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CURRENT OPINION

Should Cytochrome P450 Inducers be Used to Accelerate Clearance of Brodifacoum from Poisoned Patients?

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Abstract

A recent multi-state outbreak of life-threatening bleeding following inhalation of synthetic cannabinoids has been attributed to contamination with the long-acting anticoagulant rodenticide (LAAR) brodifacoum, a second-generation, highly potent, long-acting derivative of the commonly used blood thinner warfarin. While long-term treatment with high-dose vitamin K1 restores coagulation, it does not affect brodifacoum metabolism or clearance, and, consequently, brodifacoum remains in the human body for several months, thereby predisposing to risk of bleeding recurrence and development of coagulation-independent injury in extrahepatic tissues and fetuses. This has prompted the evaluation of pharmacological measures that accelerate brodifacoum clearance from poisoned patients. Since the induction of certain cytochrome P450 (CYP) enzymes accelerates warfarin metabolism, using CYP inducers, such as phenobarbital, to accelerate brodifacoum clearance seems plausible. However, unlike warfarin, brodifacoum does not undergo significant metabolism in the liver, nor have the effects of phenobarbital on vitamin K1 metabolism been previously determined. In addition, the safety of phenobarbital in brodifacoum-poisoned patients has not been established. Therefore, we propose that CYP inducers should not be used to accelerate the clearance of brodifacoum from poisoned patients, but that alternative approaches such as reducing enterohepatic recirculation of brodifacoum, or using lipid emulsions to scavenge brodifacoum throughout the body, be considered.

Key Points

1. Increased cases of poisoning due to the long-acting anticoagulant rodenticide (LAAR) brodifacoum requires reconsideration of methods to enhance its clearance.
2. Unlike the parent compound warfarin, brodifacoum does not undergo significant metabolism and, as such, methods to induce cytochrome P450 enzymes that can accelerate warfarin breakdown may not be effective.
3. Methods to scavenge brodifacoum from tissue storage sites or reduce its enterohepatic recirculation should be considered.

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1 Introduction

Long-acting anticoagulant rodenticides (LAARs) are second- and third-generation derivatives of the widely used anticoagulant warfarin (coumadin), and were developed following the appearance of warfarin resistance in rodents [1]. The primary mechanism of action of LAARs is the same as for warfarin, namely binding to and inhibition of vitamin K epoxide reductase component 1 (VKORC1) whose activity is necessary to maintain vitamin K1 at sufficient levels to serve as a co-factor for γ-glutamyl carboxylase (gGC)-dependent activation of thrombin proteins [2]. One of the most potent LAARs is brodifacoum (BDF), which in contrast to warfarin, possesses a greater hydrophobic nature (log*P* approximately 8.5), longer biological half-life (estimated 20 days or longer in rodents), undergoes limited metabolism, and is subject to enterohepatic recirculation [3]. These properties result in extremely low median lethal dose (LD_{50}) values, typically between 0.2 and 0.8 mg/kg in rodents, and an acute lethal dose in humans of approximately 15 mg/kg (Table 1). LAARs are used worldwide to eradicate rodent infestations; however, unfortunately, their increased

Table 1 Physical, chemical, and biological properties of brodifacoum and warfarin

	Brodifacoum	Warfarin
Melting point (°C)	232 [39]	161 [40]
p*K*a	4.5 [39]	5.08–5.19 [41]
Molecular weight	523 Da	308 Da
log*P* (25 °C)	8.5 [39]	0.7–2.7 [41]
Number of metabolites	1 [25, 39]	6 [16, 42]
Type	Glucuronide	Oxidation
Position	4-OH	C-6, 7, 8, 10, and 4`
Enzymes	UGT	CYP3A4
		1A1, 1A2, 2C8, 2C9, 2C18, 2C19
Acute oral LD_{50}		
Rat	221 ± 14 μg/kg [43]	3–300 mg/kg [44]
Mouse	300–700 μg/kg [44]	10–300 mg/kg [44]
Rabbit	192 ± 29 μg/kg [38]	800 mg/kg [44]
Human	15 mg/kg (estimated)	6–15 mg/kg [45]
Biological half-life	>20 days [46, 47]	15–58 h [48]

