



The Superwarfarins: Long-acting Anticoagulant Rodenticides

Introduction

Anticoagulants are common active ingredients in rodenticides. The term superwarfarin is used to describe the newer, longer-acting, more potent anticoagulants currently available in rodenticides. These “superwarfarins” replaced warfarin after rodents developed resistance. Warfarin-like compounds include 4-hydroxycoumarin derivatives (brodifacoum, bromadiolone, difenacoum) and indandione derivatives (diphacinone, chlorophacinone and pindone). The majority of warfarin-like compounds in commercially available rodenticides are considered superwarfarins. They are available in a variety of products. Brodifacoum (Figure 1) is the most common ingredient found in commercially available rodenticides and is usually found in a 0.005% concentration. In 2002, 17 100 exposures to long-acting rodenticides were reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System (TESS).¹ The majority (89%) of reports involved children less than 6 years of age, were unintentional (96%) and did not require treatment in a health care facility (70%).

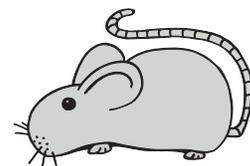
Pharmacology/Pharmacokinetics

Warfarin and warfarin-like compounds work by blocking the formation of activated vitamin K, which is a required cofactor in the synthesis of clotting factors II, VII, IX, and X. The anticoagulant effects of warfarin and warfarin-like substances are secondary to inhibition of the enzymes vitamin K 2,3-epoxide reductase and vitamin K quinone reductase. The inhibition of these enzymes prevents the activation of vitamin K and therefore prevents the production of the clotting factors. The resultant coagulopathies are manifest by an increase in prothrombin time, increase in INR and bleeding.

The onset of anticoagulant activity is dependent on the half-life of the clotting factors. Factor VII has the shortest half-life at 5 hours. Effects on prothrombin time (PT) require depression to 25% of clotting factors normal values. Initial effects on PT usually are not seen until at least 15 hours after ingestion for warfarin. Superwarfarins are highly lipid soluble, concentrate in the liver and saturate hepatic enzymes. They are much more potent and have a longer duration of action than warfarin as a result of these kinetic differences.

Clinical Toxicology

Bleeding complications are the major risk following the ingestion of warfarin and warfarin-like compounds. Coagulopathies have persisted for 6 weeks to over 6 months following intentional ingestions of superwarfarins. Prolonged prothrombin times have occurred in adults after ingesting 1-10 mg of brodifacoum (0.03-0.17 mg/kg).² The UPCC was involved in the care of three patients with significant coagulopathies following the ingestion of a superwarfarin in recent years. In one case, the patient was treated for 253 days with both oral and subcutaneous vitamin K.



Despite the potential toxicity of these agents, most pediatric ingestions result in little or no clinical effect. A review of 10 762 brodifacoum exposures in children six years of age and younger reported to TESS between 1993-1996 found only 67 (0.62 %) of children had clinical or laboratory signs of coagulopathy and only two exposures were reported with INRs greater than 1.5 times the control (2.6 and 15.1).³ A prospective study evaluated unintentional superwarfarin ingestions reported to a regional poison center in children less than 6 years of age.⁴ A total of 545 children ingested more than 1 pellet but less than one box of superwarfarin-containing rodenticide and did not receive decontamination or prophylactic vitamin K. Elevated INR was noted in 2 of 241 patients for whom laboratory information was available. No INR was greater than 1.8 and neither child developed symptoms. Three children were noted to have bleeding, 2 from single nose-bleeds and 1 child with an anal fissure had blood streaked stools.

