Surreptitious Ingestion of a Long-Acting Vitamin K Antagonist/Rodenticide, Brodifacoum: Clinical and Metabolic Studies of Three Cases

By Jeffrey N. Weitzel, James A. Sadowski, Barbara C. Furie, Rebecca Moroose, Hugh Kim, Michael E. Mount, Michael J. Murphy, and Bruce Furie

The vitamin K metabolism of three patients with factitious purpura due to brodifacoum ingestion was studied. These patients, who presented with bleeding disorders due to deficiency of the vitamin K-dependent blood clotting proteins, were refractory to vitamin K, at standard doses and required fresh frozen plasma to control bleeding until large doses of vitamin K were used. Metabolic studies demonstrated a blockade in vitamin K utilization, consistent with the presence of a vitamin K antagonist, but the patients denied use of anticoagulants. Warfarin assays were negative. We show that the factitious purpura in each patient was due to the surreptitious ingestion of brodifacoum, a potent second generation long-acting vitamin K antagonist used as a rodenticide. The coagulopathies responded to long-term therapy with large doses of vitamin K. The serum elimination half-time for brodifacoum ranged from 16 to 36 days in these patients. The anticoagulant effect is of long duration, requiring chronic vitamin K treatment. With increasing availability of new rodenticides, factitious purpura due to surreptitious ingestion of these potent vitamin K antagonists is emerging as a new problem, previously associated with warfarin, with important implications for diagnosis and treatment.

© 1990 by The American Society of Hematology.

MATERIALS AND METHODS

Prothrombin times were determined by the one-stage method using citrated plasma and Thromboplastin-C (Dade, Baxter Healthcare, Miami, FL) or Simplastin (Organon Teknika, Durham, NC) as reagents. The kaolin-activated partial thromboplastin times were determined by the one-stage method using cephalin (Diagnostica Stago). Specific coagulation factor assays were determined by standard methods using factor-deficient plasmas in the partial thromboplastin time (aPTT) assay. The native prothrombin antigen (NPT) was determined by immun assay. Serum vitamin K, vitamin K-2,3-epoxide, and urinary γ-carboxyglutamic acid were determined by high performance liquid chromatography (HPLC). Plasma samples were analyzed for warfarin, indandione, and brodifacoum using an enzyme-linked immunosorbent assay (ELISA) method. The presence of brodifacoum was confirmed by separation using HPLC and capillary gas chromatography and detection by a mass selective detector. Briefly, the mobile phase eluant corresponding to the retention time of brodifacoum was collected, dried, and reconstituted in methanol for capillary GC/MS analysis using a Hewlett-Packard model 5890 gas chromatograph with a 5970 mass selective detector. At the appropriate retention time, the exact ions were detected in the correct relative abundances.

From the Center for Hemostasis and Thrombosis Research, Division of Hematology-Oncology, New England Medical Center and Tufts University School of Medicine; USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA; Florida Hospital, Orlando; Robert Wood Johnson Medical School, New Brunswick, NJ; Department of Pharmacology and Toxicology, School of Veterinary Medicine, University of California (Davis); and Department of Veterinary Diagnostic Investigation, University of Minnesota College of Veterinary Medicine, St Paul.

Submitted May 2, 1990; accepted August 27, 1990.

Supported by Grant No. HL2443 from the National Institutes of Health.

Address reprint requests to Bruce Furie, MD, Center for Hemostasis and Thrombosis Research, New England Medical Center, 750 Washington St, Box 832, Boston, MA 02111.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1990 by The American Society of Hematology.

0006-4971/90/7612-0011$3.00/0

Blood, Vol 76, No 12 (December 15), 1990: pp 2555-2559
RESULTS

Case 1. A 20-year-old female college student was hospitalized with abdominal pain, melena, menorrhagia, and gross hematuria. Previously well except for a history of anorexia nervosa and depression, she took no medications and had no history of bleeding. Coagulation studies are shown in Table 1. Combined deficiency of the vitamin K-dependent proteins was noted. She was treated for 4 days with fresh frozen plasma and oral vitamin K, with resolution of the bleeding and normalization of the coagulation studies. Three weeks later, she represented with recurrent menorrhagia and a compartment syndrome from hemorrhage into the left calf requiring surgical drainage. The prothrombin time was greater than 50 seconds and the PTT was 98.9 seconds. Serum screening for warfarin was negative. Bleeding decreased after transfusion with fresh frozen plasma and oral vitamin K, with partial correction of her prothrombin time to 16.7 seconds and her partial thromboplastin time to 37.8 seconds. A dilatation, curetage, and laparoscopy indicated normal anatomy and histology. She was retreated with fresh frozen plasma due to bleeding from her laparoscopy site and continued menorrhagia. Vitamin K, (5 to 10 mg orally) was ineffective, and was substituted by subcutaneous and intravenous administration supplemented with fresh frozen plasma therapy.

