of rat bait taken | Peak INR | Time of peak INR post-exposure (h) | Agents detected in serum, and peak/highest bromadiolone/brodifacoum level(s) measured | Time of serum sample taken post-exposure (h) | Vitamin K1 regimen | FFP used |
|---|---|---|---|---|---|---|---|---|---|
| Age (year) | Sex | | | | | | | | |
| | | | | | | | | 10 mg IV daily for 5 days, 10 mg IV 4 times a day for 19 days, 25 mg PO 4 times a day for 13 days | |
| 40 | 30 | Male | Initially presented with hematuria; re-admitted with gross hematuria | Unknown | > 6.0 | Unknown | Bromadiolone 350 ng/mL, brodifacoum 562 ng/mL | Unknown | 10 mg IV 2 times a day for 5 days, 10 mg PO 4 times a day for 2 days, 25 mg PO 4 times a day for 188 days | Yes |
| 41 | 80 | Male | Blood stained saliva | Unknown | > 6.0 | Unknown | Bromadiolone 123 ng/mL, brodifacoum 27 ng/mL | Unknown | 25 mg PO 2 times a day for 31 days | No |

N/A, not applicable; PO, oral; IV, intravenous; FFP, fresh frozen plasma

# The peak level or the time of peak level cannot be determined, as in these cases, the first sample had the highest concentration among all samples of the same patient

*Vitamin K1, FFP, and cryoprecipitates were given as it was a trauma case requiring operation

abdominal pain, coffee ground vomiting, and limb swelling. They were subsequently diagnosed to have hemoperitoneum, coagulopathy-related gastrointestinal bleeding, and limb hematoma, respectively. Besides, the first INR was checked with a significant time lag after initial presentation in these patients (median, 66.9 h) compared with those with exposure history (median, 9.1 h). Request for anticoagulant-type rodenticide testing was promptly made by clinicians for all cases with exposure history (median, 3.1 days). In contrast, such test was requested by clinicians for only half of the occult poisoning cases, with the remaining only initiated by pathologists or clinical toxicologists upon consultation. Therefore, there was significant delay in requesting anticoagulant rodenticide test in patients without exposure history (median, 9.3 days; $p < 0.05$). Details of the diagnostic workup in the two groups of patients are shown in Table 4.

Vitamin K1 therapy was given as treatment for poisoning patients with bleeding event (PSS grade 3 or above), and prophylactically to all patients with coagulopathy without clinical bleeding (PSS grades 1 and 2). Therefore, vitamin K1 therapy were given to 11 out of 31 patients with exposure history (35.5%) and all patients without exposure history (100%; $p < 0.01$). All these patients were poisoned by either bromadiolone or brodifacoum, apart from two cases of intentional poisoning in which coumatetralyl was detected. Adequate dose of vitamin K1 was prescribed to all patients with exposure history (median, 1.0 days); in contrast, there was a significant delay in appropriate treatment in those without exposure history (median, 7.0 days; $p < 0.001$) and adequate dosage was finally achieved in only 80% of them. Moreover, after initiation of treatment, INR rebound was observed in eight out of these ten patients but not in those with exposure history ($p < 0.001$). For patients with significant coagulopathy (PSS grade 2 or above), those without exposure history took a median of 10.5 days longer to achieve a normalized INR ($p < 0.05$). Among the 19 patients suffering from severe superwarfarin toxicity, the duration of vitamin K1 treatment in six of them were guided by the trend of INR after a trial of discontinuation of vitamin K1. We observed that when the serum superwarfarin level dropped to a low level, discontinuation of antidote therapy was not associated with INR rebound. Hence, in the other patients, the trial of discontinuation of vitamin K1 was initiated only when the serum superwarfarin level has dropped to a low level. The management and treatment outcomes of the two groups of patients were summarized in Table 5.

## Discussion

Previous reports of superwarfarin poisoning in the literature mostly involved accidental or intentional exposure, and the

