ORIGINAL ARTICLES

Epidemiology and symptomatology of long acting anticoagulant rodenticide poisoning

Minh-Ha Tran*[1], Nathan C King[2]

[1] Department of Pathology and Laboratory Medicine, Irvine School of Medicine, University of California, USA
[2] Department of Internal Medicine, Irvine School of Medicine, University of California, USA

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ABSTRACT

Background: Long acting anticoagulant rodenticides (LAARs) are widely used pesticides that initiate anticoagulation through a vitamin K antagonist (VKA) mechanism. Human exposures produce presentations ranging from asymptomatic to fatal.
Methods: A comprehensive literature search and search of relevant databases was conducted. Data related to epidemiology of LAAR exposure as well as clinical manifestations of LAAR poisoning and clinical management were extracted.
Results: Between 1987 and 2012, 315,951 total exposures were reported to the American Association of Poison Control Centers. Of these, 95.6% were unintentional and 88.9% occurred in children under the age of six. Moderate or major effects occurred in only 0.6% of human LAAR exposures. Of reviewed case reports, the most common hemorrhagic manifestations were mucocutaneous. Fatalities were most commonly associated with intracranial hemorrhage and intentional misuse. Multiple routes of exposure have been reported including oral, percutaneous, and inhalational. Treatment courses required prolonged administration of high dose vitamin K.
Conclusions: Most instances represent unintentional LAAR exposures among children. Although the majority of exposures are asymptomatic, serious coagulopathy may occur, and LAAR poisoning may not immediately be considered as an etiology. A heightened awareness for this entity and awareness of diagnosis and treatment principles are critical to appropriate management.

Key Words: Rodenticide poisoning, Vitamin K antagonist, Coagulopathy, Hemorrhage, Bleeding, Long-acting anticoagulant rodenticide, Vitamin K treatment, Warfarin reversal

1. INTRODUCTION

Long Acting Anticoagulant Rodenticides (LAARs) were originally developed from the hemorrhagic agent responsible for cattle deaths in the 1920's. In 1939, Karl Link and Harold Campbell identified this agent as 3,3'-methylenebis-(4-hydroxycoumarin), or dicumarol. Oxidized coumarin within silage becomes linked to formaldehyde and then to a second coumarin moiety forming dicumarol.[1,2] In the 1940's, as dicumarol was entering clinical use, Karl Link selected # 42 from a number of synthetic dicumarol-based compounds and later named it Warfarin. The name was based upon the acronym for the Wisconsin Alumni Research Foundation in honor of the institution that had funded his research.[1–3] Various congeners of warfarin were developed through the 1950's and 1960's. These subsequent agents became known as LAARs, (see Table 1). These innovations became necessary to overcome resistance that was increasingly recognized during the 1960's among certain rodent populations.[3,4]

*Correspondence: Minh-Ha Tran; Email: minhhat1@uci.edu; Address: DO, 101 The City Dr S, Building 1, Room 3003, Orange, CA 92868, USA.

Table 1. Long acting anticoagulant rodenticides

Generation of Agent	Chemical Class	Examples	Notes
First	Inandiones	Chlorphacinone, Diphacinone	Development of resistance among various rodent populations
	4-hydroxycoumarins	Coumachlor, Coumafuryl	
Second	4-hyrdroxycoumarins	Brodifacoum, Bromadiolone, Difenacoum	Resistance not observed with Brodifacoum but has been observed with other 2nd generation agents
	Thiocoumarin	Difethiolone	

Due to their high-lipid solubility, increased affinity for hepatic enzymes, and significant increase in potency as well as their ability to overcome resistance, LAARs earned the moniker "superwarfarin", which continues in use today.[5–8] LAARs induce anticoagulation through inhibition of the Vitamin K Epoxide Reductase enzyme.[1] This inhibition leads to reduced ability to gamma-carboxylate terminal glutamine residues of Vitamin K Dependent coagulation factors.[9] The absence of this final carboxylation step prevents these factors from binding activated phospholipid membranes, where coagulation reactions proceed to eventually achieve hemostasis (see Figure 1). Importantly, coagulation related to vitamin K antagonist (VKA)/LAAR effect may be recognized by simultaneous prolongation of the prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT). In patients with otherwise normal hepatic function, coagulation factor activity demonstrates low levels of Factors II, VII, IX, and X, but preserved levels of the remainder of (non-vitamin K dependent) coagulation factors. Mixing studies, if performed, are expected to demonstrate correction. Accumulation of Vitamin K Epoxide may be present and the diagnosis confirmed by specific testing for presence of rodenticides.[10]