UGT uridine 5′-diphospho-glucuronosyltransferase, *CYP* cytochrome P450, LD_{50} median lethal dose

use has led to increased incidence of accidental poisonings, primarily in children, and unintentional exposure following accidental leakage [4]. In the majority of these cases, a single administration of fresh frozen plasma or vitamin K1 can restore coagulation to normal levels within a relatively short period; however, following ingestion of larger amounts, as often occurs in suicide attempts, daily administration of vitamin K1 is required for months to over 1 year [5], the time needed for serum LAAR levels to diminish to levels considered non-toxic (< 10 ng/ml) [6]. While effective, the long treatment duration together with the high cost of vitamin K1 can lead to poor patient adherence and could promote the use of alternative methods of detoxification that are not proven to offer any additional benefit.

2 Should Cytochrome P450 Inducers be Used to Increase Long-Acting Anticoagulant Rodenticide Detoxification?

A recent outbreak of life-threatening coagulopathy and bleeding in Illinois [7, 8] and other States was determined to be due to inhalation of synthetic cannibinoids (SCs). Several case reports have described the occurrence of intracranial bleeding following SC use. In one case, a 23-year-old male suffered intracerebral hemorrhage (ICH) that was speculated to be due to the induction of multiple intracranial arterial stenosis (MIAS) that deteriorated to ICH [9]. Other cases include a Japanese patient with intracranial bleeding who had a history of arteriovenous malformation [10], and three reports of patients with subarachnoid hemorrhage (SAH) [11, 12]. However, peripheral bleeding was not reported in any of these cases and coagulation measurements were normal. Following high performance liquid chromatography–tandem mass spectrometry (HPLC/MS–MS) analysis, it was concluded that the inhaled SCs were contaminated with long-acting anticoagulants (LAARs), primarily brodifacoum and also the less potent related molecules difenacoum and bromadiolone. The source of the LAAR contamination, which is not a byproduct of the SC synthesis reactions, has not been disclosed by law enforcement authorities investigating the outbreak. Whether it was accidental due to erroneous addition of LAARs during the SC synthesis, or intentionally added to inflict serious injury or death, is not known; however, the in-hospital treatment and follow-up care has prompted reconsideration of treatment options for these patients.

It is well-established that resuscitation of patients presenting with acute brodifacoum poisoning consists of administration of appropriate blood products along with parenteral vitamin K1 [13]. In the maintenance phase that follows, off-label, high-dose (up to 100 mg) oral vitamin K1 is prescribed daily for extended periods of time (months), with frequent monitoring of various coagulation parameters, such as international normalized ratio (INR) [5, 14]. This long, multi-pill (up to 20 tablets daily) regimen is expensive (cost estimate for a month's supply in the US = $37,000) and taxing for patients and may lead to non-adherence and recrudescence of severe coagulopathy and bleeding [15]. Hence, means to enhance clearance of brodifacoum from the human body to reduce daily dose and shorten the duration of vitamin K1 therapy during the maintenance phase may prove beneficial.

One strategy that has been considered to enhance brodifacoum metabolism and elimination from poisoned patients is simultaneous administration of an hepatic cytochrome P450 inducer, such as phenobarbital, together with oral vitamin K1. Phenobarbital induces hepatic CYP1A2, CYP2B6, CYP2C9, and CYP3A4/5, as well as several UDP-glucuronosyltransferases. R-warfarin is metabolized by CYP1A2 (forming 6- and 8-hydroxywarfarin) and by CYP3A4 (to form 10-hydroxywarfarin). S-warfarin is metabolized primarily by CYP2C9 to 7-hydroxywarfarin [16]. Studies showing that phenobarbital can reduce warfarin efficacy were reported as early as 50 years ago [17, 18]. Since that time, numerous articles have demonstrated, both in adult [19] and pediatric [20] patients, that coadministration of phenobarbital significantly reduces warfarin efficacy, requiring higher doses to normalize INRs. Direct measurements have shown that warfarin clearance is increased up to 30% by phenobarbital [21], primarily due to the induction of CYP2C9 [22]. Based on these studies, it was subsequently

