

Korean Patients with Superwarfarin Intoxication and Their Outcome

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This observational study aimed at evaluating recent superwarfarin intoxication of Korean patients. Ten patients were diagnosed as or highly suspicious for superwarfarin intoxication. Case report forms described by attending hematologists of the patients were collected and analyzed. Bleeding symptoms were varied among the patients. Patients uniformly showed prolonged prothrombin time (PT) and activated thromboplastin time (aPTT) with decreased activity of vitamin K dependent coagulation factors. Positive serum brodifacoum test results in 4 of 5 requested patients contributed to confirmatory diagnosis. Psychiatric interview revealed an attempted ingestion in one patient. High dose vitamin K1 therapy promptly corrected prolonged PT and aPTT, but hasty discontinuation caused repeated bleeding diathesis in 6 patients. Route of intoxication was unknown or not definite among 8 of 10 patients. Three patients had a possibility of environmental exposure considering their occupations: there might be intoxication by transdermal absorption or inhalation. Therefore, high dose and prolonged use of vitamin K1 therapy is necessary for effective detoxification. Further detailed investigation on environmental exposure and efforts to improve availability of the blood level test in clinic are requested.

Key Words: Superwarfarin; Brodifacoum; Vitamin K; Rodenticides

INTRODUCTION

Attempted or accidental superwarfarin exposure has become an important public problem in Western countries (1), as intoxication can cause prolonged bleeding diathesis, and sometimes fatal results. Over 10,000 cases of superwarfarin intoxication were reported in 2008 to the Poison Control Centers Toxic Exposure Surveillance System in the United States (2). In Korea, only sporadic reports of superwarfarin intoxication exist without any systemic and detailed investigations to the issue (3-5). We con-

ducted an observational study of 10 cases of superwarfarin intoxication in Korea, most of them broke out within a year.

MATERIALS AND METHODS

Case report forms (CRF) for patients with superwarfarin intoxication were requested to 8 physicians from October 2009 to April 2010 by electronic mails. Each of the physicians was an attending hematologist of the patients. A CRF contained filling up section for basic information of a patient: age, sex, residence, occu-

pation, past history of disease, and medication history of anti-coagulants or anti-platelet agents, etc. Manifestations of bleeding were surveyed and initial laboratory data including prothrombin time (PT) and activated partial thromboplastin time (aPTT) were collected. Results of plasma mixing test, activity of coagulation factors and serum brodifacoum level test were also recorded. Flow-sheet of treatment and change of laboratory data including PT and aPTT of each patient were gathered. The CRFs were analyzed by Hong J and Bang S-M and the results were reviewed by the other authors.

Ethics statement

This study was performed for the public good and had neither risk nor disadvantage for subjects. Therefore, the institutional Review Board of Seoul National Hospital Bundang Hospital permitted this study without acquisition of informed consent (Approval number: B-1007-106-105).

RESULTS

Patient characteristics, symptoms and diagnoses

Seven male patients and 3 female patients were reported in this

survey. Their age ranged 37-83. Only one patient (patient 6) lived in a metropolitan city, and outbreaks were nationwide. Most of the cases occurred since 2009, except for a male patient who diagnosed in 2007 (4). Two of them have been previously published as a case report (4, 5).

Reported bleeding events were oral mucosal bleeding (7 patients), hematuria (4 patients), easy bruising (5 patients), hematoma formation (5 patients), and epistaxis (3 patients).

Patients uniformly showed prolonged PT and aPTT with decreased activity of vitamin K dependent coagulation factors. Plasma mixing test and activities of coagulation factors were evaluated in all of the patients and the same result were showed: correction of PT and aPTT and decreased activities of factors II, VII, IX, and X. Serum brodifacoum test were requested in 5 of 10 patients by physicians and 4 of them with a positive result were definitely diagnosed as superwarfarin intoxication. One patient (patient 2) repeatedly denied any contact with rodenticides, but she confessed to trying to kill herself by taking rodenticides after an interview with a psychiatrist. One patient (patient 3) was initially witnessed ingestion of rodenticides by her neighbors so serum brodifacoum test was not performed.

