VITAMIN K_1 TREATMENT OF BRODIFACOUM POISONING IN DOGS

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ABSTRACT: Twenty dogs received a potentially lethal (15 mg/kg) dose of brodifacoum, a halogenated coumarin-type anticoagulant poison. Eleven were immediately treated with vitamin K_1 daily for 5 days, either by intramuscular injections (2 mg/kg) or oral tablets (1 mg/kg). It was necessary to give further doses of vitamin K_1 to most of the dogs for up to 2 weeks after the first treatment period to reduce their P times to normal levels (<10 seconds). Four dogs were not given further vitamin K_1 and two of these died of acute blood loss from an intrathoracic hemorrhage. Nine dogs received vitamin K_1 (2 mg/kg by intramuscular injection) when clinical signs of anticoagulant poisoning were observed. Two dogs died suddenly without premonitory clinical signs of poisoning. The remaining 7 dogs showed various signs of anticoagulant poisoning 4 to 8 days after dosing and they received a 5 day course of vitamin K_1. After this period one dog had a transient rise in its P time but this returned to normal without treatment, while another dog was treated on days 16, 20, 29 and 30. In conclusion, the authors recommended vitamin K_1 therapy, 2 mg/kg by tablet or injection, daily for 3 weeks in cases of known or suspected brodifacoum poisoning in dogs.

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INTRODUCTION

Brodifacoum, a halogenated coumarin derivative, is currently marketed as a rodenticide and has recently been shown to be suitable for rabbit control under New Zealand conditions (Godfrey and Lyman 1980, Godfrey et al. 1981a, Rammell et al. 1984). The most commonly used poison to control rabbits at the moment is sodium monofluoroacetate (1080), and dogs, which are highly susceptible to this poison, frequently die after ingesting bait material or poisoned animals (Rammell and Fleming 1978). Death usually occurs within 12 hours and there is no antidote. Brodifacoum is considerably less toxic for dogs than 1080 (LD_{50} 3.56 and 0.5 mg/kg respectively) whereas the LD_{50} in rabbits is very similar (0.5 and 0.7 mg/kg respectively) (Mount et al. 1982, Godfrey et al. 1981b, Rammell and Fleming 1978). Thus the risk of a dog ingesting a lethal dose of brodifacoum is less than for 1080. Commercial baits contain 50 mg brodifacoum per kg bait and therefore a 20-kg dog would have to consume 1.5 kg of bait to receive an acute LD_{50} dose. However, there is considerable variation between individuals in their response to anticoagulant poisoning (Coon and Willis 1970) and some dogs may be clinically affected with smaller doses. A number of dogs have been poisoned after consuming as few as 8 Talon baits (Montgomery, pers. comm.). As with all anticoagulant poisons there is a 2- to 3-day delay before a fall in blood clotting factors and the onset of clinical signs which may include lassitude, anorexia, a bloody nasal discharge, rapid thready pulse, pallid mucous membranes, rapid respiration and petechial hemorrhages in the oral and conjunctival mucous membranes. These signs should alert the owner and veterinarian to the possibility of anticoagulant poisoning.

All anticoagulants derived from coumarin are structurally related to vitamin K and interfere with the normal blood-clotting mechanism by inhibiting the vitamin K dependent synthesis of clotting factors II (prothrombin), VII, IX and X (Park et al. 1979). Thus measurement of the prothrombin time (P time) is a good indication of the degree of anticoagulant activity. The normal P time for a dog is <10 seconds. The administration of vitamin K_1 appreciably reduces a prolonged prothrombic time within 4 to 8 hours of administration. Vitamin K_1 acts on a competitive basis and larger doses are required to reverse higher doses of anticoagulant (Coon and Willis 1970). There are a number of similar analogues of naturally occurring Vitamin K_1 which are reputed to have the same activity. However, Clark and Halliwell (1963) demonstrated that a number of commercially available water- soluble analogues, such as vitamin K_3, have little or no value for treating anticoagulant poisoning. This is probably because of their more rapid conjugation and excretion (Coon and Willis 1970).

