EDITORIAL

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Can we more efficiently save patients with vitamin K-dependent coagulopathy caused by superwarfarin intoxication?

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Superwarfarins (brodifacoum, difenacoum, bromadiolone, and chlorophacinone) are anticoagulant rodenticides similar to warfarin but that contain various phenyl groups that replace the terminal methyl group. These substitutions result in a fat-soluble, long-acting anticoagulant that is almost 100-fold more potent than the parent compound [1,2]. Initially developed to overcome the rapidly developing warfarin resistance encountered in rats, superwarfarins have become commonplace in homes and businesses. As a result, human poisoning has become an increasing problem, with more than 16,000 cases of ingestion reported annually in the past several years [3,4]. Many of these ingestions are accidental; however, some are intentional, taking the form of suicide or homicide. Moreover, a small but increasing subset is related to "lacing" (the prolonging of the effect of drugs of abuse), Munchausen syndrome, exposure among factory workers, and exposure from smoking marijuana or "crack" cocaine [5,6]. In addition to ingestion or inhalation, absorption through the skin can occur, and prolonged coagulopathy may occur after inhalation [5].

In the normal physiological state, vitamin K-dependent coagulation factors (factors II, VII, IX, and X; protein C; and protein S) are produced in an inactive form in the liver. The inactive form is converted to the active form by a carboxylase enzyme. In this reaction, the amino-terminus glutamic acid is converted to g-carboxyglutamic acid. This step requires the active form of vitamin K, which is converted to an inactive vitamin K epoxide. The inactive vitamin K epoxide is converted back to active vitamin K through the action of 2,3 vitamin K epoxide reductase (VKOR). Warfarin and superwarfarins inhibit the action of 2,3 VKOR, resulting in a deficiency in active vitamin K, which in turn results in the synthesis of functionally inactive coagulation factors II, VII, IX, and X; protein C; and protein S [4,6].

Brodifacoum more potently antagonizes vitamin K than does warfarin [7]. The elimination half-life of brodifacoum in rats is 156 hours, which is much longer than that of warfarin (17 hours) [7]. Its half-life in humans is 243 to 1,656 hours [8], while that of warfarin is only 17 to 37 hours. The clearance of brodifacoum initially follows zero-order kinetics, but converts to first-order kinetics at lower concentrations [7]. Because appropriate treatment involves massive doses of vitamin K for a prolonged duration, obtaining an initial brodifacoum level on admission fol-

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lowed by a remeasurement after 24 to 48 hours can provide an estimate of the duration of treatment needed [4].

The intake of a superwarfarin by a human was first depicted by Lipton and Klass [9] in 1984, when they reported a case of brodifacoum ingestion by a 31-year-old female with a history of mental illness. The incidence of superwarfarin ingestion has increased during the past 10 years [3,4].

Given this increasing incidence, superwarfarin ingestion should be suspected in any patient with a suspicious history and/or a markedly prolonged prothrombin time (PT) and partial thromboplastin time (PTT). All practitioners should measure superwarfarin drug levels whenever they measure coumadin levels to achieve a clear diagnosis early in the patient's care. Because superwarfarins cause a relative vitamin K deficiency, assays used to detect vitamin K deficiency may be helpful. Indicative results include a low vitamin K plasma level; a high protein induced by vitamin K absence (PIVKA-II) level, which is a measurement of noncarboxylated proteins; prolonged coagulation assays (PT and PTT); low levels of vitamin K-dependent factors II, VII, IX, and X; a low urinary Gla (g-carboxyglutamic acid) level; a high vitamin K 2,3-epoxide level; and a high plasma vitamin K epoxide-to-vitamin K ratio. Typically, the PT and PTT are markedly prolonged in patients who have ingested superwarfarins. Warfarin ingestion may be detected based on the patient's history (especially access to warfarin). Although differentiating between warfarin and superwarfarin ingestion is clinically impossible, the two drugs can be distinguished by laboratory studies. High-performance liquid chromatography is an accurate and effective method of determining the presence and concentration of warfarin and superwarfarins. Unfortunately, the turnaround time of these tests is several days to weeks, making an accurate diagnosis during an emergency department visit nearly impossible. Mixing studies will result in normalization of the PT and PTT because no inhibitors are present. Measuring the coagulation factor activity will reveal deficient vitamin K factor activity (factors II, VII, IX, and X) with normal factor V activity (serving as a control).

Another method of distinguishing between warfarin and superwarfarin ingestion is by the treatment effect. Administration of fresh frozen plasma (FFP) and vitamin K should rapidly correct the coagulopathy associated with warfarin ingestion because of the relatively short half-life of warfarin. The half-life of superwarfarin, on the other hand, will result in repeated prolongation of the PT and PTT 12 to 16 hours after administration of FFP and vitamin K, even if correction to normal levels was initially achieved [4].

Upon establishment of a diagnosis of superwarfarin intoxication, the clinician should be aware of the long half-life and potency of the drug. The standard treatment for superwarfarin ingestion is administration of massive doses of vitamin K for a prolonged period, the duration of which depends on the amount of superwarfarin ingested [6]. Many of the previous published case reports on superwarfarin ingested describe patients being discharged after short-term treatment with plasma administration and vitamin K supplementation, only to have patients return with recurrent coagulopathy due to the prolonged half-life of these agents [10]. With brodifacoum poisoning, every carboxylation reaction requires a new vitamin K1 molecule because vitamin K1 cannot regenerate [6]. For these reasons, vitamin K1 (phylloquinone) should be administered continuously at high dosages (500 to 800 mg/day) and for prolonged periods of time (many days, weeks, or even months) [6,11].

