Acquired Coagulopathy Due to Anticoagulant Rodenticide Poisoning

Mirjana Huić, Igor Francetić, Ivan Bakran, Viola Macolić-Šarinić, Marinko Bilušić

Division of Clinical Pharmacology, Department of Medicine, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia

A 35-year-old woman was admitted to hospital because of epistaxis, hematomas, and metrorrhagia. Laboratory data indicated severe coagulopathy with prolonged prothrombin time and decreased serum concentrations of vitamin K-dependent clotting factors II, VII, IX, and X. The patient denied taking any oral anticoagulants. She was given transfusions of red blood cells, fresh frozen plasma (1,180 mL) and phytomenadione daily for 6 weeks (total dose 550 mg), which normalized the coagulation factors concentration. After all other possible causes of acquired coagulopathy had been excluded, rodenticide poisoning was suspected on the basis of her epidemiologic history. The patient was a war refugee from Bosnia and Herzegovina. During her absence, the troops of United Nations Protection Force performed rodent extermination in and around her house. History data and therapeutic effects suggested that the coagulopathy had been caused by prolonged exposure to long-acting anticoagulant rodenticide. This could also explain the need for protracted phytomenadione therapy.

Key words: blood coagulation disorders; poisoning; rodenticides; vitamin K deficiency

Due to the development of warfarin resistance in mice and rats, a new group of potent rodenticides, the so-called superwarfarins, has been developed (1,2). Products containing these long-acting anticoagulants can be found in shops under various protected names. In 1995, the American National Center for Poisoning received more than 13,000 reports on poisoning with these substances (3). Most cases were accidental poisoning of children, whereas poisonings in adults were usually intentional and potentially lethal. We report on a patient with acquired coagulopathy probably caused by accidental poisoning with long-acting anticoagulant rodenticide. Rodenticide poisoning should always be considered as a possible cause of an acquired coagulopathy of the prothrombin complex. Such patients need long-term treatment with vitamin K1 due to the long half-life of rodenticides.

Case Report

A 35-year-old woman from Orašje, Bosnia and Herzegovina, was transferred from the General Hospital in Vinkovci, Croatia, to our Division on April 25, 1997, because of hemorrhagic diathesis with suspicion of leukemia. The patient had never been severely ill before. In March 1997, she felt weakness, fatigue, loss of appetite, and observed fresh blood in the stool on two occasions. In April 1997, she developed intermittent epistaxis and metrorrhagia. The patient was hospitalized from April 16-25, 1997 in Vinkovci General Hospital because of hemorrhagic shock and suspected sepsis. Tamponade of the nostrils, evacuation of the uterine cavity, and vaginal tamponade were performed. Erythrocyte sedimentation rate was 70/110 mm/h, red blood cell count 0.93x1012/L, hemoglobin 31 g/L, white blood cell count 14-19.0x109/L, platelet count 114-560x109/L, and prothrombin time (PT) 0.12-0.20-0.07. Sternal needle biopsy was performed and the sample of bone marrow was suspicious of myeloid leukemia. The patient was treated with red blood cells transfusions, fresh frozen plasma, cryoprecipitate, vitamin K1 30 mg in a single dose, benzyl penicillin, gentamicin, metronidazole, and methylprednisolone. The patient told us that she was a refugee. Before she returned home, the UNPROFOR (United Nations Protection Forces – peace keeping forces in Bosnia and Herzegovina) had performed mice and rat extermination in and around her house, using an unknown rodenticide. The patient was exposed to the unknown rodenticide in her cellar, where she kept potatoes. Physical examination revealed multiple skin hematomas, paleness of the visible mucosa, and palpable liver margins. Laboratory tests showed the following results: erythrocyte sedimentation rate 42-34 mm/h, hemoglobin 118 g/L, hematocrit 0.36, prolonged PT (0.11), partial thromboplastin time (PTT) 67.9-120-
The ingestion of rodenticide was suspected. The accidental poisoning with rodenticide (identification of the substance or warfarin-like substance), malabsorption, liver disease, and acquired inhibitors of clotting factors (1). Normal D-dimer, fibrinogen, and platelet count eliminated disseminated intravascular coagulation as a cause. The patient had not been on antibiotic or anticoagulant medication. No history and laboratory data of vitamin K malabsorption were found nor was there evidence of inadequate dietary intake; liver function, and immunological test were normal.

Cases of accidental and intentional poisoning with long-acting anticoagulants, sometimes with lethal results, have been described (4-11). It is very important to suspect superwarfarin poisoning because such patients need long-term treatment with vitamin K1; if the treatment does not last long enough, fatal bleedings can occur (12).

Long-acting anticoagulants (rodenticides) can be divided into two groups: 4-hydroxycoumarin derivatives and indandione anticoagulants (13,14). The mechanism of their activity is the inhibition of vitamin K 2,3-epoxide reductase enzyme in the liver (binding up to 100 times stronger than that of warfarin). The synthesis of factors II, VII, IX, and X in the liver depends on vitamin K1 (1,13). Reduced vitamin K1 (hydroquinone) is a co-factor (together with CO2 and O2) in carboxylation of these factors. Gamma-carbonyl acid is needed for binding of calcium ions (Ca2+), which causes the activation of the factors. Vitamin K1 epoxide emerges after carboxylation, and reduced vitamin K1 appears again after reaction with epoxide reductase. Without vitamin K1, inactivated predecessors develop. Prolonged PT appears within 48 h, whereas clinical signs of bleeding appear 1-4 weeks later. Decreased concentration of factors II, VII, IX, and X and prolonged PT may last from 45 days to 8 months (7). The specific antidote is vitamin K1 (phytonemadione), which should be administered until the concentrations of factors II, VII, IX, and X return to normal. The duration of the coagulopathy in our patient (6 weeks) was comparable with previously reported range from 6 weeks to 8 months (4-9).

