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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Talon (Brodifacoum) Anticoagulant Rodenticide. Tox Chem. No. 114AA

TO: William Miller, PM-16
Registration Division (TS-767)

THRU: Robert P. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

FROM: Ray Landolt
Review Section #1
Toxicology Branch/HED (TS-769)

Registrant: ICI Americas Inc.

Registration Nos. 10182-38, -39, -40, -41, -48, -60, -61, -75 and -76

Action Requested: Revise the "Note to Physician or Veterinarian" paragraph to include veterinary administration of Vitamin K_1, as follows:

> This product may reduce the clotting ability of the blood and cause hemorrhaging. If poisoning occurs, intramuscular and oral administration of Vitamin K_1 are indicated, as in poisoning from overdose of bishydroxy coumarin. For human cases, Vitamin K_1 is antidotal at doses of 10-20 mg (not mg/kg). For animal cases, Vitamin K_1 is antidotal at 2-5 mg/kg. Repeated doses may need to be given up to two weeks (based on monitoring of prothrombin times). In severe cases, blood transfusions may be necessary.

Recommendation: The changes in the precautionary labeling for the treatment of the anticoagulant effects of brodifacoum with Vitamin K_1 therapy appears to be supported

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by the data submitted.

Toxicity Data Submitted with this Request

I. A Comparative Study of the Effect of Warfarin and Brodifacoum on the Relationship Between Vitamin K_1 Metabolism and Clotting Factor Activity in Warfarin-Susceptible and Warfarin-Resistant Rats. Jacquelin R. Leck and R. Kevin Park.

Biochem Pharmacol 30 123-128, 1981 Acc. No. 251781.

A. Procedure

The parameters investigated are prothrombin complex activity (PCA), clotting factor activity (CFA), vitamin K_1 metabolism (bile and urinary metabolites). The test materials include both labeled and unlabeled vitamin K_1, racemic sodium warfarin and brodifacoum. Adult male Wistar Rats (200-300 g) and adult male Welsh warfarin-resistant rats (250-300 g) were used in these studies. Warfarin was administered I.P. to four animals per level of 0.1 and 1.0 mg/kg. Brodifacoum was administered I.P. to four animals per level of 0.1, 1.0 and 10 mg/kg. Blood samples for measurement of PCA and CFA were collected from the tail artery. Blood for CFA was obtained at 24 hours and frozen for assay at the completion of the study, except for Factor V which was assayed within 2 hours of collection. For the metabolism studies, vitamin K_1 was administered I.V. one hour after the administration of the anticoagulant followed by collection of blood by cardiac puncture, removal and homogenization of the liver two hours later. To measure the rate of bile excretion vitamin K_1 was administered one hour after the administration of the anticoagulant with bile collected at 30 minute intervals over a five-hour interval. For urinary metabolites, vitamin K_1 was administered one hour after the administration of the anticoagulant with the animals placed in individual metabolism cages for urine to be collected every 12 hours over a 60-hour interval.

B. Results

1. Prothrombin complex activity (PCA) half life for brodifacoum was approximately 4 hours. Brodifacoum produced the same rate of PCA degradation in warfarin resistant rats as in warfarin-susceptible rats.

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2. Clotting factor activity of vitamin K_1, except for Factor V, was significantly reduced by brodifacoum.

3. Brodifacoum increased the hepatic concentration ratio of labeled vitamin K_1 epoxide to labeled vitamin K_1 in both warfarin-resistant and warfarin-susceptible rats at anticoagulant dosages.

4. Brodifacoum, at anticoagulant doses, significantly increased labeled metabolites in the bile but did not alter bile flow.

5. Brodifacoum did not alter urinary excretion of labeled vitamin K_1 metabolites.

C. Conclusion

1. Classification of Data - Minimum

2. "The results indicate that brodifacoum has the same mechanism of action as warfarin and support the concept that coumarin anticoagulants reduce vitamin K_1 dependent clotting factor synthesis by interrupting the vitamin K_1 epoxide cycle."

II. A Study of the Effect of Anticoagulants on ^3H Vitamin K_1 Metabolism and Prothrombin Complex Activity in the Rabbit, B. Kevin Park, et al.