The "first generation" anticoagulant rodenticides of the coumarin type include warfarin, and their activity lasts for up to 4 days (Coon and Willis 1970, Mount et al. 1982); therefore, vitamin K_1 therapy (1 to 2 mg/kg) daily for a minimum of 4 days has been recommended (Clark and Halliwell 1963). "Second generation" anticoagulants such as brodifacoum appear to be cleared from the body more slowly and they are pharmacologically active longer. Tissue residues have been detected in the livers of sheep for up to 4 months after they were dosed with brodifacoum at 2 mg/kg,

although these animals showed no clinical signs of anticoagulant poisoning (Laas et al. 1985). Anticoagulant activity has been detected in rabbits 6 weeks after they were dosed with 1 mg/kg brodifacoum (Park and Leck 1982). However there is no published information on the duration of brodifacoum activity in dogs nor on the recommendations for treatment of dogs poisoned with it. Therefore, the objective of this trial was to investigate the dose and duration of vitamin K_1 necessary to treat dogs acutely poisoned with a potentially lethal dose of brodifacoum.

MATERIALS AND METHODS

Twenty-one dogs of mixed age, breed and sex were individually housed in kennels, fed mutton daily and had water freely available. They all received a sandwich of bread and margarine containing brodifacoum at a dose rate of 15 mg/kg which is approximately 4 times the LD_{50} (Godfrey et al. 1981b). There were 3 treatment regimes:

Group 1: Five dogs received vitamin K_1 (2 mg/kg) by intramuscular (IM) injection daily for 5 days commencing the day after dosing. (The source of K_1 was Konakion - Roche Products (New Zealand) Ltd, Auckland, New Zealand).

Group 2: Six dogs received vitamin K_1 (1 mg/kg) orally by tablet daily for 5 days commencing the day after dosing.

Group 3: Ten dogs were observed daily for obvious clinical signs of anticoagulant poisoning, which an owner would be likely to detect, e.g., dullness, inappetence, spontaneous bleeding from orifices, sudden appearance of subcutaneous swelling, or hemorrhages in the oral mucosa. Treatment commenced immediately clinical signs appeared and constituted daily IM injections of vitamin K_1 (2 mg/kg) for 5 days.

Based on the results of a previous trial (Godfrey, unpubl.) it was estimated that 5 days' therapy would be sufficiently long to reverse brodifacoum poisoning. However, it soon became apparent that 5 days was not long enough. A number of dogs became clinically affected a few days after the initial period of treatment ended and further vitamin K_1 doses were given when indicated by the development of clinical signs or prolonged P times. Four dogs chosen at random served as controls to assess the severity of the relapse: dogs 40 and 51 in Group 1; 58 and 61 in Group 2.

Blood samples were taken using citrated vacutainers at 2 to 3 day intervals throughout the trial for determination of P times using Simplastin obtained from William R. Warner, Ltd.

RESULTS

Group 1

(Table 1) The P times during the initial treatment period rose slightly but did not exceed 11 seconds. At day 8, 3 days after the initial treatment ceased, P times rose markedly in 4 of 5 dogs and by day 11 the fifth dog's P time had also risen. Further treatments were given up to 20 days after dosing as indicated. One of the control dogs (40) died on day 18 while the other control dog (51) and the 3 treated dogs survived.

Group 2

(Table 2) P times for 2 of the 6 dogs exceeded 11 seconds during the first 5 days of therapy. Further treatments were given up to 22 days after dosing as indicated. A control dog (58) died on day 10, despite receiving treatment on day 9, when it showed signs of acute blood loss. All other dogs survived.

Group 3

(Table 3) One dog (35) vomited its sandwich the evening after the trial commenced and had normal P times despite receiving no treatment. Two dogs (45 and 52) were found dead on days 3 and 5 without showing any abnormal clinical signs. Dog 45 was a pregnant bitch which had started whelping prematurely in the night and was found dead the next day after hemorrhaging from the uterus. The remaining 7 dogs all showed a variety of clinical signs of anticoagulant poisoning which included inappetence, frank hemorrhaging from nose or mouth, blood in the faeces or petechial hemorrhages in the oral or conjunctival membranes. The 5-day treatments commenced immediately

Table 1. Porthrombin times (seconds) and occasions (*) when dogs were treated with Vitamin K_1 (intramuscular injection 2mg/kg) commencing the day after they received brodifacoum (15 mg/kg).