Environmental exposure was a possible cause in 3 patients

Table 1. Patients with superwarfarin intoxication in Korea

Patient ID	Age/sex	Regions	Presentation	Studies (seconds)	(Possible) origin of superwarfarin exposure	Superwarfarin level test
Patient 1	Male/51	Pohang-si Gyeongsangbuk-do	Oral mucosal bleeding Hematuria	PT>110 aPTT>240	Unknown (history of blackout after alcohol drinking)	Positive result
Patient 2	Female/37	Imsil-gun Jeollabuk-do	Oral mucosal bleeding Epistaxis Intramuscular Hematoma	PT 89.4 aPTT 48.6	Intentionally for suicidal attempt (confessed after psychiatric interview)	Negative result
Patient 3	Female/80	Jeonju-si Jeollabuk-do	Oral mucosal bleeding Ecchymosis Easy bruising	PT 52.3 aPTT 60.0	Intentionally for suicidal attempt	Not done (taking rodenticide was witnessed by others)
Patient 4	Male/43	Hanam-si Gyeonggi-do	Hematoma collection	PT 117.9 aPTT 87.5	Environ. Possibility; A horticulturist	Positive result
Patient 5 (5)	Male/52	Yangju-si Gyeonggi-do	Epistaxis Hematuria Easy bruising Conjunctival hemorrhage Hemoperitoneum	PT 50.7 aPTT 87.8	Unknown (ingested fluconazole for suicidal attempt and ingestion of other drugs cannot be ruled out)	Positive result
Patient 6	Male/45	Seoul	Oral mucosal bleeding Ecchymosis Easy bruising	PT no clotting aPTT 124.3	Unknown	Not done 7-OH warfarin test was negative
Patient 7	Male/75	Masan-si Gyeongsangnam-do	Oral mucosal bleeding Gluteal hematoma	PT 96.4 aPTT 96.4	Environ. Possibility; used rodenticide at his grain warehouse	Not done
Patient 8	Male/75	Goryeong-gun Gyeongsangbuk-do	Epistaxis Oral mucosal bleeding Hematuria Ecchymosis Easy bruising	PT >100 aPTT 137.6	Unknown	Not done
Patient 9	Female/83	Goryeong-gun Gyeongsangbuk-do	Oral mucosal bleeding Ecchymosis Easy bruising Hematoma collection	PT 36.6 aPTT 131	Unknown	Not done
Patient 10 (4)	Male/58	Chungcheongbuk-do	Hematuria	PT 165 aPTT 107	Environ. Possibility; A ragman	Positive result

PT, prothrombin time; aPTT, activated thromboplastin time; Environ., environmental.

(patients 4, 7, and 10) as they worked as a horticulturist, farmer, and ragman, respectively. Information for patient characteristics, symptoms and diagnoses were summarized in Table 1.

Treatment

Four patients (patient 1, 3, 4, and 6) failed to achieve sufficient correction of PT and aPTT initially so they had to increase doses of vitamin K1 administration. Repeated prolongation of PT and aPTT due to hasty discontinuation was observed in 6 patients (patient 1, 2, 3, 4, 6, and 8). FFP was initially transfused to all of the patients, but repeated FFP transfusion with low doses of vitamin K1 failed to maintain normalization of PT and aPTT in 4 patients (patient 1, 3, 4, and 6).

Durations of treatment were varied among the patients. Three patients (patient 1, 4, and 6) were completely discontinued vitamin K1 treatment, and their duration of vitamin K1 administration was 7.3, 6.2, and 3.3 months, respectively.

All of the patients recovered or are on recovering from PT and aPTT prolongation without sequelae and there was no mortality. Only a patient (patient 5) received major surgical procedure, evacuation of hemoperitoneum. He confessed that he ingested excessive amount of fluconazole, an anti fungal agent, but repeat-

edly denied superwarfarin ingestion even positive result of brodifacoum level test was reported. It seems to be that he needed operation because of potentiated action of brodifacoum by drug interactions with the fluconazole.

Information of treatment and state of recovery were summarized in Table 2.

