Case Report:
Superwarfarin Intoxication of Unknown Etiology Accompanying Hemoperitoneum in a Patient on Fluconazole Therapy

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Abstract. We report a case of brodifacoum (superwarfarin) intoxication of unknown etiology presenting as hemoperitoneum after fluconazole administration for one week before the onset of symptoms. The initial prothrombin time (PT) and partial thromboplastin time (PTT) were markedly prolonged, although a mixing study with normal plasma showed that the corrected PT and PTT were in the normal range. Vitamin K-dependent coagulation factors (Factors II (5%), VII (8%), IX (4%), and X (6%)), and Protein C (16%) and Protein S (19%) activities were reduced. Although the patient denied ingesting rodenticides or medications other than an antifungal drug, fluconazole, superwarfarin toxicity was suspected; subsequently, his serum brodifacoum level was found to be positive. After administration of fresh frozen plasma (FFP) and oral vitamin K1 for five days and following drainage of the hemoperitoneum, the patient’s bleeding tendency stopped, with slow decreases in PT and PTT. Compared to previous reports of superwarfarin intoxication of unknown exposure, this case is distinct in that the severe bleeding tendency needed surgical management and involved a suspected drug interaction with fluconazole. Therefore, superwarfarin intoxication should be suspected in subjects with markedly prolonged PT and PTT of unknown etiology, since a drug interaction could amplify the toxicity from a small exposure to superwarfarin.

Keywords: superwarfarin, brodifacoum, fluconazole, coagulopathy

Introduction

Superwarfarins are second-generation anticoagulant rodenticides that have 100-fold greater anticoagulation potency compared with warfarin [1,2]. Brodifacoum, difenacoum, bromidialone, and chlorphacinone are commercial superwarfarins that can be purchased easily and are poorly controlled [3]. Of these, the most commonly used rodenticide in Korea is brodifacoum, which is a 4-hydroxycoumarin with high lipid solubility [4]. Although several reports have emphasized the anticoagulant action of superwarfarins, its importance is still overlooked in the clinical setting.

Cases of superwarfarin intoxication have been reported in recent years. Most ingestion of superwarfarin is accidental, although ingestion can be intentional in suicide, homicide, surreptitious administration, as a drug of abuse because of its euphoric effect, or for lacing a drug of abuse, such as marijuana [5,6]. The majority of superwarfarin intoxication cases occur in the pediatric population and intoxication is rare in adults. Here, we report an unusual case of severe superwarfarin intoxication of unknown etiology in a patient on fluconazole and we review other cases with no definitely identified etiology [1,2,6-11].
Case Report

A 53-yr-old male was transferred to our medical center because of hemoperitoneum. He had been admitted to another hospital with a 1-mo history of epistaxis and gross hematuria. He had no medical history of a bleeding disorder or trauma. His initial laboratory studies were: prothrombin time (PT) of 50.7 sec with international normalized ratio (INR) of 5.2, partial thromboplastin time (PTT) of 87.8 sec, and a mixing study that demonstrated correction of the PT and PTT to the normal range. Coagulation factor levels were Factor II (5%), Factor VII (8%), Factor IX (4%), Factor X (6%), and Factor V (69%). Protein C activity was 16% (70-130%), Protein S activity was 19% (73.7-146.3%), Protein C antigen level was 25 µg/ml (72-160 µg/ml), and Protein S antigen level was 24 µg/ml (60-150 µg/ml) (Table 1).

The patient denied ingesting rodenticides or medications other than an antifungal drug, fluconazole, which he had taken for 1 wk before admission. However, since his laboratory studies demonstrated vitamin K-dependent coagulopathy, superwarfarin intoxication was suspected. Subsequently, his serum brodifacoum level was positive based on high-performance liquid chromatography (HPLC)/tandem mass spectrometry (LC-MS/MS). The patient was treated by administration of four units of fresh frozen plasma (FFP) and oral vitamin K1 (200 mg/day for 5 days) and by drainage of the hemoperitoneum. The patient’s bleeding tendency stopped and his PT and PTT levels fell slowly.

Discussion

Superwarfarin intoxication is uncommon in the clinical setting. Despite its rarity, it should be considered in patients with severely prolonged PT and PTT that are corrected in a mixing test after adding normal plasma, and after ruling out other coagulation disorders such as liver disease, disseminated intravascular coagulopathy (DIC), vitamin K deficiency, malabsorption, or long-term antibiotic treatment [7]. Reduced levels of vitamin K-dependent proteins (Factors II, VII, IX, X), Protein C, and Protein S and relative sparing of Factor V, which is not vitamin-K-dependent, is also suggestive of superwarfarin intoxication [1].

The long half-life of superwarfarin is due to its high lipid solubility, resulting in a large distribution volume and slow elimination rate. The half-life of warfarin in rats is 17 hr, whereas that of superwarfarin is 156 hr, or approximately 9 times greater [12]. In one reported case, the half-life of superwarfarin was prolonged to 487 hr and it seems to be very variable [13]. In several patients, superwarfarin intoxication tended to worsen after transient recovery from the coagulopathy [5]. The long half-life of superwarfarin, which requires a high dose and long duration of vitamin K administration, causes waxing and waning when the treatment is insufficient. Therefore, it is of great importance to differentiate warfarin and superwarfarin intoxication when planning treatment and it could be dangerous to discharge patients too early [1].

Table 1. Case reports of superwarfarin ingestion with unknown etiology.