**Table 2** Demographics and clinical presentation of the patients with or without exposure history

| | Total ($n = 41$) | Patients with exposure history ($n = 31$) | Patients without exposure history ($n = 10$) |
|---|---|---|---|
| Demographics | | | |
| Age (range (median)) | 1–90 (53) | 1–90 (47) | 30–81 (65.5) |
| Male ($n$ (%)) | 31 (75.6) | 21 (67.7) | 10 (100.0) |
| Time of presentation after exposure (median (IQR)) | – | 8.5 h (2.6–15.9 h) | – |
| Bleeding ($n$ (%)) | 10 (24.4) | 0 (0) | 10 (100.0) |
| Oral mucosal bleeding | 4 (9.8) | 0 (0) | 4 (40.0) |
| Hematoma over limbs | 3 (7.3) | 0 (0) | 3 (30.0) |
| Gross hematuria | 2 (4.9) | 0 (0) | 2 (20.0) |
| Epistaxis | 1 (2.4) | 0 (0) | 1 (10.0) |
| Gastrointestinal bleeding | 1 (2.4) | 0 (0) | 1 (10.0) |
| Spontaneous ecchymosis | 1 (2.4) | 0 (0) | 1 (10.0) |
| Hemoperitoneum | 1 (2.4) | 0 (0) | 1 (10.0) |
| Modified poisoning severity score (PSS) | | | |
| PSS grade 0 ($n$ (%); INR ≤ 1.5) | 20 (48.8) | 20 (64.5) | 0 (0) |
| PSS grade 1 ($n$ (%); INR > 1.5 and ≤ 2.5) | 5 (12.2) | 5 (16.1) | 0 (0) |
| PSS grade 2 ($n$ (%); INR > 2.5; no bleeding events) | 6 (14.6) | 6 (19.4) | 0 (0) |
| PSS grade 3 ($n$ (%); INR > 2.5; with bleeding events) | 10 (24.4) | 0 (0) | 10 (100.0) |
| PSS grade 4 ($n$ (%); fatal poisoning) | 0 (0) | 0 (0) | 0 (0) |

diagnosis was usually based on exposure history alone [4, 19, 20]. A number of occult superwarfarin poisoning cases have also been reported in recent years [5–7, 9–12], including eight patients described in a Korean study [8]. However, comparison of the clinical characteristics and outcomes in the two groups of patients with or without exposure history has not been previously described in the literature and the underlying cause of occult poisoning remained obscure. In the present study, we reported a large series of 41 anticoagulant-type rodenticide poisoning cases with laboratory confirmation, including ten cases of superwarfarin poisoning without exposure history, and the clinical characteristics, diagnostic workup, management, and outcomes between the two groups were evaluated. Similar to previous reports, bromadiolone and brodifacoum were the two most common agents identified [3, 19, 20].

**Table 3** Types of anticoagulant-type rodenticide(s) detected in the blood samples of the patients

| | Total ($n = 41$) | Patients with exposure history ($n = 31$) | Patients without exposure history ($n = 10$) |
|---|---|---|---|
| Anticoagulant-type rodenticide(s) detected | | | |
| Bromadiolone only ($n$ (%)) | 22 (53.7) | 18 (58.1) | 4 (40.0) |
| Bromadiolone and brodifacoum ($n$ (%)) | 7 (17.1) | 2 (6.5) | 5 (50.0) |
| Bromadiolone and warfarin-type agents ($n$ (%)) | 4 (9.8) | 3 (9.7) | 1 (10.0) |
| Brodifacoum only ($n$ (%)) | 2 (4.9) | 2 (6.5) | 0 (0) |
| Flocoumafen ($n$ (%)) | 1 (2.4) | 1 (3.2) | 0 (0) |
| Warfarin-type agents only ($n$ (%)) | 5 (12.2) | 5 (16.1) | 0 (0) |
| Serum quantitative result (ng/mL) | | | |
| Peak serum bromadiolone/brodifacoum level measured (median (IQR)) | | | |
| Taken solid rat bait | – | 67 (8–154) | 337 (87–562) |
| Taken stock solution | | 14,342 (3720–33,100)[#] | |

[#] For those who had taken superwarfarin stock solution (n = 3), serum superwarfarin levels were shown as mean (range)

**Table 4** Diagnostic workup of the patients with or without exposure history

| | Patients with exposure history ($n = 31$) | Patients without exposure history ($n = 10$) | $p$ value* |
|---|---|---|---|
| Time to request first INR after presentation (median (IQR)) | 9.1 h (5.5–14.8 h) | 66.9 h (41.5–520.1 h) | 0.0007 |
| Anticoagulant-type rodenticide test | | | |
| Requested by clinician ($n$ (%)) | 31 (100%) | 5 (50%) | 0.0003 |
| Suggested by pathologist/clinical toxicologist ($n$ (%)) | 0 (0%) | 5 (50%) | – |
| Time to test for anticoagulant-type rodenticide after presentation, median (IQR) | 3.1 days (1.3–4.8 days) | 9.3 days (3.3–11.6 days) | 0.0117 |