reported that pretreatment with phenobarbital decreased the anticoagulant effects of brodifacoum in poisoned rats [3]; however, the effects of phenobarbital administration after exposure to brodifacoum, as is the case in poisoned patients, was not reported in that study, nor were observations validated in a second animal species.

Nonetheless, it is not clear that induction of P450 cytochromes or glucuronosyltransferases would influence brodifacoum metabolism or clearance. In contrast to warfarin, human brodifacoum metabolism by CYP enzymes or UDP-glucuronosyltransferases in hepatic microsomes or human hepatocytes is limited and its excretion is slow [23]. Ultra-high performance liquid chromatography (UHPLC)–tandem mass spectrometric studies have shown no evidence of phase I or phase I metabolism of brodifacoum in humans [24]. Multiple human poisoning case studies have reported detection, and sometimes measurement, of brodifacoum levels in blood, but none have reported detection of brodifacoum metabolites. In addition, no brodifacoum or brodifacoum metabolite has been reported in human urine. Instead, unmodified brodifacoum appears to be excreted from the liver into bile fluid and then into the gut. The sole exception to this understanding has been an environmental protection agency (EPA) contractor report using radiolabeled brodifacoum administered to rats fitted with bile duct catheters, suggesting that a brodifacoum glucuronide might be excreted in bile [25]. However, bile could only be obtained from two of three rats in that study, there was no spectroscopic confirmation of brodifacoum glucuronide, and a rat liver profusion study by the same investigators showed no evidence of brodifacoum metabolism. In lieu of an extensive metabolizer, the parent compound is primarily excreted from the liver into bile fluid and gut essentially unchanged. In the gut, brodifacoum undergoes extensive enterohepatic circulation that results in extremely slow fecal elimination from the human body, and is a major reason for its prolonged coagulopathy. In our studies, we were unable to detect any metabolism of brodifacoum, either in vivo or in vitro [26] and in unpublished findings, nor, to our knowledge, are there any published reports that identified or characterized brodifacoum metabolites. Moreover, whether high-dose oral vitamin K1 is metabolized by phenobarbital-inducible CYP oxidase enzymes in humans, thereby reducing its efficacy, has not been determined [27].

Although no controlled clinical trials have been conducted to test the safety and efficacy of phenobarbital in brodifacoum-poisoned patients, a review of several case reports of patients treated simultaneously with oral vitamin K1 and phenobarbital (up to 200 mg daily) during the maintenance phase failed to show improved survival, consistent reduction in the daily dose of vitamin K1, and/or hasten recovery. For instance, Routh et al. [28] treated a brodifacoum-poisoned patient with phenobarbital 30 mg twice daily for 2 months, with no discernible response. Similar observations were reported by Poovalingam et al. [29] and Altay et al. [30]. In contrast, Watts et al. reported a case of recurrent brodifacoum poisoning in a 7½-year-old girl who was resistant to high-dose (up to 100 mg daily) oral vitamin K1 therapy [31]. However, patient adherence to this demanding therapeutic regimen (up to 20 tablets daily) was not reported. Nonetheless, the patient was eventually treated with oral phenobarbital 2 mg/kg daily without concomitant vitamin K1 administration, and coagulopathy resolved within 3 weeks. The authors suggested that phenobarbital accelerated the resolution of brodifacoum poisoning by promoting degradation and excretion of brodifacoum from the liver, although they did not determine brodifacoum metabolites, either in blood or feces. Given the lack of metabolism of brodifacoum in the liver, the mechanism(s) underlying the salutary effects of phenobarbital in this case remain uncertain.