	Days																								
Dogs	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
36	5	-	6	-*	6*	-*	6*	-*	6	-	6	-	-	13	-	15*	-	10	-	-	12	-	9	-	6	-	N
40	6	-	6	-*	11*	-*	7*	-*	7	-	12	-	-	21	-	28	-	34	-	-	D						
51	5	-	6	-*	7*	-*	6*	-*	7	-	11	-	-	17	-	9	-	14	-	-	11	-	15	-	6	-	N
55	6	-	5	-*	11*	-*	7*	-*	6	-	15	-	-*	10	-	8	-	6	-	-	6*	-	7	-	5	-	N
56	5	-	6	-*	6*	-*	6*	-*	8	-	21	-	-	31*	-*	8	-	17	-	-	16	-*	8*	-	6	-	N

N = Normal (<10 second prothrombin times)
D = Dead

Table 2. Prothrombin times (seconds) and occasions (*) when dogs were treated with Vitamin K_1 (oral tablets 1 mg/kg) commencing the day after they received brodifacoum (15 mg/kg).

	Days																								
Dogs	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
58	6	-*	11*	-*	35*	-*	-	44	-	52*	D														
59	6	-*	8*	-*	10*	-*	-*	12*	-*	7*	-*	6	-	-	8	-	25	-*	9	-	-	6	-	6	N
60	6	-*	8*	-*	8*	-*	-*	7*	-*	10	-*	7	-	-	10	-	15	-*	48	-*	-	5	-	6	N
61	6	-*	10*	-*	8*	-*	-	16	-	16*	-	15*	-*	-	13	-*	8	-	10	-	-	12	-*	7	N
62	6	-*	11*	-*	13*	-*	-	14	-	13*	-	10*	-*	-	6	-	8	-	6	-	-	6	-	7	N
63	7	-*	8*	-*	7*	-*	-*	8*	-*	8*	-*	6	-	-	6	-	6	-	6	-	-	5	-	7	N

N = Normal (<10 second prothrombin times)
D = Dead

after these signs were first observed between days 4 and 8. Additional treatments were given to dog 41 when the P times rose above 15 seconds. All other dogs' P times remained at normal levels after the 5-day treatment except for dog 39 which went up to 14 seconds on day 18 but returned to normal levels by day 20 without further treatment. None of the dogs showed clinical signs of anticoagulant poisoning subsequent to the 5-day treatment period.

Postmortem examinations of dogs 40, 58 and 52 showed massive intrathoracic hemorrhage.

Table 3. Prothrombin times (seconds) and occasions (*) when dogs were treated with Vitamin K_1 (intramuscular injection 2 mg/kg) commencing when clinical signs of brodifacoum poisoning appeared.

	Days																																
	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Dogs																																		
35	6	-	6	-	5	-	6	-	6	-	6	-	-	5	-	N																		
39	5	-	6	-	12	-	25	-	17*	-*	6*	-*	-*	6	-	10	-	9	-	-	14	-	8	-	6	N								
41	6	-	6	-	13	-	21*	-*	7*	-*	6*	-	-	12	-	17	-	F	-*	-	7	-	F*	-	12	-	-	29	-	17	-	F*	-*	N
45	6	-	6	-	17	D																												
46	5	-	6	-	12	-	20	-*	6*	-*	7*	-*	-	6	-	6	-	6	-	-	5	-	5	-	6	N								
49	6	-	6	-	15	-	20	-	14	-*	8*	-*	-*	5*	-	6	-	6	-	-	6	-	6	-	5	N								
50	5	-	6	-	12	-	20	-	17	-*	9*	-*	-*	6	-	6	-	6	-	-	6	-	6	-	5	N								
52	6	-	7	-	15	-	17	D																										
53	4	-	6	-	13	-	26	-	13	-	22*	-*	-*	7*	-*	7	-	8	-	-	7	-	7	-	6	N								
54	6	-	6	-	17	-	16	-*	11*	-*	6*	-*	-	8	-	7	-	6	-	-	6	-	5	-	6	N								

N = Normal (<10 second prothrombin times)
D = Dead, F = Failed to clot (>60 seconds)

DISCUSSION

The dose rate of brodifacoum used in this experiment is potentially lethal for most dogs, being 4 times the LD_{50} and equivalent to an LD_{90} (Godfrey et al. 1981b).

