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Long-Acting Anticoagulant Rodenticide (Superwarfarin) Poisoning: A Review of Its Historical Development, Epidemiology, and Clinical Management

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ABSTRACT

Long-acting anticoagulant rodenticides (LAARs) inhibit vitamin K epoxide reductase (VKOR). Related bleeding may present a diagnostic challenge and require administration of blood component therapy, hemostatic agents, and vitamin K. This article intends to provide the reader a comprehensive understanding of LAAR poisoning. An exhaustive literature search of PubMed, Science Direct, US National Library of Medicine Toxicology Data Network, and Google Scholar yielded 174 reported cases of LAAR poisoning from which clinical data were extracted and reviewed. In addition, 25 years of epidemiologic data from the American Association of Poison Control Centers was reviewed. In the United States, on average, there were 10 413 exposures reported with 2750 patients treated annually. For 25 years, there were 315 951 exposures reported with nearly 90% among children and more than 100 000 patients treated in a health care facility. Fortunately, only 2% of all exposures result in morbidity or mortality. Inhalational, transcutaneous, and oral routes of exposure have been documented. Most exposures are unintentional. The most frequently reported bleeding sites are mucocutaneous, with hematuria being the most common feature. Deaths were most commonly associated with intracranial hemorrhage. Long-acting anticoagulant rodenticide–induced paradoxical thrombosis and thrombotic complications accompanying hemostatic therapy have also been observed. Most patients present with coagulation assay values beyond measurable limits. Long-acting anticoagulant rodenticides have an extremely high affinity for VKOR compared with warfarin, characterized by rebound coagulopathy and bleeding after initial treatment and the need for high-dose, long-term therapy with vitamin K_1. Treatment of acute hemorrhagic symptoms often required intravenous vitamin K_1 in excess of 50 to 100 mg; chronic maintenance with 100 mg PO vitamin K_1 daily was the most frequently used dose required to suppress coagulopathy. Treatment courses averaged 168 days. Adjunctive hemostatic therapy with recombinant factor VIIa and prothrombin complex concentrate has been reported, and phenobarbital has been used to expedite LAAR metabolism.

Contents

In March of 1953, Joseph Stalin died of an intracranial hemorrhage. Although the exact circumstances surrounding his death remain somewhat mysterious, it is suspected that he had been poisoned with warfarin [1]. Vitamin K antagonists have played an important role in the last century of human history as a farmer's blight, a medical breakthrough, an industrial tool, and a human toxicant. After the use of warfarin as a therapeutic agent, more potent vitamin K antagonists were developed

Abbreviations: PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; LAAR, long-acting anticoagulant rodenticide; PCC, prothrombin complex concentrate; VKA, vitamin K antagonist; VKOR, vitamin K epoxide reductase.

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and used as rodenticides, a class of agents known as long-acting anticoagulant rodenticides (LAARs). Never intended for human use, cases of human poisoning can be dramatic and yet difficult to recognize. Long-acting anticoagulant rodenticide poisoning is a global health issue with cases reported in Turkey, Croatia, Taiwan, China, Australia, Argentina, and the United States [2–8]. This review will provide the reader with a comprehensive understanding of LAAR poisoning by presenting the historical development of vitamin K antagonists, epidemiology, pharmacology, and clinical aspects of LAAR poisoning and its diagnosis and clinical management.

Materials and Methods

An exhaustive literature was performed using the following search terms: "anticoagulant poisoning," "superwarfarin toxicity," "long-acting anticoagulant," "anticoagulant rodenticide poisoning," "history of anticoagulants," "history of warfarin," "coumarins," "vitamin K antagonism," "brodifacoum poisoning," and "brodifacoum kinetics." Databases queried included PubMed, Science Direct, US National Library of Medicine Toxicology Data Network, and Google Scholar. A search of the archives of the journals of *Hematology*, *Blood*, *Circulation*, *Nature*, *The British Medical Journal*, *The Journal of the American Medical Association*, *New England Journal of Medicine*, *Chest*, and *Thrombosis and Haemostasis* was also conducted. In addition, a search of the institutional Web sites of the American Association of Poison Control Centers (AAPCC) (www.aapcc.org) and the Environmental Protection Agency (www.epa.gov).

Articles were targeted for evaluation if they included information relevant to the history of warfarin and LAARs, the epidemiology of LAAR poisoning, LAAR poisoning case report data, or the treatment, diagnosis, and nature of LAAR poisoning. Data were extracted from individual case reports, case series, and epidemiologic reports regarding the age, sex, offending agent, coagulation assay values, symptoms, treatment course, and outcomes of reported cases. Effort was taken to exclude redundantly reported cases. Data were recorded and analyzed using Excel (MicroSoft Corporation, Los Angeles, California).

