

Long- Acting Anticoagulant Rodenticides

Introduction

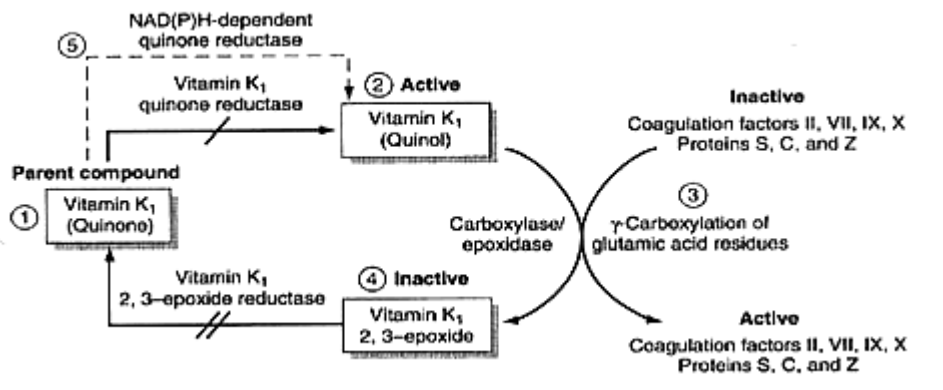
At the turn of the century, the rodenticides depended upon heavy metals such as arsenic, thallium and phosphorus along with red squill and strychnine. This changed in the 1940's as investigators uncovered warfarin to be the cause of death in cattle who consumed sweet clover. The mechanism of its action was elucidated as impeding coagulation, which lead to hemorrhage as the cause of death. Warfarin was quickly adopted as the major rodenticide. Rodent resistance to warfarin, however, became prevalent in the 1960's via autosomal dominant gene transmittance (1). Novel compounds were synthesized to combat rodent resistance, thereby creating a new class of anticoagulants- the superwarfarins (2).

The term superwarfarin refers to a group of compounds, second-generation anticoagulants, which are extremely long-acting. In 2001, the American Association of Poison Control Centers reported 15,855 exposures to anticoagulant compounds. Standard warfarin accounted for < 3% of the total amount, leaving greater than 97% of exposures in the superwarfarin group. Thus, the emergence of these compounds as a source of exogenous coagulopathy in humans has become more evident in recent years.

Pathophysiology

Mechanism of Action

The oral anticoagulants can be divided into two groups, the 4-hydroxycoumarins and the indandiones (4). The most common of these include brodifacoum, difenacoum, and chlorphacinone. Regardless of their classification, all anticoagulants work by inhibiting the generation of an active form of vitamin K1 via inhibition of vitamin K1 reductases. Activation of clotting factors II, VII, IX, and X require the presence of vitamin K as a cofactor. When vitamin K cannot be regenerated, clotting factors cannot be activated and a coagulopathy results involving both the extrinsic and intrinsic pathways (3). The ratio of vitamin K1 2,3-epoxide to vitamin K1 is increased because the inactive compound cannot be reduced back to the active parent form. This ratio has also been documented to be increased in human overdoses (5,6).



Pharmacokinetics/dynamics

Studies in rats and rabbits demonstrate that the clinical effects of the superwarfarins at a cellular level relate to their being highly lipid soluble and highly concentrated in the liver. Brodifacoum has been demonstrated to have zero-order kinetics following overdose (7). Overall, these compounds are 100 times more potent than warfarin (8, 9, 10, 11). The typical warfarin-containing rodenticide contains approximately 0.025% active compound, whereas brodifacoum packages contain 0.005% (3). The half-lives of the coagulation factors vary from 5 hours for factor VII to 60 hours for factor II, accounting for the delayed onset of anticoagulation clinically, which can vary from 24-36 hours after an overdose. Finally, the elimination half-life of the superwarfarins is much prolonged when compared to warfarin. Warfarin's half-life averages 37 hours with a duration of action from 2-5 days (12), whereas the half-life of brodifacoum can be demonstrated to be as long as 156 hours in rats (10). In human studies, the elimination half-life of brodifacoum is weeks to months (13, 14).

Clinical Presentation

Clinical effects are varied dependent upon many variables, the most important being the dose of the superwarfarin ingested. Thus, it becomes crucial to distinguish between accidental and intentional exposures, as the former usually results in a smaller dose. Acute exposure can present as vague symptoms involving the GI tract, such as nausea, vomiting, and abdominal pain (22). Chronic exposures or overdoses present with bleeding from essentially any organ system, usually involving more than 1-2 systems simultaneously. Epistaxis, hematuria, friable gums, petechiae, hematomas, compartment syndrome, hematemesis and melena, hemoptysis from alveolar hemorrhage, ecchymoses, and vaginal bleeding are possible presentations (5, 6, 13, 14, 16, 17, 30, 34, 35, 44-51). To date, five deaths have been reported in the literature with the direct causes as follows: subdural bleeding (15, 19), subarachnoid hemorrhage (16), massive pulmonary hemorrhage (17), and vaginal bleeding (18). It should be noted that the clinical signs of bleeding are usually delayed in comparison to the time of ingestion.