DISCUSSION

The discovery of warfarin dates back to outbreaks of cattle death in the northern United States and Canada in the 1920s (6). After isolation of the hemorrhagic compound in moldy silage which led to the death of the cattle, first generation anticoagulants including warfarin were introduced. Warfarin is now widely used as a therapeutic anticoagulant, but its use as a rodenticide has declined because many rat populations have developed resistance to it (6).

To overcome this resistance, second generation anticoagulants, superwarfarins were invented in the 1970s: brodifacoum and bromadiolone. They are highly lipid soluble and about 100 times more potent than warfarin because of the phenyl groups replacing the terminal methyl group in the structure (7). In a

Table 2. Treatment outcomes in our series and four others from the literature

Patients (Ref.)	Vitamin K1 treatment		Recovery
	Initial dose, route and tapering schedule	Duration (months)	
Patient 1	10 mg IV q.d. intermittently→poor response→60 mg IV q.d. for a day→90 mg IV q.d. for a day→120 mg IV q.d. for 2 days→100 mg q.d. PO for 4 months→tapered for 3 months	7.3	Recovered without sequelae
Patient 2	40 mg PO/day for a month→30 mg PO/day for 3 months→20 mg PO/day for a month→30 mg PO/day for 2 months→20 mg PO/day for a month→keep on therapy	>10	On recovering
Patient 3	30 mg PO/day for a week→poor response→60 mg PO/day for a month→40 mg PO/day for a month→30 mg PO/day for 3 months→15 mg PO/day for 3 months→10 mg PO/day for a month→keep on therapy	>7.7	On recovering
Patient 4	10 mg IV q.d. or 15 mg PO q.d. for 3.5 months→poor response→30 mg PO/day for 12 days→poor response→60 mg PO/day for about 6 months→negative for follow up brodifacoum level→stop therapy	6.2	Recovered without sequelae
Patient 5 (5)	200 mg PO/day for 5 days with surgical drainage of hemoperitoneum →10 mg/day for 2 months→transfer to other hospital then F/U* loss	>3.6	On recovering
Patient 6	10 mg IV q.d. for 10 days→poor response→50 mg IV twice a week or 100 mg IM on the day IV was not performed for 5 weeks→50 mg IV once a week for a month→stop therapy	3.3	Recovered without sequelae
Patient 7	10 mg IV bid for 5 days→15 mg IV bid for 3 weeks→F/U loss	1.0	Once recovered, then F/U loss
Patient 8	30 mg IV/day for 5 days→30 mg PO/day for 7 days→60 mg PO/day for 60 days →keep on therapy	>2.2	On recovering
Patient 9	30 mg IV/day for 4 days→10 mg IV/day for 5 days→10 mg PO/day for 14 days →keep on therapy	>0.8	On recovering
Patient 10 (4)	10 mg IV once for a week for 2 weeks→5 mg PO q.d. for 2 months and a week →stop therapy	>2.6	Recovered without sequelae
Bruno et al. (19)	150 mg PO q.i.d. for 5 days →periodic tapering over the next 40 days	1.5	Recovered without sequelae
Pavlu et al. (14)	10 mg IV t.i.d. for 3 days→no response→100 mg PO q.d. for 7 days →30 mg PO for 77 days→F/U loss	2.9	Once recovered, then F/U loss
Zupancic-Salek et al. (17)	40 mg PO q.d. for 3 months→20 mg PO q.d. for 1 months →10 mg PO q.d. for 1 months→stop therapy	5.0	Recovered
Hui et al. (11)	100 mg IV q.d. for 2 weeks→50 mg IV q.d. for 1 week →50 mg PO q.d. (Further treatment duration is not stated.)	Not stated	Died 6 months after treatment

*F/U, follow up.

field test, 1-2 days feeding of brodifacoum was sufficient to achieve complete mortality in most of rodent species, compared to 21 days of warfarin (8). The reported half life of brodifacoum in humans is much longer than that of warfarin (16-36 days vs 17-37 hr) (9).

The most common clinical feature of superwarfarin intoxication is bleeding, and this can occur from any mucosal site or organ. Various symptoms of bleeding were reported in the literatures (1, 3, 4, 9-17) as in our study.

