衞生署
Department of Health

Poisoning Watch

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Inside This Issue

Superwarfarin poisoning

Introduction

Many rodenticides used today belong to anticoagulant compounds (also referred as "blood thinner") that interfere with blood clotting and cause death of mice and rats from excessive bleeding.

In Hong Kong, pesticides, including rodenticides are regulated by the Pesticides Ordinance (Cap. 133), which stipulates that no person shall import, manufacture, sell (including retail) or supply any registered pesticides unless he/she is holding a valid Pesticides Licence. Warfarin and several types of superwarfarin are registered pesticides in Hong Kong under Cap. 133.

While anticoagulant rodenticides are very effective for controlling rodents, their potential risks should not be overlooked. Indeed, people can be exposed to rodenticides from eating, drinking, inhaling, and by skin contact. Exposure to these agents, especially superwarfarin with long-acting anticoagulant effect, can cause life-threatening coagulopathy (blood clotting disorder) in humans.

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Why warfarin and superwarfarin can cause bleeding?

In the 1950s and early 1960s, warfarin-based rodenticides were introduced to kill rodents. Warfarin interferes with the synthesis of coagulation factors in rats, which kill them from bleeding after eating warfarin-containing bait. Superwarfarins are long-acting anticoagulant rodenticides developed from warfarin in the 1970s to overcome warfarin resistance in rats [2,3]. Examples of superwarfarin are bromadiolone, brodifacoum, difenacoum and difethialone. These anticoagulant rodenticides are widely used in domestic, industrial and agricultural settings nowadays.

Both warfarin and superwarfarin work by inhibition of vitamin K epoxide reductase enzyme complex, so that the body cannot recycle vitamin K. Vitamin K deficiency thereafter hinders the synthesis of vitamin K-dependent coagulation factors including factor II, VII, IX, and X, leading to prolonged blood clotting time [4].

Superwarfarin is much more potent than warfarin and has a much longer half-life, from 16 to 36 days for brodifacoum [5,6,7] and between 10 and 24 days for bromadiolone [8,9]. The elimination half-life of warfarin in humans was estimated to be 36 to 42 hours [10,11]. Hence, exposure to superwarfarins results in a much prolonged period of anticoagulation which can result in clinical bleeding.

Causes of superwarfarin poisoning

Common causes of superwarfarin poisoning include accidental ingestion and suicide attempts [12]. Less common causes include surreptitious administration [13,14], malicious poisoning, psychiatric conditions [15], occupational exposure [16] and by mixing with recreational drugs [17].

Clinical presentation of superwarfarin poisoning

Upon exposure to superwarfarin, coagulopathy does not take place until existing stores of vitamin K and active coagulation factors in the body are depleted. In general, coagulopathy can usually be detected within 48 hours following exposure [18]. Bleeding symptoms occur later, usually 3 to 9 days upon exposure [4].

Patients with accidental exposure to superwarfarin usually ingest a small amount only and will remain asymptomatic. Those who have substantial or repeated chronic ingestions of superwarfarin will mostly present with bleeding such as gross haematuria, mucosal bleeding, gastrointestinal bleeding, soft tissue bleeding, bleeding that is disproportionate to the level of the injury, internal organs haemorrhage, which may result in anemia. The most common clinical presentation is gross hematuria with abdominal or flank pain [5,6,18].

Coagulopathy may persist for many months and recurrent bleeding may occur [19,20]. Cases with severe blood loss may develop shock, coma and even death. Most deaths due to superwarfarin poisoning result from intracranial haemorrhage [21].

Investigations for superwarfarin poisoning

Although rodenticide poisoning is uncommonly encountered in clinical practice locally, warfarin/superwarfarin poisoning should be suspected in all patients with unexplained bleeding and/or prolongation of clotting time especially with lack of response to standard treatment.