Our report shows how a diagnostic approach based on history data and therapeutic effect can yield a correct diagnosis. Poisoning with long-acting anticoagulants, in this case – rodenticides, must be always taken into differential diagnosis of an acquired coagulopathy of the prothrombin complex because poisoning with superwarfarins requires long-term therapy with high doses of phytomenadione due to

### Table 1. Prothrombin time and concentrations of vitamin K-dependent clotting factors in our patient during daily phytomenadione (K1 vitamin) treatment

<table>
<thead>
<tr>
<th>Parameter (reference interval)</th>
<th>FFP</th>
<th>FFP</th>
<th>FFP</th>
<th>Day of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II (0.75-1.2 kIU/L)</td>
<td>0.41</td>
<td>0.50</td>
<td>0.42</td>
<td>0.84</td>
</tr>
<tr>
<td>Factor VII (0.70-1.2 kIU/L)</td>
<td>0.31</td>
<td>0.50</td>
<td>0.15</td>
<td>0.88</td>
</tr>
<tr>
<td>Factor IX (0.60-1.8 kIU/L)</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor X (0.75-1.2 kIU/L)</td>
<td>0.14</td>
<td>0.16</td>
<td>0.14</td>
<td>0.65</td>
</tr>
</tbody>
</table>

29.8 s, decreased concentrations of factors II (0.41 kIU/L), VII (0.31 kIU/L), IX (0.63 kIU/L), and X (0.14 kIU/L), gama glutam transferase (GGT) 80 U/L, cholesterol 7.9 mmol/L, triglycerides 5.39 mmol/L, and anti HBSAg +. Urin analysis showed 18-20 red blood cells in sediment. Normal fibrinogen level, platelet count, and negative D-dimer eliminated the possibility of disseminated intravascular coagulation, whereas normal concentrations of liver enzymes (alanine amino-transferase and aspartat amino-transferase), bilirubin, and factor V eliminated hepatocellular disease. Malabsorption was excluded by normal D-xyllose tolerance test, fats in the stool, normal serum iron, magnesium, potassium, sodium, and calcium concentration. Abdominal ultrasound, sternal needle biopsy, electrophoresis, and immunoelectrophoresis were normal. All immunological tests, including lupus anticoagulant test, were normal. On the basis of history data, accidental poisoning with rodenticide was suspected. The patient was treated with three doses of fresh frozen plasma (total dose 1,180 mL), and daily intravenous vitamin K1 doses for the first 26 days, followed by oral vitamin K1 for another 2 weeks (total dose 550 mg) (Table 1). The attempt to decrease the vitamin K1 dose from 20 mg to 10 mg in the beginning of the second week of therapy caused decrease in PT and concentrations of factors II, VII, IX, and X. The second decrease of factors VII and X was registered after cessation of intravenous vitamin K1 therapy (day 26). Oral administration of 10 mg vitamin K1 daily was continued for another two weeks. After the cessation of therapy, all findings on subsequent check-ups were normal.

### Discussion

We described a case of a woman with acquired coagulopathy probably caused by ingestion of a long-acting anticoagulant. On the basis of her epidemiologic history data, the accidental exposure to rodenticide was suspected. The ingestion of rodenticide was probably a result of hand-to-mouth transfer due to inadequate hygienic conditions in a war-ruined village. Although there was no direct evidence of the causative agent (identification of the substance in serum was not possible), the sequence of events, laboratory data, and therapeutic effect supported this hypothesis. The differential diagnosis for increased PT and decreased concentrations of factors II, VII, IX, and X in our patient included disseminated intravascular coagulation, plasma inhibitors (ie, lupus anticoagulant), ingestion of a vitamin K antagonist (warfarin or warfarin-like substance), malabsorption, liver disease, and acquired inhibitors of clotting factors (1). Normal D-dimer, fibrinogen, and platelet count eliminated disseminated intravascular coagulation as a cause. The patient had not been on antibiotic or anticoagulant medication. No history and laboratory data of vitamin K malabsorption were found nor was there evidence of inadequate dietary intake; liver function, and immunological test were normal.

### Abbreviations

- FFP – fresh frozen plasma
- PT – prothrombin time
- ex – therapy terminated.
the long half-life of rodenticides and their high effectiveness. It is important that the treatment lasts until the complete normalization of factors II, VII, IX, and X.

Acknowledgment
This case report was presented as a poster on the European Congress of Clinical Pharmacology and Therapeutics 2001 in Odense, Denmark.

References
7 Lipton RA, Klass EM. Human ingestion of a "superwarfarins" rodenticide resulting in prolonged anticoagulant effect. JAMA 1984;252:3004-5.

Received: April 9, 2002
Accepted: August 26, 2002

Correspondence to:
Mirjana Huić
Division of Clinical Pharmacology
Department of Medicine
Zagreb University Hospital Center and School of Medicine
Kišpatičeva 12
10000 Zagreb, Croatia
nuspojave.adrcentre@kbc-zagreb.hr