*By Mann-Whitney $U$ test

In this study, patients without exposure history had more severe clinical features, as shown by the presence of bleeding events in all ten patients. More delayed investigation and diagnosis as well as initiation of treatment was observed in this group, as illustrated in Tables 4 and 5, respectively. These findings were actually not surprising; while the diagnosis of anticoagulant-type rodenticide poisoning was straightforward in patients with an obvious history of exposure, the occult poisoning cases, given their rarity, often went unrecognized and misdiagnosed, hence leading to a delay in management. Enhancing the clinical awareness to this uncommon but severe poisoning is the key to proper management. Early clotting profile testing is essential in patients with unexplained or prolonged bleeding. The frontline clinicians should have a high index of suspicion for superwarfarin poisoning in patients with marked coagulopathy of unknown etiology, even though the clinical presentation may be seemingly innocuous as a "simple case of gum bleeding." A median lapse of 66.9 h between time of presentation and time to request for clotting profile testing, in patients with active bleeding, is clearly less than satisfactory. Clotting factor testing, if performed, would show deficiency of all vitamin K-dependent factors II, VII, IX, and X [18]. Serum testing for anticoagulant-type rodenticides is the definitive test to confirm or exclude the diagnosis but unfortunately, this is not widely available.

In the present study, all patients without history of exposure were referred to specialized toxicology center(s) for treatment and monitoring after the diagnosis was made. Detailed family, occupational, dietary and drug history (including the use of alternative medicine or over-the-counter drug or health supplement), living and working environment were reviewed by medical officers with toxicology training, in an attempt to identify the potential causes, such as accidental or environmental exposure to rodenticides and to look for possible clustering of cases. In a number of cases, the local Department of Health has also been involved in the investigation of possible exposure from food and environment. Despite thorough investigation, the context of how the poisoning occurred in patients without exposure history remained a puzzle to be solved. The cases apparently occurred in isolation with no evidence of clustering. All patients had no history of psychiatric diseases and denied any suicidal ideations. One peculiar observation was that all patients in the group without exposure history were males, though there was also male predominance in the group with known exposure to rodenticides (67.7%). Although females were generally reported to have a higher

**Table 5** Management and treatment outcomes of the patients who required vitamin K1 therapy

| | Patients that required vitamin K1 therapy | | $p$ value* |
|---|---|---|---|
| | Patients with exposure history ($n = 31$) | Patients without exposure history ($n = 10$) | |
| Number of patients ($n$ (%)) | 11 (35) | 10 (100) | 0.0015 |
| Adequate dose of vitamin K1 given ($n$ (%)) | 11 (100) | 8 (80) | 0.4150 |
| Time to achieve adequate vitamin K1 dose, median (IQR) | 1.0 days (1.0–2.5 days) | 7.0 days (4.5–13.5 days) | 0.0128 |
| INR rebound after initiation of vitamin K1 ($n$ (%)) | 0 (0) | 8 (80) | 0.0009** |
| Time to normalize INR, median (IQR) | | | |
| INR > 1.5 and ≤ 2.5 | 3.0 days (2.0–3.0 days) | – | – |
| INR > 2.5 | 8.0 days (4.0–12.0 days) | 18.5 days (14.0–23.0 days) | 0.0299 |

*By Mann-Whitney $U$ test unless otherwise specified

**By $t$ test

frequency of intentional drug poisoning compared with males [21], whether the sex difference observed in the group without exposure history suggested against intentional poisoning was yet inconclusive. Possibilities of environmental exposure, malicious poisoning, and factitious disorder cannot be excluded. Nevertheless, our biochemical findings did provide some clues for the possible form of the culprit. Most commercially available rodendicides are in form of solid bait and contain superwarfarins 0.005% (*w*/*w*). Superwarfarins at 0.005% (*w*/*w*) is considered relatively "safe" for humans as the reported lethal dose is at least 300 g of bait [22]. Superwarfarins are also available in the form of stock solution used as industrial reagent, with a concentration of 0.5% (*w*/*w*) which is 100 times higher than those of the solid rat bait. Though the highly concentrated superwarfarin stock solution is not a registered domestic product in Hong Kong, it is still available on the market based on our observation. Despite a presumable delay in presentation and sample collection, the serum superwarfarin levels detected in the group without history of exposure were still significantly higher than the peak levels in those who reported to have taken a potentially lethal dose of rat bait. These findings suggested the highly concentrated stock solution, instead of the rat bait, probably was the poison involved in the group with poisoning from unknown source.