Treatment

Vitamin K is the antidote for warfarin and warfarin-like compounds. Vitamin K should be reserved for those patients who have a documented coagulopathy and should not be administered prophylactically. The majority of exposures reported to TESS are unintentional exposures in children less than 6 years of age. In the series of brodifacoum exposures reported to TESS in children less than 6 years of age, neither child with an elevated INR received vitamin K and neither developed bleeding.³ The majority of unintentional exposures in children less than 6 years of age are managed at

home with telephone follow-up. Unintentional ingestions of less than 1mg of brodifacoum (1/2 of 1.5 ounce container) in a child pose little risk for development of a coagulopathy. The value of gastrointestinal decontamination in treating superwarfarin ingestions has been debated. An analysis of the brodifacoum exposures reported to TESS showed that there was no improvement in outcomes for patients who received decontamination therapy.³

Specific therapy is usually required for patients who have intentionally ingested large amounts of superwarfarins. Patients who are acutely bleeding should be treated with fresh frozen plasma. Patients with documented coagulopathies should also receive vitamin K. Prophylactic vitamin K is not recommended because it will mask evidence of a toxic effect and make initial monitoring and diagnosis difficult.

Vitamin K can be administered orally, subcutaneously, and intravenously. The intravenous route should be reserved for acutely-ill patients who require doses higher than can be administered subcutaneously and require immediate onset of action. The main risks associated with rapid IV administration are anaphylaxis and hypotension. Vitamin K requirements can be quite high in order to correct the prothrombin time. Severe cases of superwarfarin poisoning have required months of vitamin K treatment at doses ranging from 50-250 mg/day. Doses of up to 600 mg per day have been reported for initial management of severe coagulopathies.⁵ The onset of action of vitamin K will depend on the route. However, in most cases, a decrease in the INR will be noted in several hours. It may take 8-24 hours to reach the target INR and longer if inadequate doses are given. Superwarfarins have a long duration of action. Patients may require months of vitamin K therapy before the INR returns to normal without the need for supplemental vitamin K.

Laboratory Monitoring

The prothrombin time and INR should be monitored at 24 and 48 hours after ingestion to identify patients at risk for serious coagulopathies. Prothrombin time and INR should be monitored at least once daily and up to twice daily in patients with documented coagulopathies. Patients will require long-term PT-INR monitoring. Following stabilization on vitamin K and discharge from the hospital, prothrombin time and INR should be monitored every other week and more often depending on the reliability for medication compliance of the patient.

Serum brodifacoum concentrations are useful in documenting the exposure, compliance with outpatient therapy and to make decisions about when vitamin K therapy can be discontinued. Local Utah laboratories do not

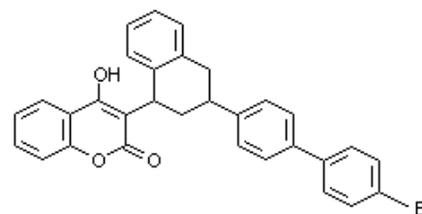
measure brodifacoum concentrations but can arrange transport of the sample to a reference laboratory for analysis. Results, although not immediate, are usually available within 7-10 days. Our experience is they can be very helpful in monitoring patient progress. Vitamin K therapy can be discontinued when serum brodifacoum concentrations fall below 10 ng/mL.⁵

Summary

Serious complications from superwarfarin ingestion are uncommon. Patients at risk for significant coagulopathies are those who ingest massive quantities of superwarfarin containing rodenticides, usually intentionally. Vitamin K requirements for patients with significant coagulopathies can be quite large and the duration of treatment is often weeks to months. The UPCC is available 24-hours a day to assist you in managing these difficult and unusual cases.

DeVere Day, PharmD

Figure 1. Brodifacoum



References

1. Watson WA, Litovitz TL, Rodgers GC, et al. 2002 Annual Report of the Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2003; 21:353-421.
2. Editorial Staff: Long Acting Anticoagulants (Management/Treatment Protocol). In: Klasco RK (ed): *POISINDEX® System*. Thompson MICROMEDEX, Greenwood Village, Colorado (Volume 120 expires [6/2004]).
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4. Ingels M, Lai C, Tai W, et al. A Prospective Study of Acute, Unintentional Pediatric Superwarfarin Ingestions Managed Without Decontamination. *Ann Emerg Med* 2002;40:73-8.
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Poisoning Deaths Appear on the Rise