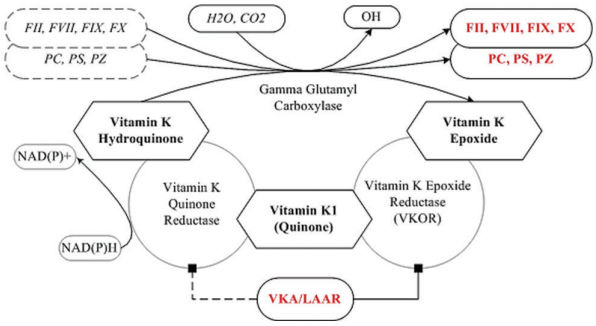

Figure 1. Vitamin K cascade and sites of VKA/LAAR antagonism

Long-acting anticoagulant rodenticides are readily available at home supply stores for around-the-house use by consumers. Once opened, the product is often brightly colored and may have the appearance of a cereal. Despite the mandated addition of bitterants to rodenticide baits,[11] inadvertent and intentional exposures continue to occur, some of which leading to coagulopathy, bleeding complications, and death. Epidemiologic data suggest that over 10,000 exposures are reported annually; the American Association of Poison Control Centers (AAPCC) estimates mortality from 315,951 reported LAAR exposures to be 0.01%.[12–35] This review will therefore discuss the epidemiology and symptomatology of LAAR exposures in order to better facilitate clinical recognition and diagnosis.

2. METHODS

A literature search 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." Electronic database queries of PubMed, Science Direct, U.S. National Library of Medicine Toxicology Data Network, and Google Scholar, and institutional websites of the American Association of Poison Control Centers (`www.aapcc.org`) and the Environmental Protection Agency (`www.epa.gov`) were undertaken. Journal archives 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, were also searched.

Articles 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 were reviewed. Authors extracted data from individual case reports, case series and epidemiologic reports regarding the age, gender, offending agent, coagulation assay values, symptoms, treatment course, and outcomes of reported cases. Effort was taken to exclude redundantly reported cases. Data was recorded and analyzed using Excel (MicroSoft Corporation, Los Angeles, CA). Further evaluation of case and literature derived data was conducted and the manuscript was prepared by both

3. RESULTS

3.1 Routes and severity of exposure

Various routes of exposure have been reported (see Table 2). The lipophilic natures of these agents increase poten-

tial routes of systemic exposure. Surreptitious use can be particularly concerning as patients may not be forthcoming regarding their exposure history. Drugs of abuse may be "laced" with rodenticides in an attempt to increase euphoric effect. Lacing may not be immediately considered by providers unfamiliar with drug abuse patterns.

Table 2. Routes of exposure and likelihood for clinical sequelae

Scenario	Route	Notes	Likelihood for Clinical Sequelae
Unintentional	Oral	Majority of human LAAR exposures represent unintentional childhood exposures	Low/Possible
	Cutaneous	Accidental spill (liquid diphacinone)	
	Inhalational	Rodenticide Factory Worker	
Intentional	Oral	Munchausen's, Munchausen's-by-proxy, suicide/homicide attempts, drug "lacing"	Moderate/Likely
	Inhalational		

3.2 Epidemiology and symptomatology of LAAR Exposures

3.2.1 *Epidemiology of exposures*

Annual reports from the AAPCC's National Poison Data System from 1987-2012 were reviewed. Of the 315,951 total exposures reported, the vast majority–95.6%, were unintentional and 88.9% occurred in children under six years of age. Moderate or major effects (including death) occurred in only 0.6% of human LAAR exposures with any reported effects occurring in only 2.3% of total cases. Treatment in a health care facility was reported in 32% of cases (101,152). Thirty deaths attributable to LAAR poisoning were reported within this data system; the majority, 25/30, involved harmful intent with 23 suicides and 2 murders and (when reported) 19 cases involved brodifacoum. Twenty nine of 30 involved individuals over the age of 20 (mean age 40) and the gender distribution was equal. The incidence of reported exposures is represented in Figure 2.[12–35] The total number of human exposures is likely much greater; two studies suggest that only about 25% of identified cases were actually referred to local poison control centers.[36,37]