Biochem Pharmacol 28, 1323-29, 1979, Acc. No. 251781.

A. Procedure

The parameters investigated are prothrombin complex activity (PCA) and vitamin K_1 metabolism. The test materials include both labeled and unlabeled vitamin K_1, racemic sodium warfarin, racemic acenocoumarol, difenacoum, brodifacoum and 2-chloro-3-phytyl-1,4-naphthoquinone (Cl-K). Four adult male New Zealand White rabbits (2.5-3.0 kg) were used per dosage level. Warfarin, acenocoumarol and Cl-K were administered intravenously(I.V.) followed one hour later with labeled vitamin K_1 (I.V.) Difenacoum and brodifacoum were administered intramuscularly followed two hours later with labeled vitamin K_1 (I.V.). For PCA determinations blood samples were collected initially then at six hours after vitamin K_1 for four hour intervals. For vitamin K_1 metabolism blood was drawn at 1, 2, 3, 4, 5, and 6-hour intervals.

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B. Results

1. Prothrombin complex activity half life for brodifacoum and difenacoum was approximately 7 hours. An approximate 6 hour PCA half life was reported for the other anticoagulants.

2. The approximate half life of labeled K_1 for all five anticoagulants was approximately two hours.

3. The ratio of labeled vitamin K_1 epoxide to vitamin K_1 in the plasma increased with warfarin, acenocoumarol, brodifacoum and difenacoum, but decreased with Cl-K.

C. Conclusion

1. Classification of Data - Minimum

2. The pharmacological effect of warfarin by inhibiting vitamin K_1 epoxide reductase appears similar for brodifacoum, acenocoumarol and difenacoum.

III. Investigation into the Effectiveness of Vitamin K_1 as an Antidote to Brodifacoum Induced Anticoagulation in Rats.

ICI Central Toxicology Laboratory Report No. CTL/P [illegible]05, 1982, Acc. No. 251781.

A. Procedure

The parameters investigated are the effect of vitamin K_1 therapy on mortality and prothrombin time due to warfarin and brodifacoum. Five Alderley Park pathogen-free (SPF) albino rats of each sex were used per dosage level tested. Animals receiving oral doses were fasted 16-20 hours prior to dosing. Warfarin and brodifacoum were administered orally in polyethylene glycol. Vitamin K_1 was administered intramuscularly at 2 mg/kg.

For the effect of vitamin K_1 therapy on mortality, two groups of rats were dosed with brodifacoum at 0.25, 0.5, 0.75, 1.0 and 1.25 mg/kg. Control groups included warfarin (35 mg/kg), solvent (PEG 200) and an untreated group. One of the brodifacoum groups was treated with vitamin K_1 and the other received no vitamin K_1. The initial dose of vitamin K_1 was administered 24 hours after brodifacoum, then repeated every 12 hours for eight days. A third group

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received brodifacoum at 1.25 mg/kg and a single dose of vitamin K_1 at 24 hours. All animals were observed daily. Body weights were recorded initially then on days 8, 15, 22, and 29. At the termination of the study blood was drawn by cardiac puncture for determination of prothrombin times and livers removed and weighed.

For the effect of vitamin K_1 on these anticoagulants, two groups of rats received brodifacoum at 1.25 mg/kg and warfarin at 35 mg/kg accompanied by solvent and untreated control groups. One of the test groups was left untreated the other was treated with vitamin K_1 24 hours later and repeated every 12 hours for 9 days. All rats were observed daily. At the termination of the study blood was drawn by cardiac puncture for determination of hemoglobin, hematocrit, WBC, RBC, mean cell volume, mean cell hemaglobin concentration, differential count and prothrombin time.

B. Results

1. Effect of Vitamin K_1 on Mortality from a Single Dose of Brodifacoum

a. Untreated with Vitamin K_1

The 1.25 mg/kg level killed 10/10 animals by day 6. At the 1.0 mg/kg level, 10/10 animals died, males by day 6 and females by day 10. The 0.5 mg/kg dose killed 4/10 by day 6. No deaths 0/10 were reported for the 0.25 mg/kg level.

b. Multiple dose of Vitamin K_1 (2 mg/kg every 12 hrs. for 8 days). No deaths were reported for the 1.0 mg/kg level with 4/10 surviving the 1.25 mg/kg level.

c. Single dose of Vitamin K1 (2 mg/kg) to a 1.25 mg/kg level of brodifacoum resulted in 10/10 animals dead by day 7.

d. Signs of toxicity reported for brodifacoum were depressed behavior, piloerection, ungroomed and pale appearance, and subcutaneous hemorrhage. No decrease in body weight gain was apparent for the treated or untreated groups.