Two months later, the prothrombin time was 44.5 seconds, partial thromboplastin time 68 seconds, and native prothrombin antigen 23 μg/mL (normal 108 ± 19). Circulating inhibitor and warfarin assays were negative. The serum vitamin K, level was 1.1 nmol/L (normal 0.3 to 2.7 nmol/L) and the vitamin K epoxide level was 26.8 nmol/L (normal <0.3 nmol/L). Despite the absence of warfarin in the serum, the presence of a vitamin K antagonist in this patient was inferred by demonstration of a blockade in the vitamin K cycle. The ratio of vitamin K epoxide to vitamin K, was markedly elevated at 24.1. The normal ratio of epoxide to vitamin K, is less than 0.1, and is 2 to 3 in patients receiving therapeutic doses of warfarin. These results showed that the vitamin K deficiency was not the cause of this coagulopathy. The high vitamin K epoxide level was consistent with the inhibition of the vitamin K epoxide reductase, an action of warfarin and other vitamin K antagonists. The urine γ-carboxyglutamic acid content was 7.6 μmol/L (normal 49.5 ± 27.8 μmol/L). Oral vitamin K, 100 mg daily, led to high serum levels of vitamin K, (427 nmol/L) and vitamin K, epoxide (5,034 nmol/L); the ratio of vitamin K, to vitamin K epoxide of 11.8 confirmed the presence of a block in vitamin K reutilization. The urine γ-carboxyglutamic acid content, 32.3 μmol/L, returned to the normal range within 48 hours. Titration of the prothrombin time initially required 100 mg of vitamin K daily but the dosage was tapered (Fig 1A).

A search for vitamin K antagonists in her serum showed the presence of brodifacoum at 382 nmol/L, as measured by immunoassay, and 289 nmol/L, as determined by HPLC analysis. Samples were negative for warfarin and indandione. She subsequently ingested seven packets of D-Con (17.5 mg), a rodenticide, just before her initial presentation. Serial serum brodifacoum concentrations showed a serum half-disappearance time of approximately 34 days (Fig 2). Serum brodifacoum was 7.6 nmol/L 8 months after her initial presentation, but not detectable at 12 months despite evidence for continued inhibition of the vitamin K cycle.

Case 2. A 48-year-old businessman was hospitalized with severe epistaxis and abnormal coagulation parameters (Table 1). Treated with fresh frozen plasma and parenteral vitamin K, his epistaxis subsided. Two weeks later he represented with acute bleeding into the left calf resulting in a compartment syndrome. There was no past history of bleeding. Warfarin was not detectable in the blood. After treatment with fresh frozen plasma and vitamin K, he underwent a fasciotomy for decompression of the compartment syndrome. Postoperatively, his coagulopathy persisted until the vitamin K, dosage was increased to 100 mg daily. The presence of a vitamin K antagonist was confirmed by the ratio of vitamin K epoxide to vitamin K, of 5.9. Screening of the serum for vitamin K antagonists showed brodifacoum (270.7 nmol/L); levels decreased over the ensuing 2 months (Fig 2). Oral vitamin K, administration for 100 days was necessary to correct his coagulopathy (Fig 1B). His residence contained numerous packages of Contrac, a brodifacoum-containing rodenticide, but he denied ingesting the rodenticide.

Case 3. A 37-year-old shirt manufacturer was in good health except for mild hypertension controlled with hydrochlorothiazide. He initially presented with gross hematuria and deficiency of the vitamin K-dependent coagulation proteins (Table 1). Past history was negative and he had undergone vasectomy and dental extractions without problem. He denied ingestion of any anticoagulants or rodenticides. Warfarin was detected in his serum by photometric assay at 4.4 μg/mL, but was negative for warfarin by HPLC. He was

<table>
<thead>
<tr>
<th>Table 1. Laboratory Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (normal value)</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Prothrombin time (s) (10.8-13.2)</td>
</tr>
<tr>
<td>PTT (s) (29.2-40.4)</td>
</tr>
<tr>
<td>Factor VII (60%-150%)</td>
</tr>
<tr>
<td>Factor IX (60%-150%)</td>
</tr>
<tr>
<td>Factor X (60%-150%)</td>
</tr>
<tr>
<td>Prothrombin (60%-150%)</td>
</tr>
<tr>
<td>Factor V (60%-150%)</td>
</tr>
<tr>
<td>Protein C antigen (2.7-5.6 μg/mL)</td>
</tr>
<tr>
<td>Protein C activity (&gt;70%)</td>
</tr>
<tr>
<td>Platelets (x10^3/μL)</td>
</tr>
<tr>
<td>Fibrinogen (200-300 mg/dL)</td>
</tr>
<tr>
<td>Circulating inhibitor</td>
</tr>
<tr>
<td>Serum warfarin (HPLC assay)</td>
</tr>
<tr>
<td>Bleeding time</td>
</tr>
<tr>
<td>Vitamin K, epoxide/vitamin K, (&lt;0.1)</td>
</tr>
</tbody>
</table>