Superwarfarin intoxication should be suspected in any patient who presents with a suspicious history and marked prolongation of both PT and aPTT without advanced liver disease or congenital coagulation factor deficiency. Mixing studies result in complete correction of PT and aPTT due to lack of inhibitors. Measuring the activity of vitamin K dependent coagulation factors (Factor II, VII, IX, and X), plasma vitamin K levels, or PIVKA-II can be helpful in narrowing down the differential diagnosis. The definitive diagnosis is made by superwarfarin blood level testing with high performance liquid chromatography (HPLC) an accurate and effective way of determining the presence and concentration of superwarfarin. Recent advances in HPLC technology has made considerably accurate and rapid diagnosis possible (18), but such technology is not yet easily accessible in Korea. In our study, although one patient (patient 2) was highly suspicious for superwarfarin intoxication and she even confessed ingestion, a negative result was reported. Weitzel et al. (9) evaluated half-life of brodifacoum in 3 patients with superwarfarin intoxication by measuring serial serum brodifacoum concentrations. They reported the half-life ranged from 16 to 36 days in 3 patients and serum brodifacoum had been no longer detected after 2 months from the time of initial diagnosis, although bleeding tendency continued more than 100 days. Considering of their result, serum brodifacoum level in the patient of our study might be decreased to undetectable range at the time of sample request, as superwarfarin level test had been requested about 100 days after initial symptom presentation by her physician.

Administration of vitamin K1 is the cornerstone of therapy in patients with superwarfarin intoxication. Oral vitamin K1 is preferred to intramuscular or intravenous injection, as it avoids hematoma formation and hypersensitivity reactions. An optimal dose and duration of vitamin K1 therapy has yet to be established (19). However, most previous studies support multiple, prolonged, and high dose vitamin K1 supplementation (1, 14-16, 19). As the half-life of vitamin K1 is 6 hr (7), multiple divided doses of vitamin K1 has the advantage of maintaining therapeutic effect. Prolonged use of high dose vitamin K1 is necessary as the half-life of superwarfarins is substantially long (9). Early tapering or discontinuation will result in repeat prolongation of PT and aPTT even after normal levels have been achieved (12). This repeat prolongation due to hasty discontinuation was observed in 6 of our patients (patient 1, 2, 3, 4, 6, and 8) and in pre-

vious reports (10, 14). A phased and prudent tapering of vitamin K1 with regular follow up is thus mandatory (15). In a case series of 9 patients in Taiwan (16), treatment duration ranged from 72 to 185 days. Table 2 shows the doses and durations of vitamin K1 therapy performed in our study and several previous reports. In a situation of emergency due to bleeding, transfusion of coagulation factors is effective, although the effect of this will be transient because of long half-life of superwarfarin. Urgent treatment with vitamin K1 and transfusion of coagulation factors based on clinical suspicion alone is justified because most detailed laboratory tests require several days to weeks.

Identifying the source of exposure is sometimes challenging in patients who deny ingestion of superwarfarin. After stabilization of symptoms, psychiatric interview should be recommended for patients in whom intentional administration is highly suspected as patient 2 of this study. We were unable to definitively identify the route of intoxication in 8 of the patients in this study. Environmental exposure was a possible cause in 3 patients (patients 4, 7, and 10) considering their occupations. As these patients had no symptoms or history of mental illness, and taking into account the potency, lipid solubility and long-half life of superwarfarin, we can cautiously consider transdermal absorption and inhalation as potential routes of their superwarfarin exposure. Such possibilities were highlighted in a previous report on 2 patients who worked in superwarfarin manufacture (3).

The incidence of superwarfarin intoxication should be surveyed nationwide in light of these recent cases. Supervision for rodenticide use and education of people who deal with rodenticides in their workplace are also necessary, along with further scientific research to achieve more accurate diagnosis and treatment of superwarfarin intoxication.

In conclusion, early suspicion with a prompt request of serum brodifacoum test and sufficient dose and duration of vitamin K1 therapy is necessary for effective treatment of superwarfarin intoxication. Further detailed investigation on the possibility and the actual condition of environmental exposure, and improving availability of the blood level test is mandatory.

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