While some cases of superwarfarin poisoning may be evident based on the definite history of anticoagulant rodenticide exposure, symptoms and signs of bleeding and/or coagulopathy, some patients may not volunteer such information. For patients with unexplained bleeding, it is important to perform blood tests for clotting function to look for abnormalities of coagulopathy. After ingestion of a quantity of superwarfarin sufficient to cause coagulopathy and/or bleeding, blood clotting indicators will typically be abnormal at 12 to 24 hours and peak at 36 to 72 hours [5]. The presence of long-acting superwarfarin(s) in clinical specimen including blood or urine can confirm the diagnosis [8,22,23,24].

Management of superwarfarin poisoning cases

The public should always seek medical advice as soon as possible in case of accidental ingestion of rodenticides.

Patients with active bleeding or symptoms of coagulopathy require treatment by vitamin K (either via intravenous route or oral form) and/or transfusion of blood products that contain clotting factors.

Some patients may require prolonged inpatient care for parenteral therapy because of poor compliance to oral vitamin K [25]. As coagulopathy after exposure to superwarfarin may persist for months, long-term outpatient care is often required and good compliance to treatment is essential.

Global situation

Across the globe, the majority of anticoagulant rodenticide exposures occur in young children, who usually ingest small amount of rodenticide and do not develop significant coagulopathy [18,26,27,28,29,30]. Most exposures were accidental. In contrast, the source of warfarin exposure often could not be established in adults. While some cases admitted intentional exposure as suicide attempts, most cases did not report any exposure to rodenticides during initial presentation to medical services [31,32,33,34].

In the United States, children accounted for around 90% of exposures to superwarfarin. More than 30% exposed patients required treatment in a healthcare facility, and 2% of all exposures resulted in morbidity or mortality. Most exposures were reported to be unintentional. Inhalational, transcutaneous, and oral routes of exposure had been documented. The most common clinical presentation was hematuria. Fatalities were most commonly associated with intracranial hemorrhage [35].

In east China, suicide (19.7%) and accident (12.0%) were the most common causes of intoxication, followed by homicide (0.8%), but the poisoning cause remained unknown for a large number of positive cases (67.5%). Bromadiolone was the most commonly observed anticoagulant rodenticide found in the blood samples, followed by brodifacoum [30].

Epidemiological findings in various places suggested that many superwarfarin poisoning cases had unidentified exposures, highlighting again the importance of investigations for deranged blood clotting profile in patients with unexplained bleeding symptoms.

Local situation

The Department of Health (DH) receives notifications of poisoning cases with potential public health implications, investigates for the underlying exposure and conduct epidemiological measures to limit the affected populations.

From 2012 to 2021 (up to November), the DH had received a total of 17 notifications of superwarfarin poisoning (Figure 1), with 1-3 notifications per year. Most of them were males (12 males and 5 females) and their ages ranged from 24 to 85 years old (median: 54 years old) (Figure 2, 3).