Differential Diagnosis

When a patient presents with a coagulopathy, other sources must be ruled out unless the history is obvious. Decreased coagulation factors can result from congenital deficiencies of coagulation factors (hemophilia, Von Willebrand's disease, etc), acquired liver dysfunction, and vitamin K deficiency from malnutrition. In contrast, consumption of coagulation factors can be present in DIC, sepsis, snake envenomation, and hyperthermia. Coagulation inhibitors must also be ruled out. Finally, thrombocytopenia can cause bleeding (3).

Laboratory

Prolongation of the PT or INR (a PT ratio) is usually the first laboratory indication that a coagulopathy exists. In severe cases, the PTT can also be prolonged, representing involvement of both the intrinsic and extrinsic coagulation systems. Other sources of bleeding must be eliminated. For example, in both DIC and even envenomation fibrinogen will be decreased and fibrin split products increased (3). Furthermore, coagulation inhibitors can be ruled out by mixing the patient's plasma with normal plasma (6). Measurement of the specific clotting factors clinches the diagnosis in that all four vitamin-K dependent factors will be decreased (II, VII, IX and X), while others will be normal (3). The vitamin K1 2,3-epoxide/K1 ratio can also be measured, with a normal ratio of 2-3 (6, 20). Finally, the actual suspected rodenticide can be measured by a variety of assays: radioimmunoassay, enzyme-linked immunosorbent assay, and HPLC (3).

Treatment

Decontamination

Issues regarding decontamination revolve around whether home decontamination with syrup of ipecac or emergency department treatment with activated charcoal alters the clinical outcome. One early case series of patients (n = 88) recommended early gastric emptying with syrup of ipecac, concluding that emergency dept visits could be avoided in those with small exposures (21). Although not specifically addressed in another case series (n = 110) of children, it was noted that those receiving dilution (oral fluids) only versus ipecac or activated charcoal had a higher percentage of abnormal PT values at 24-48 hours post-ingestion (22). More specifically, 6/110 patients had a prolonged PT with dilution only versus 2/110 with ipecac or activated charcoal. However, no short-term signs of bleeding were observed. Another case series (n= 1790) compared patients who had received decontamination with syrup of ipecac to those who received none; the results were based upon clinical symptoms of bleeding, for which they report no difference between the two groups (1). Larger case series of child exposures have also reported the same findings, namely that decontamination by a health care facility had no effect on the distribution of outcome, with PT prolongation only noted in 0.36% (23). The Illinois Poison Center formulated triage criteria for pediatric ingestions, comparing their results to the national TESS data. Specifically, they recommended home observation if < 1 mouthful of rodenticide bait was ingested, home decontamination with ipecac if > 1 mouthful and < 1 hour, and referral to a hospital if > 1 mouthful and > 1 hour post-ingestion. The results showed that more patients were managed at home as compared with TESS data, but without any adverse clinical outcomes (24). The only prospective study involving unintentional pediatric ingestions (n = 465) showed no clinically significant bleeding in those who did not receive any form of decontamination (25). Taken together, these trials indicate no added benefit for home or health care facility decontamination for those patients with unintentional exposures. However, limited numbers of adults, in whom superwarfarin overdose is more likely, were enrolled in these studies. From the available data, it can be inferred that patients who present with a history of ingesting a large or unknown amount of superwarfarin should receive gastric decontamination, either by syrup of ipecac if at home and if < 1 hour or activated charcoal at a hospital (3). One study reports no added benefit of multiple doses of activated charcoal with brodifacoum (26).

Reversal of coagulopathy

Symptomatic Anticoagulated Patient

If the amount of bleeding is severe, such as with intracerebral or GI hemorrhage, vaginal bleeding, or compartment syndrome, FFP is indicated to replace the deficit coagulation factors. This can be given as needed to correct the PT and stop any clinical bleeding (3). Simultaneously vitamin K1 therapy should be started, preferably by the subcutaneous route. Intravenous vitamin K has been associated with anaphylactoid reactions and should be avoided (27, 28). Dosages in the literature have ranged from 10-25 mg; the American College of Chest Physicians recommends the following (29):

serious bleeding: 10 mg

non-serious bleeding INR 6-10: 0.5-1 mg

INR 10-20: 3-5 mg

INR > 20: 10 mg

Asymptomatic Anticoagulated Patient

If there is not active or life-threatening bleeding, but a prolonged PT, oral vitamin K1 administration is preferred. A starting dose has been suggested as 100 mg divided TID-QID (3). However, there are cases where >100 mg/d has been necessary to reverse a coagulopathy (30). The half-life of vitamin K1 has been estimated as 6 hours based upon animal data (31). In one study with a patient having an INR of 38, oral therapy was begun at 150 mg every 6 hours. After 1 and ½ days, the INR and PTT had returned to normal; the dose was presumed to be supertherapeutic with the assumption that oral vitamin K1 poses little toxicity (32). No official recommendations based upon presenting INR have been postulated. For now, the approach appears to involve titrating the dose as needed to correct the INR, with a gradual taper as time progresses (3).