Abbreviation: NL, normal.
FACTITIOUS PURPURA DUE TO BRODIFACOUM

Fig 1. The effect of oral vitamin K₁ on the prothrombin time and vitamin K metabolism following ingestion of brodifacoum, a potent vitamin K antagonist used as a rodenticide. (A) Case 1. The total brodifacoum ingested was about 17.5 mg. Vitamin K₁ was administered daily by the oral route. The minimal dosage of vitamin K necessary to correct the prothrombin time was used. No additional therapy was employed. (B) Case 2. The amount of brodifacoum ingested is unknown. Fresh frozen plasma infusion was required during two hospitalizations to control bleeding until the dose of vitamin K₁ was increased to 100 mg/d. The transient elevation of the prothrombin time after day 50 was due to noncompliance. (C) Case 3. Fresh frozen plasma and high doses of oral and parenteral vitamin K₁ were required to control the bleeding disorder. Initially, vitamin K₁, at 280 mg/d was necessary to maintain a prothrombin time under 20 seconds. Prothrombin time (O--O); vitamin K₁ (shaded area); ratio of vitamin K epoxide (KO) to vitamin K₁ (O--O) (normal <0.1).

treated with fresh frozen plasma and parenteral vitamin K₁, which controlled his bleeding disorder. After being lost to follow-up, he represented with hematuria, epistaxis, and hematomas due to deficiency of the vitamin K₁-dependent blood clotting proteins (Fig 1C). He was restarted on vitamin K₁ and fresh frozen plasma. He required 150 to 280 mg per day of vitamin K₁ to achieve partial correction of his prothrombin time and PTT. Studies of vitamin K metabolism confirmed blockade in the vitamin K cycle with an elevated vitamin K epoxide of 298 nmol/L and vitamin K₁ of 122 nmol/L (ratio 2.4). Screening of the serum for anticoagulants revealed brodifacoum at 2759 nmol/L (Fig 2).

DISCUSSION

Acquired deficiency of the vitamin K₁-dependent blood coagulation proteins in an adult without vitamin K deficiency and without therapy with oral anticoagulants is due to accidental or factitious ingestion of vitamin K₁ antagonists, specifically warfarin sodium. Factitious purpura as a manifes-
tation of warfarin ingestion is not an uncommon problem. Typically, it is seen in an emotionally disturbed patient with a history of mental illness. Patients are often young, female, and have access to these medications as members or associates of members of the health professions. Although warfarin has also had wide use as a rodenticide, rodenticides have been more commonly associated with accidental poisoning than with factitious purpura. With the development of warfarin-resistance among the rat targets of rodenticide programs, new “superwarfarins” have been developed that are potent and highly effective in the warfarin-resistant rat. Like warfarin, these compounds inhibit the epoxide reductase, but are approximately 100-fold more potent than warfarin. These 4-hydroxycoumarin derivatives, including brodifacoum, are characterized by a long in vivo half life, high fat solubility leading to a large distribution volume and high concentrations in the liver, and slow plasma disappearance. The plasma half-life in rats is 156 hours, compared with 17 hours for warfarin. In dogs, the elimination of brodifacoum follows a classic exponential decay with a distributive phase half-life of 1.4 days and an elimination phase half-life of 6 days. The plasma half-life of brodifacoum determined in our patients was approximately 16 to 36 days (Fig 2), compared with 20 days reported previously in a single patient. The anticoagulant effect may persist long after the brodifacoum is no longer detectable in the serum. Previously reported cases of accidental or intentional ingestions of brodifacoum in humans have shown a duration of anticoagulant action ranging from 51 days to 8 months. Large daily doses of vitamin K, of 20 to 125 mg per day were required to maintain normal hemostasis.

The analysis of vitamin K metabolites in serum is a sensitive method for detecting the presence of vitamin K antagonists. With these studies one can make a presumptive diagnosis of anticoagulant poisoning, allowing rational vitamin K therapy. In general, the vitamin K epoxide to vitamin K, ratio reflects the degree of inhibition of vitamin K action.

Vitamin K, is the treatment of choice for cases of anticoagulant rodenticide poisoning. Except in the face of serious bleeding, fresh frozen plasma should be avoided due to the risk of transmission of viral diseases. The amount of vitamin K, administered varies, but doses in excess of 100 mg daily may be necessary to obtain and maintain a normal prothrombin time. Although initial parenteral vitamin K is often indicated, the long-term administration of vitamin K is preferably given by the oral route. Treatment is usually necessary for many months, but the dosages of vitamin K should be the minimum necessary to maintain a normal prothrombin time.

The increasing availability of second generation vitamin K antagonists marketed as rodenticides suggests a possibility for increased human morbidity associated with their ingestion. A bleeding disorder caused by deficiency of the vitamin K-dependent blood coagulation proteins in a patient without cause for vitamin K deficiency and without evidence of warfarin in the blood should suggest a diagnosis of factitious or accidental poisoning with brodifacoum or related agents. Because brodifacoum is not detected in warfarin assays, specific measurements are indicated. Long-term treatment with vitamin K, is an effective antidote for this long-acting vitamin K antagonist.

ACKNOWLEDGMENT

We thank Gary Cohen, MD for contributing case 3 and Ken Davidson for technical assistance.

REFERENCES

Surreptitious ingestion of a long-acting vitamin K antagonist/rodenticide, brodifacoum: clinical and metabolic studies of three cases

JN Weitzel, JA Sadowski, BC Furie, R Moroose, H Kim, ME Mount, MJ Murphy and B Furie