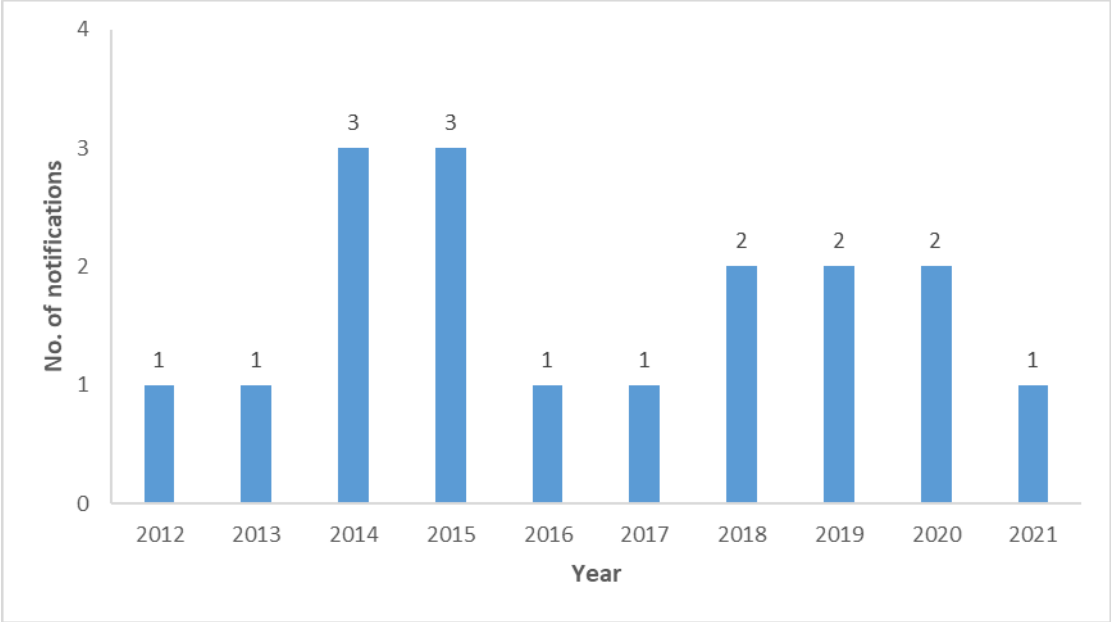

Figure 1: Number of notifications of superwarfarin poisoning from 2012 to 2021 (as of November, 2021)

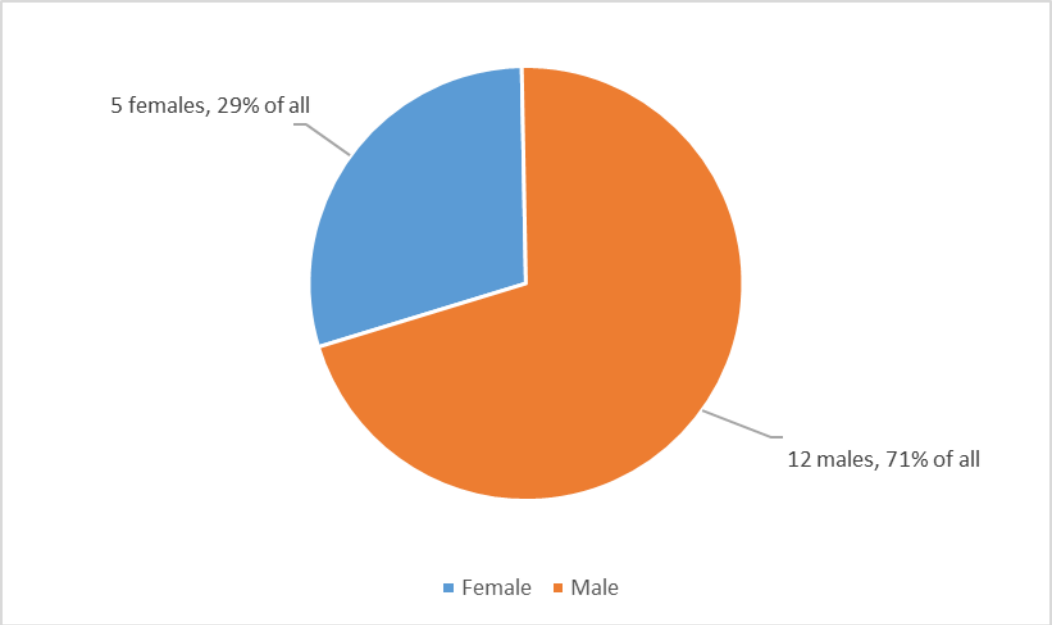

Figure 2: Sex distribution of superwarfarin poisoning cases from 2012 to 2021 (as of November, 2021)