For those patients who do not develop clinical symptoms or coagulation abnormalities at 48 h after anticoagulant rodenticide exposure, they were kept under observation without treatment as suggested previously [18]. In this study, vitamin K1 therapy was offered to all patients with PSS grade 1 or above. High-dose vitamin K1 given multiple times per day for a prolonged period is the cornerstone of treatment for superwarfarin poisoning [2, 18, 22]. In superwarfarin poisoning, the recycling of vitamin K1 is abolished, and thus the vitamin K1 administered and the subsequent activated clotting factors would be rapidly consumed. The administration of vitamin K1 should henceforth follow the half-lives of clotting factors produced which are in the order of a few hours. Currently, there is no established guideline on vitamin K1 dosage for superwarfarin poisoning. However, based on data from previous studies [2, 18, 22] and our local experience, a minimum of 30 mg vitamin K1/day in divided doses is generally accepted as an appropriate starting dose in our local practice. Subsequent dosing is based on titration against clotting profile. Intravenous vitamin K1 is mainly reserved for patients who are hemodynamically unstable due to potential adverse effect of anaphylactoid reactions with early switch to oral regimen once the clinical condition has been stabilized. For those who are hemodynamically stable with no symptoms and signs suggestive of clinical bleeding, oral vitamin K1 regimen would be preferred. It is also essential to give vitamin K1 therapy for a prolonged period in view of the long half-lives of superwarfarins. For those with mild anticoagulant poisoning, if adequate dose of vitamin K1 is given, coagulopathy should be corrected in a day or two. In this study, the time to resolution of coagulopathy was quite long; this could be contributed by the relatively inadequate dose, and the delay in initiation or up-titration of vitamin K1 therapy. For those who experienced severe anticoagulant toxicity, such as those presented with symptomatic bleeding or those with extremely high serum superwarfarin levels, correction of coagulopathy could be even more challenging. Inadequate dosage or hasty discontinuation of vitamin K1 would lead to relapse of PT and aPTT prolongation and bleeding risk, as illustrated by the INR rebound in 80% of the patients without exposure history, mostly before the definitive diagnosis was made. It is therefore of great importance to have frequent monitoring of clotting profile and review of vitamin K1 regimen. Early involvement of local medical toxicology services is advisable in suspected or confirmed cases of anticoagulant poisoning.

We have developed an in-house LC-MS/MS method for testing both warfarin- and superwarfarin-type rodenticides. In addition to providing a definitive diagnosis, the test, which also allows measurement of serum bromadiolone and brodifacoum level, may also be useful for guiding vitamin K1 treatment. End point of the antidote therapy is traditionally guided by the trend of clotting profile after discontinuation of vitamin K1. Recurrence of PT and aPTT prolongation signifies premature termination of treatment and re-initiation of vitamin K1 would be indicated. However, this clinical "trial-and-error" approach may put the patient at risk of complication. On the other hand, serum bromadiolone or brodifacoum levels of less than 10 ng/mL do not cause coagulopathy and do not require specific treatment based on our and others' experience [23, 24]. In the present study, the patients who had vitamin K1 therapy stopped at serum superwarfarin levels below 10 ng/mL did not develop further coagulopathy. We proposed serum superwarfarin level monitoring as an objective means to guide treatment end point, in adjunction to clinical and clotting profile monitoring.

One limitation of this retrospective study is ascertainment bias as the data collection is a passive procedure depending on test or consultation requests by the clinicians, and our authors responsible for data abstraction were not blinded to the study hypothesis. For those with history of exposure but mild clinical symptoms, toxicology testing or consultation may not be requested; while for those mild cases without a history of exposure, the diagnosis may be missed. Our case series might therefore represent the cases with more severe outcome in the overall continuum of anticoagulant rodenticide poisoning. Besides, it is not possible to pinpoint an accurate peak serum superwarfarin level or the time of reaching peak level in all patients because this depends on continuous monitoring of superwarfarin concentrations from early phase before the peak level is reached, through the distribution phases where there are continuous drops from the peak level. However,

continuous monitoring of superwarfarin concentrations is technically impossible. In our experience, the peak serum superwarfarin level usually occurs within 24 to 48 h of single-dose ingestion. But in 20% of the cases, the sample collection might be delayed, as the first sample taken had the highest superwarfarin concentration where the peak level might be missed.

## Conclusions

Occult superwarfarin poisoning is a potentially life-threatening yet under-recognized condition, leading to delayed workup and initiation of management. Clinicians should have a high index of suspicion for this uncommon poisoning in patients with unexplained coagulopathy. Particularly, coagulopathy cases with suboptimal INR response to standard dosing of vitamin K1, rebound of INR during vitamin K1 treatment, or unusual presentation of isolated vitamin K-dependent clotting factor deficiency may warrant further toxicological investigation. The underlying cause of occult superwarfarin poisoning remains obscure and warrants further study.

### Compliance with Ethical Standards

**Sources of Funding for Project** None

**Previous Presentation of Data at Meetings or in Abstract Form** None

**Conflicts of Interest** The authors declare that they have no conflict of interest.

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