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e. Liver weights relative to body weights of the treated and untreated groups were comparable to controls.

f. Clotting time of animals surviving the 28-day observation period were comparable to controls.

2. Effect of Repeated Doses of Vitamin K_1 on the Anticoagulant Brodifacoum and Warfarin.

a. Hematology after 2 days.

i. Male rats, treated and untreated with vitamin K_1, showed a significant increase in clotting time (5x control values), increased WBC, monocyte and lymphocyte count. Clotting time of warfarin rats treated with vitamin K_1 was comparable to controls.

ii. Female rats, treated and untreated with vitamin K_1 showed a significant increase in clotting time (5x control values) and monocyte count. Clotting time of warfarin rats treated with Vitamin K_1 was increased 2-3 times as compared to control values.

b. Hematology after 4 days.

i. Male and female rats treated with vitamin K_1 showed a 4 fold increase in clotting times as compared to controls. Clotting times of female warfarin rats treated with vitamin K_1 were comparable to controls.

c. Hematology after 7 days.

i. Male rats, treated with vitamin K_1, showed a 2-3 fold increase in clotting time as compared to controls.

ii. Female rats, treated with vitamin K_1, showed a 3-4 fold increase in clotting time as compared to controls.

d. Hematology after 9 days treatment with vitamin K_1.

i. Male rats showed a 2-fold increase and females a 3-fold increase in clotting times.

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C. Conclusion

1. Classification of Data - Minimum

2. Approximate acute oral LD_{50} of brodifacoum is 0.5 mg/kg with repeated daily administration of vitamin K_1 the approximate LD_{50} value increased to between 1.0 and 1.25 mg/kg.

   Intramuscular doses of vitamin K_1 (2 mg/kg) repeated every 12 hours for 8 days is effective in reducing mortality from the anticoagulant effects of brodifacoum (1.0 mg/kg) in rats.

IV. An Evaluation of Vitamin K_1 Therapy in the Treatment of Brodifacoum Poisoning in Dogs.

M. E. R. Godfrey, J. Gill and T. C. Reid. Unpublished, 1981, New Zealand Ministry of Agriculture and Fisheries Acc. No. 251781.

A. Procedure

Fifteen dogs of mixed breed, age and sex were divided into three groups of five animals per group. Technical brodifacoum was administered in the feed at 8 mg/kg (LD_{75}) to all three groups. Vitamin K_1 was administered as a single intramuscular dose of 2 mg/kg to two groups, one at 3 days and the other at four days after brodifacoum. The other group was untreated with vitamin K_1. All animals were fasted 24 hours prior to dosing. Prothrombin times were determined for all animals initially, two days prior to dosing with brodifacoum then at 2-3 day intervals.

B. Results

1. Dog oral LD_{50} 3.56 mg/kg (Godfrey et al. 1981, N.Z.J. Exp. Ag. 9:147-149)

2. The controls, untreated with vitamin K_1, resulted in 3/5 deaths with lassitude, anorexia and bloody nasal discharge reported prior to death.

3. Treatment with a single dose of vitamin K_1 three days after brodifacoum when the prothrombin times were about twice of normal result in a near normal prothrombin time within 4 days of treatment followed by a regression and death (3/5).

4. Treatment with a single dose of vitamin K_1 four days after brodifacoum when the prothrombin times were about 3 to 4 times normal resulted in near normal values within 3 days of treatment followed by a three fold increase in prothrombin at 10 days, then a return to normal in seven days with no deaths.

C. Conclusion

1. Classification of Data - Minimum

2. Vitamin K_1 (2 mg/kg IM) therapy in dogs should start no later than three days after ingestion of brodifacoum and repeated daily for a least four days or until prothrombin times return to normal.