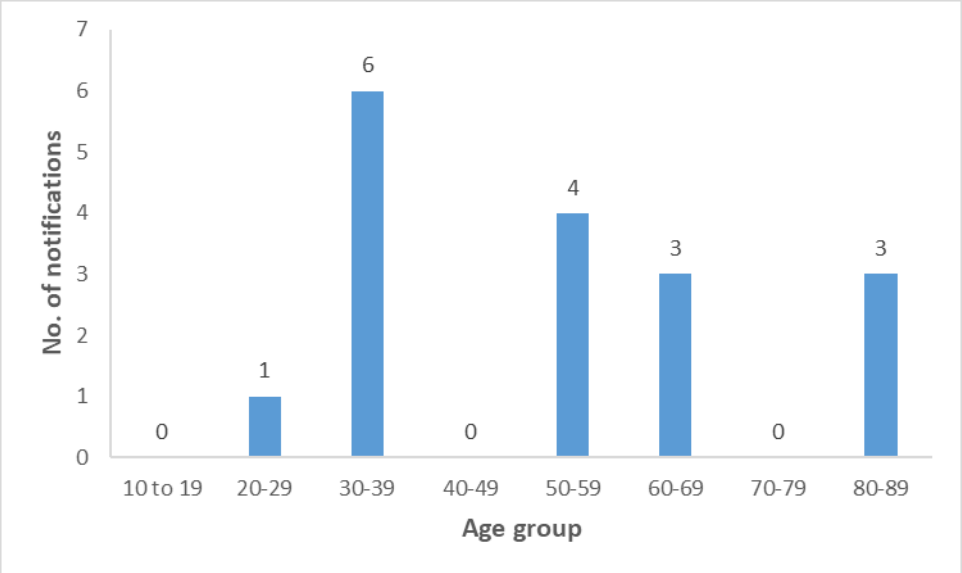

Figure 3: Age distribution of superwarfarin poisoning cases from 2012 to 2021 (as of November, 2021)

Clinical presentation

Most patients (16/17, 94.1%) developed symptoms, while the remaining one (5.9%) was asymptomatic and offered a clinical consultation because of diagnosis of a superwarfarin poisoning case in the same household. The symptomatic patients mostly presented with bleeding and/or coagulopathy [1], such as gross haematuria (11, 64.7%), gum bleeding (4, 23.5%), haemoptysis (2, 11.8%), haematoma (2, 11.8%, blood-stained saliva or vomitus (2, 11.8%), bruising (1, 5.9%) and other symptoms (6, 35.3%) such as loin pain, epigastric pain and dizziness (Figure 4).

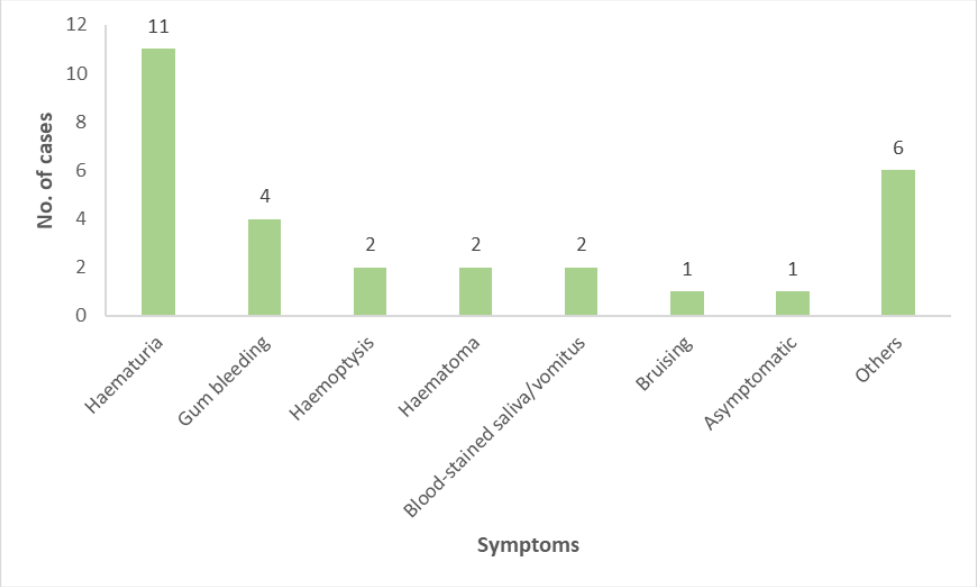

Figure 4: Clinical presentation of superwarfarin poisoning cases from 2012 to 2021 (as of November, 2021)
* Most patients presented with more than 1 symptom.

All but the asymptomatic case required admission to hospitals (16/17, 94.1%). None of them required admission to the intensive care unit nor died from poisoning.