The Development of Warfarin

In the early 1900s, farmers in the North American plains began planting sweet clover to be stored as silage for cattle, a practice crucial to maintaining feed supplies through winter. The crop was hardy and widely available and thus ideally suited to this purpose. As early as 1921, cattle began dying of a spontaneous hemorrhagic illness. Initially thought to be a "hemorrhagic septicemia," a Canadian veterinarian (Schofield 1924) not only was able to determine the source but also demonstrated that cattle could be treated by removal of "spoiled silage" from their feed and transfusion from healthy cows [9]. The authors have speculated that depression era farmers of the 1920s, hard pressed, were more likely to have fed their cows spoiled silage than in previous years [10].

In 1933 Karl Link, a researcher at the University of Wisconsin, was presented with an expired cow, a milk tin of its uncoagulated blood, and a large quantity of spoiled sweet clover. Link, who had already been tasked with developing a more palatable, coumarin (a natural bitterant)-depleted sweet clover, thereafter began his search for the suspected "hemorrhagic agent." Wilhelm Schoeffel, a senior student in the laboratory, began experimenting on the blood that very night [9,10].

In 1939, Link and his associate Harold Campbell isolated a crystallized form of the "hemorrhagic agent"—a compound later found to be 3,3′-methylenebis-(4-hydroxycoumarin) and subsequently named *dicumarol*. In a reaction catalyzed by mold (*Aspergillus* or *Penicillium*) in the silage, oxidized coumarin is linked to formaldehyde and then to a second coumarin moiety forming dicumarol. Link found that coumarin itself was nonpathologic [9,10]. In fact, of the 3400 known, naturally occurring coumarins, only 7 have been found to possess anticoagulant activity and most have no known biologic activity. Important exceptions include dihydroxybergamottin, a coumarin in grapefruit known for its inhibition of cytochrome P450, and aflatoxin B_1, associated with hepatic carcinoma [11].

In 1940, clinicians demonstrated the anticoagulant effects of dicumarol in humans, and in 1942, Irving Wright demonstrated the therapeutic use of dicumarol for treatment of thrombosis. By 1944, dicumarol had become widely available. Link then set out to develop a "better mouse trap." He reviewed a collection of 150 synthetic compounds developed in the wake of dicumarol and chose the more potent compound #42. Link named the compound "WARF-arin" in honor of the institution that had funded and owned the rights to his research, the *W*isconsin *A*lumni *R*esearch *F*oundation. After reaching the marketplace in 1948, warfarin became the predominant rodenticide for many years to come [9,10,12].

In 1950, with dicumarol becoming less competitive in a growing field of coumarin-based agents, Link began appealing to clinicians to trial warfarin in human subjects. A year later, after a naval recruit made a full recovery from an attempted suicide with 567 mg of warfarin, 2 clinicians agreed to trial warfarin. Warfarin was found to be vastly superior to dicumarol in trials conducted in 1953 to 1954, and it was marketed for use in humans beginning in 1954. Regarding their use as antithrombotics, Link was said to have joked that after he gave patients "cow poison," he then gave them "rat poison" [9,10].

The Development of LAARs

Warfarin's unique properties made it an ideal rodenticide. Being a colorless, odorless substance with a delayed onset of action prevents pests from associating its consumption with its toxic effects, a phenomenon known as "bait shyness." In addition, warfarin had the supreme advantage of having an antidote. If any nontarget exposures occurred, the effects could be reversed by vitamin K [2,12]. Through the 1950s to 1960s, additional rodenticide agents were developed with increased potency and length of action compared with warfarin. These subsequent agents have become known as the *LAARs*—see Table 1. Based on core molecular structure, 2 basic classes emerged, 4-hydroxycoumarins and indandiones. However, as early as 1960, scientists began discovering rodent populations with heritable resistance to warfarin, and by 1965, some populations were demonstrating cross-resistance to all of what would later be called the *first-generation agents*. Multiple mechanisms of resistance have been elucidated including increased clearance, reversible inhibition of vitamin K epoxide reductase (VKOR), and reduced or complete insensitivity of VKOR to the agents [12,14,15].

The second-generation agents were heralded in 1975 with the discovery of difenacoum, followed by brodifacoum in 1978. These second-generation agents were able to overcome resistance that had developed among rodents. Researchers had found that substitution of the methyl group of 4-hydroxycoumarin with long, phenyl side-chains yielded a tremendous increase in potency and duration of action [12,16]. For example, with the same molar dose as warfarin, brodifacoum yielded a 100-fold greater decrease in vitamin K–dependent coagulation factors [17]. The biologic effects of second-generation agents are thought to be attributable to their high lipid solubility and increased affinity for hepatic tissue and hepatic enzymes [4,7,18]. Given their dramatic increase in toxicity, the term

Table 1
Long-acting anticoagulant rodenticides

Generation	Classes	Examples
First	Inandiones	Chlorphacinone, pindone, diphacinone
	4-Hydroxycoumarins	Coumachlor, coumafuryl, coumatetralyl
Second	4-Hydroxycoumarins	Difenacoum, bromadiolone, brodifacoum, flocoumafen
	Thiocoumarin	Difethiolone

Examples of LAARs [12,13].