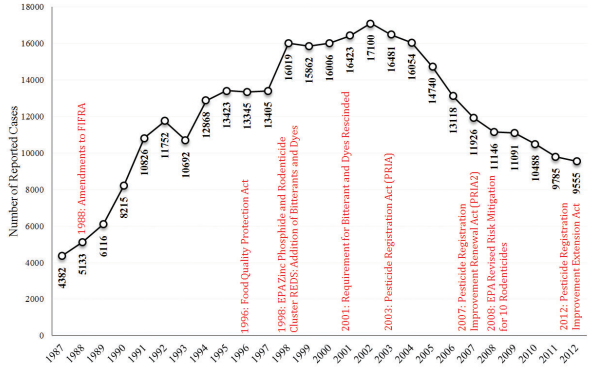

Figure 2. Reported cases of human LAAR exposures, 1987-2012

As noted in Figure 2, reported human exposures peaked in 2003 then began declining thereafter. This trend is in large part the result of successive amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA–[P.L. 80-104] originally enacted in 1947), the efforts of the Environmental Protection Agency (EPA) in carrying out the associated mandates, and of registrants (*i.e.*, manufacturers) in adhering to registration and reregistration rules. Many of the pesticides and rodenticides in use prior to FIFRA and its amendments were not subject to modern safety laws. The 1972 Federal Environmental Pesticide Control Act (P.L. 92-516) completely replaced FIFRA and required "reregistration" of some 35,000 older products.[38] Nearly half of these products would not make it through the reregistration process (a task assigned to EPA), upon which a 10 year schedule was imposed in the FIFRA amendments of 1988 (P.L. 100-532). Fee collection from (re)-registrants was allowed to support the enormous task of data safety review and approval.[38] Although the 1996 Food Quality Protection Act–(FPQA[39])–did not reauthorize FIFRA, the authority within FIFRA to issue and enforce regulations is considered permanent.[38]

Empowered by the FIFRA amendments, and out of concern for harm to children, the EPA in 1998 rendered its Zinc Phosphide and Rodenticide Cluster (including brodifacoum, bromadiolone, chlorphacinone, diphacinone, bromethalin, and pival) Reregistration Eligibility Decisions. Interim measures made eligible for reregistration only those rodenticide bait products which included reduction in palatability to children through addition of a bitterant and incorporation of indicator dyes that would leave stains upon children's hands and mouths thus allowing identification of potential exposure.[40]

The EPA ultimately rescinded these measures in 2001 in accordance with recommendations from the Rodenticide Stakeholders Workgroup–which included representatives from var-

ious government agencies, the rodenticide industry, and others.[40]

This decision was subsequently challenged in court: West Harlem Environmental Action *vs*. US EPA (380 F.Supp.2d 289 US District Court, New York, 2005)[41] in which addition of a bitterant was subsequently upheld as a safety measure and remanded to EPA for further consideration. The decision of EPA to rescind addition of an indicator dye was upheld.

In its 2008 Risk Mitigation Decision for Ten Rodenticides, the EPA rendered a final decision on the reregistration eligibility for rodenticide bait products containing the following active ingredients: brodifacoum, bromadiolone, bromethalin, chlorophacinone, cholecalciferol, difenacoum, difethiolone, diphacinone (and its sodium salt), warfarin (and its sodium salt), and zinc phosphide.[40] The two major components of this decision include 1) the requirement that all rodenticide bait products marketed to general and residential consumers be sold only with tamper resistant bait stations (loose bait forms representing a prohibited form) and 2) restrictions and distribution limits were imposed for bait products containing four of the ten rodenticides posing the greatest harm to wildlife (second generation agents: brodifacoum, bromadiolone, difenacoum, and difethiolone).

In regards to the latter component, it was recognized by EPA that second generation agents were associated with greater harm to non-target species than first generation agents. With second generation agents, only a single feeding is required for lethality – an event that typically occurs 5-7 days following ingestion hence providing opportunity for predatory species exposure. The danger of these agents to non-target and protected species has been a longstanding concern and has recently made news with the death of P-34–a revered Southern California Mountain Lion–on September 30, 2015[42,43] as well increased deaths in the Sierra Nevadas and Northern California of a weasel-like mammal, the fisher, from rodenticide exposure.

The latter exposures were brought to light in studies by Gabriel *et al*.[44,45] who performed necropsies on and assessed for presence of anticoagulant rodenticides in the carcasses of VHF-tagged fishers (*Pekania pennanti*). It was determined that the cause of death in over 10% of fishers, a candidate for the endangered species list, was rodenticide poisoning. The route of exposure was likely through rodenticide use on illegal marijuana farms.[46]

3.2.2 *Symptomatology of LAAR Poisoning in humans*

A comprehensive literature search for LAAR exposure-related case reports and case series yielded 174 individual cases. Data specific to bleeding complications were extracted and compiled according to frequency. The most common hemorrhagic features involved mucocutaneous bleeding (hematuria, gingival bleeding, epistaxis, and GI bleeding), followed by mixed presentations of spontaneous ecchymoses, soft-tissue hematoma, and intramuscular hemorrhage (see Table 3). The hemorrhagic event most closely associated with death was intracranial hemorrhage. Of note, 10 (71%) of the 14 deaths from case report data were associated with intracranial hemorrhage; and of the 10 reported cases of intracranial hemorrhage, only 1 (10%) survived. Within this closer review of LAAR exposures, brodifacoum was the most common offending agent – Brodifacoum: 83/174 (48%), Chlorphacinone: 24/174 (14%), LAAR not otherwise specified 67/174 (38%).[47–86]