It was calculated to be the maximum acute dose a dog could reasonably consume at one time in the form of baits (i.e., 6-kg baits for a 20-kg dog). However, it would be relatively easy for this dose to be consumed over a period of a few days.

The trial was designed so that Groups 1 and 2 mimicked immediate prophylactic treatment while Group 3 represented the emergency treatment of dogs which have developed obvious clinical signs of anticoagulant poisoning. The results show that in the case of immediate prophylactic therapy a 4-5 day vitamin K regime as recommended for treating warfarin poisoning in dogs (Clark and Halliwell 1963, Mount et al. 1982) is of insufficient duration in cases of brodifacoum poisoning.

The results also suggest that oral therapy with vitamin K_1 at a dose rate of 1 mg/kg is insufficient to maintain normal P times in dogs which have received a high dose of brodifacoum. Clark and Halliwell (1963) demonstrated that oral and injectable forms of vitamin K_1 therapy both produced similar effects although the intramuscular route gave a slightly slower onset of action but appeared to have a slightly more prolonged effect. They concluded that with both routes dosage at 24-hour intervals should be sufficient. They recommended dose rates of 1 to 2 mg/kg to treat warfarin poisoning. The present trials suggest that 2 mg/kg for both oral and injectable routes should be used in cases of brodifacoum poisoning.

The 2 deaths in Group 3 demonstrate how rapidly the coagulation factors can be depleted leading to acute, massive hemorrhage and highlight the susceptibility of pregnant bitches to hemorrhage at whelping.

In most cases 5 days' treatment of the clinically affected dogs was sufficient and suggests that there is little brodifacoum activity after 10 or 11 days. Two dogs, whose last treatments were on days 8 and 10, each had a transient rise in P times 3 to 8 days later. Dog 39 returned to normal 2 to 3 days later without treatment. However, dog 41 was treated on days 16, 20, 29 and 30, although not all of these may have been necessary as some of the Simplastin tests failed to clot, and the results appear to be anomalous because the animal showed no clinical signs of poisoning despite very prolonged P times.

RECOMMENDATIONS

If a dog is known or thought to have eaten baits or dead animals containing brodifacoum, then vitamin K_1 therapy, 2 mg/kg either by IM injection or oral tablets, should be given daily for 3 weeks. Periodic blood samples for P time measurement may be taken to monitor the effectiveness of the treatment.

If a dog develops clinical signs of anticoagulant poisoning, it must now be assumed to be due to brodifacoum and treated accordingly. If the dog shows signs of acute massive hemorrhage, then it is advisable to give a transfusion of whole blood or plasma which should immediately supply hemostatic concentrations of clotting factors. The amount transferred should approximate 5-10% of the patient's total blood volume, which is approximately 90 ml/kg (Mount et al. 1982). In cases of hemothorax the blood should be aspirated and autotransfusion (where aspirated blood plus vitamin K_1 is transfused back into the dog) may be performed (Crispin 1977). In acute cases, vitamin K_1 (1 mg/kg) diluted with saline may be given by slow intravenous injection, and prior administration of an antihistamine is recommended to prevent histaminoid reactions (Clark and Halliwell 1963, Crispin 1977). This should restore a proportion of clotting factors within 2 hours. Tablets or intramuscular injections of vitamin K_1 may be used initially in less acute cases. Vitamin K_1 therapy by IM injection or oral tablets (2 mg/kg) should continue for 3 weeks. The effectiveness of the therapy can be monitored by measuring the P time. Pregnant bitches close to whelping should receive particular attention to assure that their P time is <10 seconds when whelping begins.

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