Except for the asymptomatic case, all other cases (16/17, 94.1%) had deranged clotting profile. In all cases, there were positive detections of superwarfarin(s) in their serum. In addition, there were also positive detections of superwarfarin(s) in the urine samples of 4 cases (23.5%). The most common type of superwarfarin detected was bromadiolone (15/17, 88.2%), followed by brodifacoum (9, 52.9%) and difenacoum (1, 5.9%) [2] (Figure 5). Regarding the case detected with difenacoum, as difenacoum has not been registered as pesticides in Hong Kong under Cap. 133, this case was reported to Agriculture, Fisheries and Conservation Department (AFCD) for action as appropriate. Since the patient claimed to have accidentally ingested rodenticides collected at the back alley of his workplace, AFCD conducted a site investigation at the alleged premises. Nevertheless, no irregularities pertaining to Cap. 133 was found during AFCD's investigation and the exact source of rodenticides could not be ascertained. Educational leaflets and advice were given to the management office of the alleged premises by AFCD in order to enhance awareness on exposure and safe use of rodenticides at work. Health advice regarding proper personal hygiene, storage and disposal of rodenticides was given to the patient and his family members by Department of Health (DH). They were also reminded to seek medical advice as soon as possible in case of any inadvertent exposure to rodenticides.

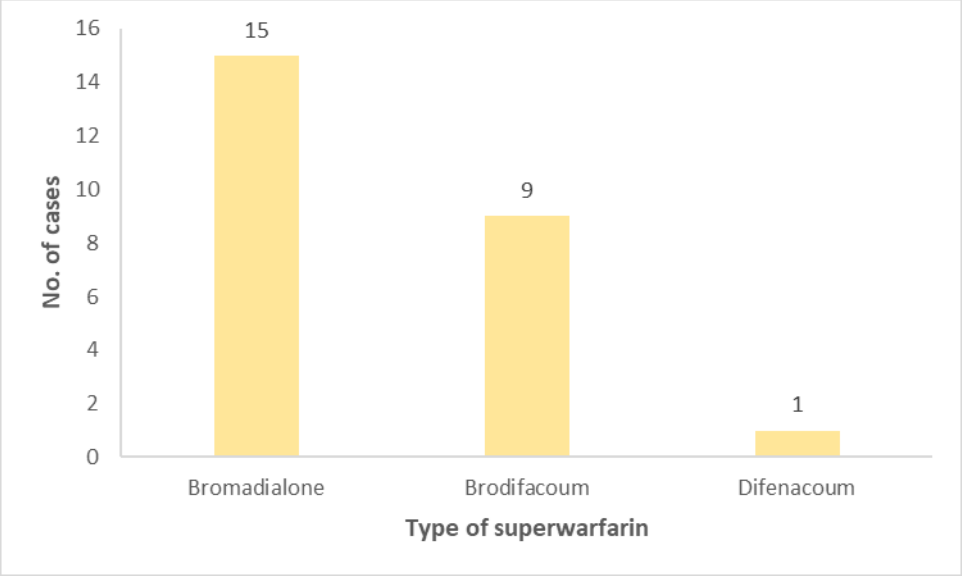

Figure 5: Type of superwarfarin exposure among cases from 2012 to 2021 (as of November, 2021)
* Some patients were exposed to more than 1 type of superwarfarin .

Exposure

Similar to the epidemiological findings in other places, the source of superwarfarin in a large proportion of the local cases could not be identified. Among the 17 cases, only 2 (11.8%) reported definite exposure to rodenticides, while others could not recall any exposure to rodenticides or rats. A food sample collected from the home of one case was detected to have bromadiolone. However, subsequent investigation did not reveal any evidence of contamination of the food by bromodiolone at the retailer and importer levels. The exact source of contamination of bromodiolone in the concerned food sample could not be ascertained.

As revealed in the findings of a local study conducted in a tertiary referral clinical toxicology laboratory from 2010 to 2014, the most common exposures were bromadiolone (91.7%) and brodifacoum (25%) which were similar to our current findings. 69.4% had exposure during suicidal attempts, 2.8% had accidental exposure, and the exposure for the remaining 27.8% cases remained unidentified [33].

Treatment

Majority of the cases were treated by transfusion of blood products with clotting factors and vitamin K (9, 52.9%), or vitamin K only (7, 41.2%). The asymptomatic case (1, 5.9%) did not need any treatment (Figure 6).