Table 3. Symptomatology of clinically significant LAAR poisoning

Symptom	n(%)	Symptom	n(%)	Symptom	n(%)
Hematuria	59(34%)	Guaiac Positive Stool	18(10%)	Vaginal Bleeding	10(6%)
Gingival Bleeding	52(30%)	Flank Pain	18(10%)	Easy Bleeding	10(6%)
Epistaxis	41(24%)	Melena	15(9%)	Hemoptysis	6(3%)
GI Bleeding Total	40(23%)	Deaths	14(8%)	Hematemesis	7(4%)
Spontaneous Ecchymoses	38(22%)	Loss of Consciousness	14(8%)	Thrombosis	5(3%)
Soft Tissue Hematoma	22(13%)	Easy Bruising	17(10%)	Hematochezia	2(1%)
Abdominal Pain	24(14%)	Intracranial Hemorrhage	10(6%)	Spontaneous Abortion	2(1%)
Intramuscular Hemorrhage	19(11%)	Headache	10(6%)	Rectal Bleeding	1(1%)

3.3 Treatment of LAAR poisoning

Treatment for cases of LAAR poisoning associated with profound or symptomatic coagulopathy has recently been reviewed.[10] In contrast to typical doses of vitamin K used for warfarin reversal–1-5 mg PO for nonbleeding patients, 5-10 mg PO/IV for bleeding patients,[87] therapeutic vitamin K doses for LAAR poisoning are 10-20 fold higher. In addition, duration of treatment involves extended courses (median of 140 days, range 28-790 days) of high dose vitamin K, with mean maintenance (per oral) doses of 100 mg daily (median

60 mg, range 15-600). At the outset of therapy (*i.e.*, first day or several days), patients frequently received loading doses of vitamin K, frequently in the range of 20-50 mg IV with many receiving 75-100 mg IV loading doses or higher.

Additional options for acute therapy include infusion of fresh frozen plasma or administration of either Prothrombin Complex Concentrates or recombinant Factor VIIa; these options would have a limited duration of effect therefore simultaneous vitamin K is necessary.[10] Patients with apparent response followed by recrudescence of coagulopathy may represent resumption of surreptitious LAAR consumption, and psychiatric consultation, particularly with suicidal patients is recommended.[10] The requirement for long-term therapy is directly related to the extended half-lives of these agents. Whereas warfarin is associated with a half-life of 17-37 hours, the half-lives of difenacoum and brodifacoum are 11.5 days and up to 34 days, respectively.[10]

4. DISCUSSION

A comprehensive literature search determined that between 1987 and 2012 there were 315,951 reported cases of LAAR exposure. Fortunately, the vast majority were not clinically significant. Of those with clinical relevance, the most common symptoms involved mucocutaneous bleeding but more serious hemorrhagic events also occurred. These included Intracranial Hemorrhage, which often resulted in death. The mechanism of LAAR coagulopathy, outlined in Figure 1, recapitulates a VKA pathway.

LAARs have been intentionally selected for their lipophilic properties and high enzyme affinity, features that contribute to extended half-lives and significantly greater potency than VKAs used therapeutically for anticoagulation in humans. As a result, the duration of effect following discontinuation can often be measured in weeks to months. Children presenting with unintentional LAAR exposure most commonly are asymptomatic, although appropriate coagulation testing and assessment remain indicated. Individuals with intentional exposure are more likely to present with coagulopathy and hemorrhagic sequelae. As opposed to limited vitamin K dosing needed for reversal of warfarin effect, treatment of significant LAAR poisoning will require weeks to months of replacement therapy.

5. CONCLUSION

Long acting anticoagulant rodenticides are economically important and useful chemicals for the control of rodent infestations. However, both accidental and intentional exposures occur at a rate of approximately 10,000 per year. Successive amendments to FIFRA and continued diligence by the EPA has resulted in declining human exposures. Sequestration of household/residential-use rodenticide baits into tamper-resistant bait stations and additional restrictions placed on loose-meal applications have been particularly effective measures. While the majority of cases are asymptomatic, those cases particularly related to intentional ingestion may present with bleeding complications or abnormal coagulation values. In the setting of drug abuse, "lacing" has been reported which may escape history taking. The issue of non-target animal exposures remains an issue and further actions are needed to further protect vulnerable species.

The majority of clinical (human) presentations involve mucocutaneous bleeding as noted in Table 3. Recognition of a VKA/LAAR effect rests upon the combination of history, characteristic laboratory abnormalities and bleeding manifestations (if present) as well as response to vitamin K treatment. Recognition of LAAR poisoning is critical since treatment significantly differs from that traditionally associated with warfarin reversal. Patients will often require extended courses of high-dose vitamin K supplementation as well as possible psychiatric referral in situations where the ingestion was intentional.

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