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Treatment for long acting anticoagulant rodenticide poisoning - beyond INR monitoring?

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Abstract

Poisoning by long acting anti-coagulant rodenticides (LAARs) requires long-term treatment with oral vitamin K1 (VK1). However, discontinuing treatment based on normalization of INR, may leave some patients with serum LAAR concentrations above a level considered safe. To address this, we carried out a retrospective analysis of 21 case reports of LAAR poisoning having at least two serum LAAR concentrations quantified during treatment with oral VK1. We identified the case reports by survey of existing peer-reviewed literature in which a patient presented to emergency department exhibiting bleeding or elevated INRs, and had quantitative measurements of serum LAAR concentrations. Of 21 case reports, measurement of serum LAAR concentrations following VK1 treatment showed that over half (n=11) had serum LAAR concentrations that were above a concentration considered to be safe (10 ng/mL), despite having received higher daily and total VK1 dosing, over an equivalent treatment duration. Since residual amounts of serum and tissue LAAR could contribute to symptom recurrence and repeated hospitalization, these results indicate that normalization of INR is not a sufficient criterion to discontinue VK1 treatment and that measurements of serum LAAR concentrations should be included to help guide decisions to continue or discontinue VK treatment.

Keywords

Rodenticide; Vitamin K1; superwarfarin; brodifacoum

The consequences of accidental or intentional ingestion of long-acting anticoagulants (LAARs) include life-threatening internal hemorrhage, for which current recommended treatment consists of resuscitation with blood products followed by high-dose (up to 100 mg or more per day), long-term (weeks to months) oral vitamin K (VK1) therapy [1]. In addition to ingestion, LAAR poisoning can occur topically as well as by inhalation, as

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GW is officer, shareholder and paid consultant to ResQ Pharma, Inc.
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illustrated by a current nationwide outbreak of cases, in which inhalation of synthetic cannabinoids contaminated with the LAAR brodifacoum (BDF) have led to close to 300 hospitalizations and 8 deaths [2]. The high cost and prolonged treatment requirement for VK1 raise concerns about access to care and adherence to therapy. Currently, the key biomarker of response to oral VK1 therapy is INR. However, whether normalization of INR is a sufficient criterion to recommend discontinuing VK1 treatment is not clear. Moreover, VK1-independent actions of LAARs, including renal [3] and neurological damage [4, 5], may persist even though coagulation is normalized.

We carried out a retrospective analysis of 21 case reports with serum LAAR concentrations quantified before and after oral VK1 treatment (Table 1). Across all cases, the average initial serum LAAR concentration was 318±77 ng/mL; mean treatment duration was 113±16 days with a mean of 109±29 mg daily VK1. After treatment, LAAR concentrations declined to a mean of 50±16 ng/mL; however, many patients at that time had LAAR concentrations above 10 ng/mL, a level at which brodifacoum induced coagulopathy was not observed [6, 7, 8]. Although the estimated LD_{50} values for LAARs differ (ranging from 0.27 mg/kg to over 1 mg/kg in rodents), we used 10ng/mL as a value to stratify patients into 2 groups, In the group (n=10) with lower post-treatment concentrations, the mean starting plasma LAAR concentration was 183±68 ng/mL and treatment with 48±13 mg/day of oral VK1 lasted an average of 119±24 days (Figure 1). The cohort with higher post-treatment LAAR concentrations (n=11) had initial mean concentrations of 449±124 ng/mL and were treated with 164±50 mg/day VK1 for an average of 109±21 days. Despite similar treatment duration, and higher daily and total VK1 doses, treatment duration in the latter cohort was insufficient to reduce serum LAAR to acceptable concentrations.

Since higher serum LAAR concentrations are typically associated with longer prothrombin times and INRs [7, 9, 10], these data suggest that discontinuing VK1 treatment based on normalization of INR poses a risk since over half the patients retained elevated serum LAAR concentrations. Protracted tissue LAAR content can potentially lead to recurrence of life-threatening bleeding requiring hospitalization and intensive treatment [11]. These findings suggest a need to establish a system to monitor and study the relationship of blood LAAR concentrations and clinical outcomes of survivors of LAAR poisoning for prolonged periods. Consistent with this, current recommendations from the American Society of Hematology include weekly quantitative serum LAAR determinations [12], to help guide dose and duration of oral VK1 therapy.