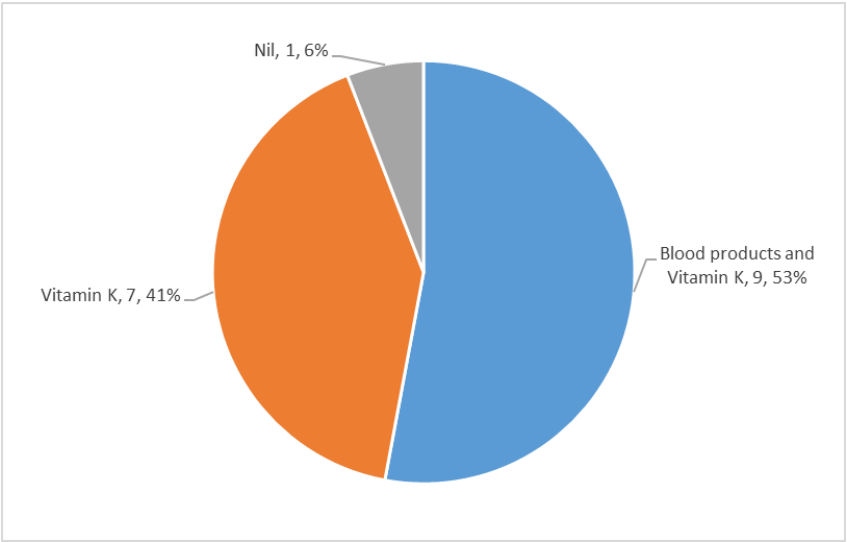

Figure 6: Treatment of 17 superwarfarin cases from 2012 to 2021 (as of November, 2021)

A cluster of superwarfarin poisoning cases in 2020

In the past 10 years, one cluster of two superwarfarin poisoning cases was recorded. These two cases involved a mother (case 1) and her son (case 2) and were recorded in 2020.

Case 1 was a 59-year-old woman who was not on warfarin. She presented to the hospital with loin pain, lower abdominal pain and gross hematuria. Investigation revealed her clotting profile was deranged with anaemia. Coagulation factor assay showed reduced vitamin K-dependent clotting factors (II, VII and X). Bromadiolone was also detected in her serum sample. She was given vitamin K and transfusion of blood products. Upon discharge from the hospital, she was given oral vitamin K which was gradually tapered off. Her clotting profile gradually normalised during the subsequent follow-ups and her serum specimen also became negative for bromadiolone.

Case 2 was a 37-year-old man, the son of case 1. He enjoyed good past health and was not on warfarin. He attended a public hospital for screening with blood test for clotting profile and superwarfarin level. His clotting profile was normal but trace amount of bromadiolone was detected in his serum specimen. He remained asymptomatic with no bleeding symptoms all along. He did not require hospitalisation.

Both patients could not recall any history of rodenticide exposure. They denied any suicidal ideation. They were not aware of any malicious intent towards them. Home visit was conducted with the consent of the patients. No suspicious item was identified in patient's home. No rodenticide or dead rats were found in patient's home. Food samples were collected from patients' home and sent for testing for superwarfarin. Bromadiolone was not detected in any of the specimens. In other words, the comprehensive history taking, home visit and testing of food samples did not reveal any exposure history to rodenticides. The source of superwarfarin in these two cases remained unknown.

Advice to the public

Pesticides especially rodenticides should only be used when they are absolutely necessary.

To reduce the risk of accidental exposure to pesticides (including rodenticides), the public should

- Keep pesticides away from food, drinks and feedstuffs and out of reach of children.
- Always wash hands thoroughly after touching any pesticides.
- Do not reuse the container box of any pesticides for any other purpose.
- Dispose of pesticides as standard municipal waste after use.
- Always seek medical advice as soon as possible in case of accidental ingestion of pesticides, whether symptomatic or not.

For more information on safe and proper use of pesticides, please visit AFCD's website at https://www.afcd.gov.hk/english/quarantine/qua_pesticide/qua_pes_safe/qua_pes_safe.html .

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