To avoid hematoma formation, the oral route is typically preferred to intramuscular or intravenous injection (oral vitamin K is no longer available for purchase in Korea). Intravenous administration is preferred only if severe bleeding is present because of the risk of an anaphylactic reaction with this route of administration.

Administration of FFP is indicated for patients who are actively bleeding or at high risk of bleeding. Replacement of the necessary coagulation factors can be calculated, and enough FFP to replenish the deficiency should be administered. Given the long half-life of superwarfarins, the effect of FFP will be short-lived. FFP should be administered in conjunction with vitamin K, and may need to be repeated as indicated by the severity of clinical bleeding. Other urgent treatment options include the administration of prothrombin complex concentrate and recombinant factor VIIa. These agents have been shown to be effective in controlling bleeding secondary to superwarfarin ingestion; again, however, their effects are short-lived because of the prolonged half-life of superwarfarins. They have a lower fluid volume than FFP and thus may be preferred in patients who cannot tolerate high-volume infusions yet require rapid correction of a coagulopathy [4,12]. As coagulopathy reversal becomes more aggressive, clini-

cians must also be aware of more recent case reports that highlight the potential simultaneous occurrence of coagulopathy and thrombosis with superwarfarin intoxication [6,10].

Patient risk profiling has recently made significant headway with the recognition of genetic markers of warfarin sensitivity or resistance. Dosage requirements and the likelihood of toxicity are dependent on allelic variants of pharmacokinetic (cytochrome P4502C9) and pharmacodynamic factors, including the immediate target of warfarin, VKOR, and proteins involved in the vitamin K mediation of coagulant activation [12]. Indeed, mutations in the VKOR protein underlie the rare multiple vitamin K-dependent coagulation factor deficiency type 2, which, like warfarin toxicity, presents with frequent intracranial hemorrhages and warfarin resistance in humans and rats. Moreover, predicting patients at risk of intracranial hemorrhage—the most feared complication of warfarin therapy—might be possible through genetic (APOE type 2) or magnetic resonance imaging markers, such as extensive small-vessel white matter disease [12]. Overexpression of wild-type VKORC1, but not VKORC1 carrying the VKCFD2 mutation, leads to a marked increase in VKOR activity, which is sensitive to warfarin inhibition [13].

In Korea, only sporadic reports of superwarfarin intoxication and one observational study involving a few cases of superwarfarin intoxication in Korea have been reported to date [14]. In the article that accompanies this editorial, Lee et al. [15] reported on the individual risk factors for coagulopathy and hemorrhagic symptoms in patients with suspected superwarfarin intoxication. The authors tried to determine how to effectively treat vitamin K-dependent coagulopathy due to suspected superwarfarin intoxication in Korean patients in a single institution. This study showed that a low albumin level ($p = 0.014$) and rodenticide ingestion with concurrent alcohol drinking ($p = 0.023$) might be factors associated with the development of coagulopathy. The authors concluded that the complications of superwarfarin poisoning might be related to the serum albumin level and concurrent alcohol ingestion and that to identify vitamin K-dependent coagulopathy in adult patients, the serum brodifacoum test should be performed despite no history of definitive rodenticide poisoning. The source of exposure for patients with superwarfarin toxicity of unknown origin might be transdermal absorption or inhalation over a long period of time. The authors were unable to identify typical genetic factors (i.e., CYP2C9 and VKORC1 genotyping) among the patients despite the fact that these factors are known warfarin sensitizers in patients suspected to have warfarin poisoning. Additionally, chronic heavy alcohol drinkers might be at risk of hemorrhagic complications because of chronic transdermal absorption or respiration.

This study represents the first attempt to report individual risk factors associated with superwarfarin intoxication, investigate other routes of poisoning besides oral ingestion, and examine treatment outcomes of superwarfarin intoxication, especially in patients without a definite history of ingestion. However, the original study includes too few patients, and of the included patients, many had a relatively low amount of intoxication. Furthermore, too few chronic alcohol drinkers, or patients in whom a superwarfarin had been ingested with alcohol, have been studied. Therefore, the results of this report seem insufficient for application to a typical patient with superwarfarin intoxication. Thus, the incidence of superwarfarin intoxication should be surveyed nationwide, and further studies are required to ascertain whether the albumin level or acute or chronic alcohol consumption is an important factor.

Because previous authors have identified the source of exposure in Korean patients with superwarfarin toxicity of unknown origin to possibly be transdermal absorption or prolonged inhalation time [15], we suggest that public health authorities work with the agricultural department to provide public health education regarding the properties and dangers of these new rodenticides. Restriction of the sale of high-concentration liquids should also be considered.

In summary, clinicians must include superwarfarin ingestion as a differential diagnosis in any patient with an unexplained coagulopathy. Clinicians should also understand that these patients will likely need continuous vitamin K supplementation for a prolonged duration because of the considerable half-life of these drugs. Further detailed investigation of possible and actual environmental exposure as well as improvement in the accuracy of blood level tests is mandatory.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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