Vital statistics data from 11 states (including Utah) were analyzed for unintentional and undetermined poisoning deaths for the years 1990-2001. Confirmed suicides were not included. There was an average increase of 145% in state death rates due to poisoning during this time period. The increase was greatest for persons aged 45-54 years. Persons aged greater than 64 years had a 28% decrease in death rates. Drugs and other biological substances were involved in 89% of the deaths. Narcotics and "psychodysleptics" (e.g. cocaine) accounted for 51% of all poisoning deaths. The most frequent substances involved in poisoning deaths were cocaine, alcohol, heroin, antidepressants, benzodiazepines and methadone. For 1999-2000 there were 359 unintentional or undetermined poisoning deaths reported in Utah. Cocaine, heroin, methadone, and other opiates accounted for 60% of Utah cases. Carbon monoxide accounted for 1.3% and alcohol for 5% of Utah deaths.¹

The UPCC has observed a steady increase in methadone and oxycodone related exposures over the past few years and will address this through professional education in the near future.

1. CDC, Unintentional and Undetermined Poisoning Deaths- 11 States, 1990-2001. MMWR 2004;53:233-238.



M-44 Sodium Cyanide Device

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The device is tubular and is placed in the ground with 1.5 inches sticking out of the ground baited with meat. This device is used in specific situations to control coyotes, redfox, gray fox and wild dogs. The purpose of the device is to protect livestock, poultry, and endangered species and to prevent the spread of disease. Although this device is primarily used on private lands, it may also be used on federal land in any county in the state. Areas where it is used are marked with signs. While human exposure to this device would be extremely unlikely, it is important to know that this device contains 91% sodium cyanide. Please report any exposure to this device to the Utah Poison Control Center at (800) 222-1222. We thank you in advance for your assistance.

New Employees

The Utah Poison Control Center is pleased to welcome Christine McMillan, PharmD as a Specialist in Poison Information-Pharmacist and two new student interns: Joel Arvizo as the Health Education Intern and Gouri Mahajan as the Information Technology Intern. Christine graduated from the St. Louis College of Pharmacy in 2001 and joins us from Smith's Food and Drug Pharmacy.

Meet the UPCC Staff

Kathy Anderson

Kathy joined the UPCC as a Specialist in Poison Information in July 2002. Previous to joining the UPCC, Kathy completed a Pharmacy Practice Residency at the Veteran



Affairs Medical Center in Salt Lake City, Utah in 2002. In 2001, Kathy completed a Doctor of Pharmacy from the

Health Sciences Center, University of Colorado in Denver, Colorado. Her hobbies include traveling, backpacking, snowboarding, skiing and gardening. Favorite poisonings: hydrogen peroxide and ethylene glycol.

Employment Opportunities

The UPCC has two positions available. The UPCC is looking for nurses or pharmacists to work as Specialists in Poison Information. You can find out more about these positions on our website at <http://uuhs.c.utah.edu/poison/employment>.

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Or send e-mail to poison@hsc.utah.edu

*CSPI denotes Certified Specialist in Poison Information.



Education Conference



The UPCC is offering two regional update conferences to the Train-the-Trainer program. There will be a review of the Trainer program, as well as many new and interesting topics such as poisonous plants, carbon monoxide, bites and stings, and inhalants and club drugs. Attendees will have the opportunity to hear from expert pharmacists and doctors in the field of toxicology and poison prevention. This conference provides up to 5 CECH's for CHES credit and 0.5 CEU's for ACPE credit.

The Northern Regional Conference is in Salt Lake City on June 16th at the Heritage Center on the University of Utah campus. The Southern Regional Conference is in Cedar City on June 25th at the Crystal Inn.

Please visit our website for more information: <http://uuhsc.utah.edu/poison>. This program is supported by a grant from the Maternal and Child Health Bureau, Health Resources and Services Administration.

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