The endpoint of oral therapy is empirical. Many case reports have continued treatment until the PT becomes normal (33, 13), with a follow-up INR 24-48 hours after discontinuation of therapy (3). It has been hypothesized that the coagulation factor levels could be monitored until normal as an alternative to waiting for the INR to rise or clinical symptoms to develop (5); this has yet to be reported in the literature. Finally, monitoring the vitamin K1 2,3-epoxide/vitamin K1 ratio may also prove to be of benefit (6) as INR and PTT values alone may be normal over a wide range of coagulation factor levels (5).

Asymptomatic Nonanticoagulated Patient

Acute doses of prophylactic vitamin K should not be given to a patient with a known or suspected ingestion of superwarfarin who is asymptomatic. Such treatment will render any future PT value (obtained if clinical symptoms develop) useless for an estimation of the amount of superwarfarin-induced coagulopathy. Furthermore, a life-threatening coagulopathy would develop gradually. Therefore, giving 1 or 2 doses of vitamin K will not assist in preventing this condition (4).

Disposition

Adults

Adults will usually present with clinical symptoms of bleeding that lead to an investigation of the coagulopathic etiology. Depending upon the patient's presenting symptoms and circumstances (i.e. accidental versus intentional), the patient should be managed as discussed above. A search of the MEDLINE literature reveals no case reports regarding cognizant adult accidental ingestion of a superwarfarin. Most of the adult presentations are that of intentional suicide (5, 16, 17, 30, 32, 33) or psychiatric disturbances (34, 35). In general, adults should be referred to a health care facility for psychiatric if not medical evaluation.

Children

Except for children who present via Munchausen syndrome by proxy (41), the majority of pediatric ingestions are accidental and incidental (see Table 1). Very few serious clinical symptoms and no deaths have been reported in the pediatric exposure literature. The most serious complications resulted from possible chronic exposure versus acute accidental ingestion. For example, in one case series bromodialone, used as a rat poison, was accessible to two children who had presumptive chronic ingestions until they presented symptomatically with a neck hematoma and hemarthrosis (38). Another case resulted in a calf hematoma and bilateral occipital hemorrhagic infarcts from brodifacoum pellets and rat droppings that contained the poison. Although direct ingestion of these substances was never witnessed, it was inferred (42). Finally, easy bruising and epistaxis had been noted in one child

whose parents used brodifacoum rat poisoning in the home (43). Thus, for children in whom a small amount of acute exposure to a superwarfarin can be documented, the likelihood of clinical effects is rare.

The challenging aspect of disposition lies in estimating to how much poison a child was exposed. It has been shown that the presence of the characteristic blue-green dye around a child's mouth is not predictive of an abnormal INR (22). That same study demonstrated that by history alone, the amount of superwarfarin ingested is not predictive of an abnormal laboratory value or clinical symptoms. The authors' conclusion was that the only reliable indicator of anticoagulant effects was a 24-to-48 hour PT/INR determination. This was subsequently incorporated into a recommendation by POISINDEX (MICROMEDEX, Englewood, CO). Several studies since have disputed the notion that a follow-up PT/INR is necessary in asymptomatic patients based upon reviews involving larger populations of patients (1, 23, 25, 40). One prospective study investigated the incidence of untoward effects by newly adopted triage criteria from a poison center. The criteria relied upon determination of the ingested amount as less than or more than a mouthful. Less than a mouthful, home observation was warranted. Greater than a mouthful and less than one hour, home decontamination was performed with ipecac. Greater than a mouthful and greater than one hour post-ingestion resulted in referral to a doctor. 82% of the calls to the poison center were managed at home. 6% of the calls were referred to a health care facility, whereas 12% of calls originated from a health care facility. At the hospital, patients were recommended to receive activated charcoal and a baseline PT/INR. 48% of the hospital cases received PT/INR values, all which were normal. No adverse outcomes (not defined) were recorded in any of the patients in the study (24). In collective, these studies argue that small amounts of superwarfarin ingestion may be managed at home with parental education and observation. More prospective studies are necessary to exactly define what is a "safe" amount of superwarfarin.

Table 1- Case series of children ingesting superwarfarins

Author	n	Type	Prolonged PT/INR	Treatment	Complications	Ref
Katona (1986)	8	variable	0/2	none	none	36
Bennet (1987)	25	Brodifacoum/diphacinone	0/16	Ipecac	Epistaxis (1)	3
Greeff (1987)	2	Bromodialone	2/2	Intubation, vit K1	Neck hematoma (1), hemarthritis (1)	38
Sullivan (1989)	82	variable	0/39	Ipecac, AC	none	21
Smolinske (1989)	110	variable	8/110	Dilution, ipecac	Vomiting (2), heme positive stool (3)	22
Morrissey (1995)	1790	variable	1/78	Ipecac	none	1
Chua (1998)	8	variable	1/8	Ipecac, vit K1	none	39
Shepherd (1998)	10733	Brodifacoum	39/10733	GI decontamination-not specified	Minor bleeding (16)- not specified	23
Wahl	751	variable	0/64	Ipecac, AC	none	24

(1999)						
Ingels (2000)	465	variable	2/243	none	Epistaxis (2)	25
Mullins (2000)	542	variable	1/456	Not specified	none	40

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