<table>
<thead>
<tr>
<th>Case [reference]</th>
<th>PT/PTT (sec/sec)</th>
<th>Mixing study</th>
<th>Factor II (%)</th>
<th>Factor VII (%)</th>
<th>Factor IX (%)</th>
<th>Factor X (%)</th>
<th>Protein C activity/Ag (%)</th>
<th>Protein S activity/Ag (%)</th>
<th>Brodifacoum</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [1]</td>
<td>&gt;60/100</td>
<td>Corrected</td>
<td>11</td>
<td>2.5</td>
<td>17.5</td>
<td>9</td>
<td>NT</td>
<td>NT</td>
<td>2759 nmol/L</td>
<td>VitK1, oral, FFP</td>
</tr>
<tr>
<td>2 [2]</td>
<td>396/180</td>
<td>Corrected</td>
<td>17.5</td>
<td>&lt;1</td>
<td>3.8</td>
<td>4.7</td>
<td>6/25</td>
<td>18/45</td>
<td>Positive</td>
<td>VitK1, iv, rVIIa</td>
</tr>
<tr>
<td>3 [6]</td>
<td>156/102</td>
<td>Corrected</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>NT</td>
<td>NT</td>
<td>848 ng/ml</td>
<td>VitK1, iv, FFP</td>
</tr>
<tr>
<td>4 [7]</td>
<td>73.8/150</td>
<td>Corrected</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>9</td>
<td>NT</td>
<td>NT</td>
<td>42 ng/ml</td>
<td>VitK1, iv</td>
</tr>
<tr>
<td>5 [8]</td>
<td>42.5/64.6</td>
<td>Corrected</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>NT</td>
<td>NT</td>
<td>0.86 mg/L</td>
<td>VitK1, iv</td>
</tr>
<tr>
<td>6 [9]</td>
<td>&gt;150/92</td>
<td>Corrected</td>
<td>NT</td>
<td>3.5U/dl</td>
<td>NT</td>
<td>1.3U/dl</td>
<td>NT</td>
<td>NT</td>
<td>0.86 mg/L</td>
<td>VitK1, iv</td>
</tr>
<tr>
<td>7 [10]</td>
<td>66.6/62.4</td>
<td>Corrected</td>
<td>11</td>
<td>3</td>
<td>21</td>
<td>12</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>VitK1, iv</td>
</tr>
<tr>
<td>8 [11]</td>
<td>100/60</td>
<td>Corrected</td>
<td>43</td>
<td>3</td>
<td>27</td>
<td>28</td>
<td>d</td>
<td>d</td>
<td>22 ng/ml</td>
<td>FFP, Vit K1</td>
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<tr>
<td>9 [11]</td>
<td>100/71</td>
<td>Corrected</td>
<td>4.8</td>
<td>2.1</td>
<td>4</td>
<td>NT</td>
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<td>NT</td>
<td>327 ng/ml</td>
<td>FFP, VitK1</td>
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<td>10 [11]</td>
<td>&gt;50/84.4</td>
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<td>NT</td>
<td>&lt;15</td>
<td>NT</td>
<td>&lt;15</td>
<td>NT</td>
<td>NT</td>
<td>167 ng/ml</td>
<td>VitK1</td>
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<tr>
<td>11*</td>
<td>50.7/87.8</td>
<td>Corrected</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>16/25</td>
<td>19/24</td>
<td>Positive</td>
<td>VitK1, oral, FFP</td>
</tr>
</tbody>
</table>

* present study; NT, not tested; d, decreased

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One report indicated that the anticoagulant effect can persist when no brodifacoum is detected in blood [3]. Accumulation of inactive metabolites might contribute to the prolonged anticoagulopathy despite the disappearance of brodifacoum. Protein-induced in vitamin K absence (PIVKA-II) is one of these inactive metabolites, and increased PIVKA-II levels as well as decreased vitamin-K-dependent factors may give a clue to superwarfarin intoxication [7]. For this reason, the drug concentrations and the coagulation test results must be monitored in patients with severe intoxication symptoms. If the prolonged coagulation times result from a shortage of active coagulation factors, the prolongations may be corrected by adding normal plasma in mixing tests, as shown in Table 1.

The metabolism of superwarfarin or warfarin is affected by many classes of drugs and hepatic enzymes, such as cytochrome P450 isoenzymes (CYP2C9, 1A2, 2C19, and 3A4) and VKORC1 [14]. Therefore, polymorphism of the cytochrome P450 and VKORC1 genes can result in individual differences in superwarfarin and warfarin metabolism. In drug interactions, fluconazole decreases the elimination of warfarin, hinders CYP2C9 activity, and reduces vitamin K production, resulting in decreased warfarin clearance [15-18]. No study has examined the direct relationship between superwarfarin and fluconazole, the CYP2C9-hindering action, or the vitamin K reduction by fluconazole, which all might interfere with superwarfarin metabolism. Our patient was apparently not exposed to superwarfarin directly (such as via ingestion), so possible routes of entry include laced drugs, absorption through the skin, inhalation, or fecal-oral routes, probably in small amounts [6,19]. Nevertheless, his clinical symptoms were severe, implying that fluconazole interaction may have strengthened the superwarfarin toxicity, which supports the notion that use of azole class drugs in patients suspected of superwarfarin intoxication could be hazardous.

Previously reported cases of superwarfarin intoxication of unknown etiology are listed in Table 1. These patients had hematuria (the most common symptom), prolonged PT and PTT, and coagulation-factor deficiencies, although these features varied in degree. Compared with these reports of unknown exposure, our case was distinct in the severe bleeding tendency, requiring surgical management, and the suspected drug interaction with fluconazole, which had been administered for one week before the onset of symptoms [8].

We conclude that superwarfarin intoxication should be suspected in patients with long-term coagulopathy of unknown etiology, and we suggest that drug interactions can amplify the toxicity caused by exposure to small amounts of superwarfarin.

Acknowledgments

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References