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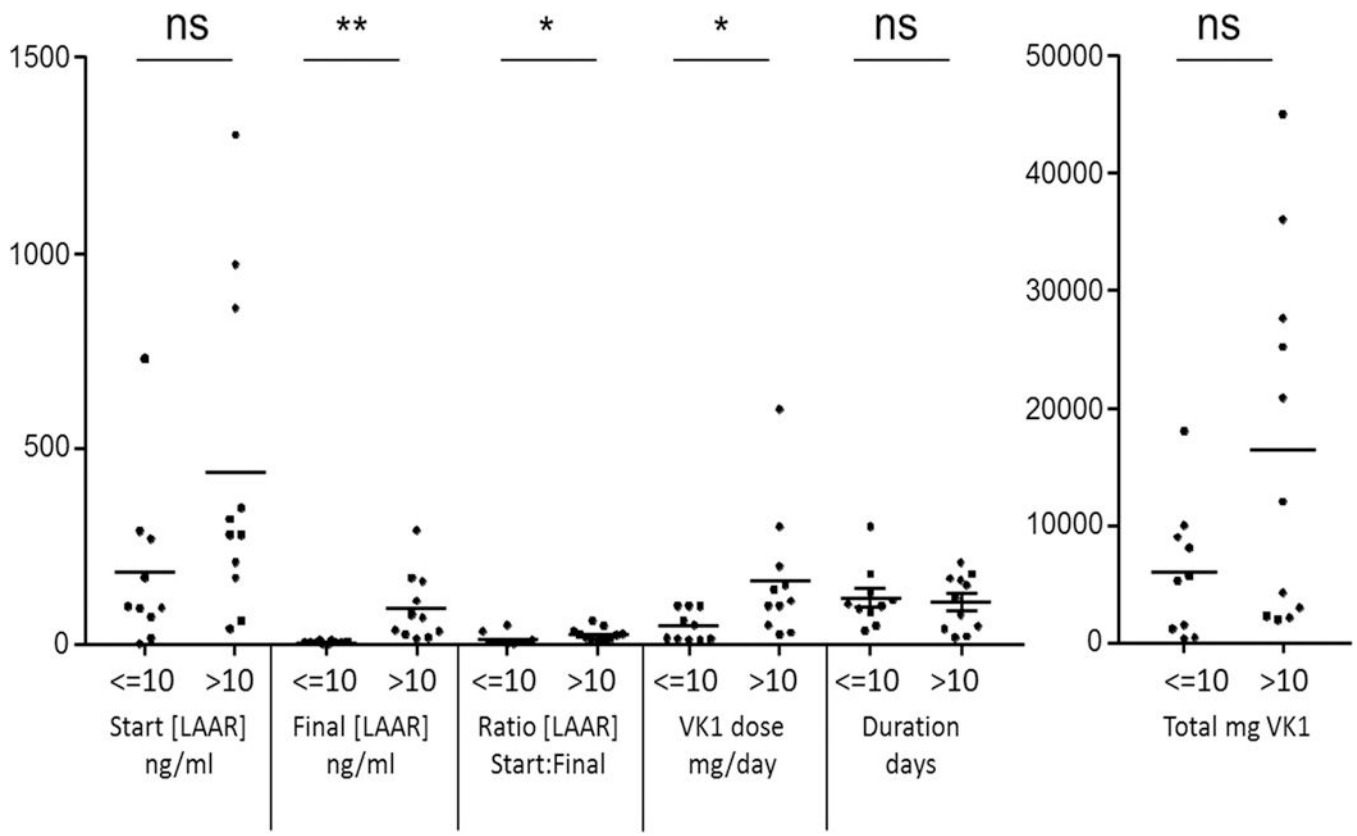

Figure 1.

Values for the indicated parameters in patients whose initial serum LAAR concentrations were <= 10 ng/mL (n=10) or > 10 ng/mL (n=11). After testing revealed non-normal distribution, groups were compared by Mann Whitney non-parametric test. *, P <0.05; **, P<0.005. Bars indicate means.

Table 1:

Summary of 21 case reports organized by serum [LAAR] at discharge

		[LAAR] ng/mL	[LAAR] ng/mL	[LAAR]	mg VK1	Duration		
	LAAR	Start	Final	% Start	Daily dose	Days	Total mg VK1	Ref
	BDF	1	0.5	50%	15	83	1245	[13]
	BDF	270	1	0%	100	100	10000	[14]
	BDF	70	4	6%	100	90	9000	[9]
	BDF	98	4.2	4%	15	102	1530	[8]
	BDF	170	5	3%	100	180	18000	[9]
	BDF	93	5	5%	60	135	8100	[15]
	FLF	61	5	8%	10	48	480	[16]
	BDF	289	7.6	3%	17.5	300	5250	[14]
	BDF	731	10	1%	50	114	5700	[17]
	BDL	92	10	11%	10	34	340	[7]
	BDF	61	15	25%	26	164	4264	[18]
	BDF	42	20	48%	140	21	2940	[19]
	BDF	170	25	15%	600	46	27600	[6]
	BDF	320	31	10%	50	42	2100	[20]
	BDF	350	36	10%	300	150	45000	[21]
	BDF	210	66	31%	150	168	25200	[22]
	BDF	280	78	28%	111	18	1998	[23]
	DFN	970	110	11%	200	180	36000	[24]
	BDF	860	160	19%	30	77	2310	[25]
	BDF	280	170	61%	100	120	12000	[26]
	BDF	1302	291	22%	100	209	20900	[10]
Mean	**All**	318	50	19%	109	113	11427	
	<=10 ng/mL	183	5	11%	48	119	5965	
	> 10 ng/mL	440	91	25%	164	109	16392	
SEM	**All**	72	15	4%	27	15	2595	
	<=10ng/mL	68	1	5%	13	24	1761	
	> 10ng/mL	124	26	5%	50	21	4655	

Data base screening was carried out by searching PubMed and Google between 1989 and 2018 for existing peer-reviewed literature in which a patient presented to emergency department exhibiting bleeding or elevated INRs, and in which quantitative analysis of LAAR concentrations in serial serum samples was performed.

BDF, brodifacoum, estimated LD_{50} 0.27 mg/kg in rats

BDL, bromadiolone, estimated LD_{50} 1.125 mg/kg in rats

DFN, difenacoum, estimated LD_{50} >1 mg/kg in rats.

FLF, flocoumafen, estimated LD_{50} 1 mg/kg in rats.