Brodifacoum-poisoned patients considered for daily oral phenobarbital and high-dose vitamin K1 would be required to adhere to both medicines for an extended period, a task that may not be readily accomplished. The lack of adherence for multiple-tablet regimens has been well documented, as has the case for antiretroviral treatment, which also requires excellent adherence [32, 33]. The fatal case reported by Kruse and Carlson [34] in which both medicines were prescribed but the poisoned patient failed to take them, clearly illustrates this point. In addition, Lipton and Klaas [35] described a brodifacoum-poisoned woman with a long history of mental illness who did not adhere to both oral vitamin K1 and phenobarbital therapy during the maintenance phase, resulting in repeated admissions to the hospital for serious bleeding episodes.

Importantly, potential adverse events associated with long-term phenobarbital therapy at anticonvulsant doses, such as sedation, should be considered in brodifacoum-poisoned patients. The mental status of these patients who may be prone to spontaneous intracranial hemorrhage and falls would then have to be closely monitored throughout the maintenance phase. To this end, Hui et al. [36] treated a 76-year-old, brodifacoum-poisoned patient with high-dose vitamin K1 and phenobarbital; however, phenobarbital provoked nocturnal confusion and was discontinued after 1 month.

2.1 Alternatives to Cytochrome P450 Inducers

In lieu of using CYP inducers as a means to increase brodifacoum metabolism, alternative approaches should be considered that could accelerate brodifacoum clearance or alter its pharmacokinetic properties, for example by increasing protein binding or modifying its tissue distribution. Infusion of US FDA-approved lipid emulsions,

such as those typically used for parenteral nutrition, have been shown to accelerate clearance and prevent toxicity in animal models of bupivacaine overdose [37]. The infusion of lipid emulsion (ILE) has been clinically translated to treat overdose associated with a variety of compounds, including local anesthetics, antidepressants, and barbiturates. The mechanism of action includes scavenging toxins from target organs and redistributing them to the liver for degradation and elimination. The efficacy of this approach is correlated to the lipid solubility of the toxin, suggesting it may be effective against molecules such as brodifacoum with extremely high log*P* values. Studies to assess the efficacy of ILE in animal models of brodifacoum poisoning are ongoing, and initial findings indicate partial reductions in overall mortality (Feinstein et al., unpublished observations). While ILE could increase brodifacoum delivery to the liver, as well as its biliary excretion, efficacy may be limited by both enterohepatic recirculation of brodifacoum and its lack of metabolism. Treatment with compounds that reduce recirculation, such as bile sequestrants, could be considered for use alone or in conjunction with ILE, to lower total body brodifacoum burden by accelerating clearance from the gut. In support of this, we showed that administration of the bile sequestrant cholestyramine to brodifacoum-poisoned rabbits increased survival to almost 100% [38]. Approaches that utilize other scavengers to sequester circulating brodifacoum, or reduce its binding to serum albumin, allowing for increased redistribution to the liver, should be considered.

3 Conclusions

Given these data, we propose that in the absence of controlled clinical trials, the routine use of phenobarbital to induce CYP oxidase enzymes in the liver to accelerate clearance of brodifacoum from poisoned patients, thereby shortening the duration of vitamin K1 therapy during the maintenance period, is not warranted. Other methods, such as lipid emulsions to scavenge brodifacoum from tissues, or bile sequestrants to reduce enterohepatic recirculation should instead be pursued.

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Compliance with Ethical Standards

Conflict of interest Israel Rubinstein, Richard van Breemen, Daniel G. Nosal, Guy Weinberg, Ronald C. Hershow, and Douglas L. Feinstein declare that they have no conflicts of interest. Guy Weinberg is founder of Lipid Rescue, Inc., and Douglas Feinstein and Israel Rubinstein are co-founders of EnSol Therapeutics, LLC.

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