ISSN 2689-8268 | Volume 4

American Journal of Surgery and Clinical Case Reports

Research Article Open Access

Analyzing the Clinical Characteristics of Anticoagulant Rodenticide Poisoning in 82 Patients

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Received: 13 Mar 2022
Accepted: 30 Mar 2022
Published: 05 Apr 2022
J Short Name: AJSCCR

Keywords:

Anticoagulant rodenticide poisoning; Impaired coagulation function; Vitamin K1

Citation:

Fangtian Fan. Analyzing the Clinical Characteristics of Anticoagulant Rodenticide Poisoning in 82 Patients. Ame J Surg Clin Case Rep. 2022; 4(8): 1-5

1. Abstract

1.1. Objectives: To explore the clinical characteristics of anticoagulant rodenticide poisoning and the efficacy of vitamin K1 therapy.

1.2. Methods: Eighty-two patients with anticoagulant rodenticide poisoning, treated in the Emergency Internal Medicine Department of our hospital, from January 2013 to December 2018, were selected as subjects. Clinical data, including poisoning details, time from poisoning to treatment, clinical manifestations, coagulation functions, treatment regimens and treatment outcomes were retrospectively collected and analyzed. All patients were followed up for three months.

1.3. Results: Among patients, 70 had a confirmed diagnosis of anticoagulant rodenticide poisoning. All patients showed significant improvements in prothrombin time (PT), activated partial thromboplastin time (APTT) and PT% at hospital discharge ($P < 0.05$). Poisoning times were correlated to patient coagulation function at time of admission ($P < 0.05$). Thirty-two patients presented to the emergency room with bleeding symptoms and were divided into two groups (A and B). Vitamin K1 was administered to 19 patients at a daily dosage of 60 mg (group A), and to 13 patients at a daily dosage of 80 mg (group B). There were no statistically significant differences between the disappearance of bleeding symptoms and for coagulation function recovery for the two groups ($P > 0.05$).

Conclusions: There were no significant differences in efficacy between a daily dose of 60 mg and 80 mg for patients with obvious bleeding symptoms. Timely treatment with vitamin K1 and adherence to maintenance therapy are extremely important for these cases.

2. Introduction

Indanedione and dicumarol are major ingredients of anticoagulant rodenticides. At present, second-generation anticoagulant rodenticides, such as bromadiolone and brodifacoum are widely used. In recent years, the number of poisoning cases has gradually increased in line with their widespread use. The poisons are fat soluble, and therefore, accumulate in the body. With an incubation period of 3–5 days, anticoagulant rodenticide poisoning is characterized by a prolonged onset of symptoms, and a very slow elimination process from the body (half-life = 24.2–56 days) [1, 2]. Patients with anticoagulant rodenticide poisoning tend to experience systemic bleeding, and are very likely to be misdiagnosed with other hemorrhagic diseases if they cannot provide a definitive history of contact with such poisons. Currently, there are no consensus guidelines on treatment and maintenance doses of vitamin K_1, as well as the duration of vitamin K_1 therapy for anticoagulant rodenticide poisoning. We herein report clinical data from 82 patients with anticoagulant rodenticide poisoning, who were treated in the emergency department of our hospital, from January 2013 to December 2018. We aim to provide a reference for the diagnosis and treatment of this kind of poisoning.

3. Materials and Methods

3.1. Patients

Clinical data from 82 patients, with anticoagulant rodenticide poisoning treated in the emergency department of our hospital from January 2013 to December 2018 were collected and reviewed. There were 22 males and 60 females (age range, 15-93 years). The time from initial poisoning to treatment (poisoning time) was 1-360 hours (average time; 95.67 ± 164.21 hours). The length of hospital stay was 1-10 days (average length; 4.51 ± 1.83 days).

3.2. Diagnostic Criteria

Diagnoses were made and confirmed based on patient medical

histories, clinical manifestations and laboratory tests. The main diagnostic criteria were: (1) patients were unsure whether or not they had ingested or made contact with anticoagulant rodenticides, but the possibility of poisoning could not be ruled out; (2) patients had bleeding symptoms; (3) coagulation function tests showed prolonged prothrombin times (PT) and activated partial thromboplastin times (APTT), but routine bloods indicated normal platelet levels (coagulation factor activity tests were performed when necessary); (4) Vitamin K therapy was effective; (5) relevant toxins or metabolites were detected in gastric lavage samples, blood or urine; (6) coagulation disorders such as hemophilia and severe hepatitis were excluded [3]. A tentative diagnosis was made if patients met criteria 1–3, and a clinical diagnosis was made if patients met criteria 1-4. A definitive diagnosis was made if patients met criteria 1-5 and/or 6.

3.3. Methods

Clinical data, including the cause of poisoning, time from poisoning to treatment, length of hospital stay, bleeding sites, vitamin K_1 dose, duration of vitamin K_1 therapy and changes in coagulation functions (PT, APTT, PT%) were analyzed, retrospectively. Poisoning severity scores (PSS) were performed in 32 patients with obvious bleeding symptoms at admission. PSS is a severity-grading scale developed by the European Association of Poisons Centers and Clinical Toxicologists (EAPCCT), and is widely used in assessing poisoning severity [4].

3.4. Treatment Regimens

Gastric lavage was performed for those who had definitive ingestion of poisons within the previous six hours. Cathartics were also given to accelerate defecation and prevent further toxin absorption. Coagulation function tests were performed immediately, and then repeated every 1-3 days. Vitamin K_1 was given via intravenous drip at a daily dose of 30-80 mg. In addition, routine treatments were also provided to replenish bodily fluids, increase urine production and protect internal organs.

3.5. Statistical Methods

The SPSS 13.0 statistical software package was used to analyze data. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). T-tests were used to compare data between groups. Pearson correlation coefficients were used to compare continuous variables. $P < 0.05$ indicated differences were statistically significant.

4. Results

4.1. Basic patient information

Most patients in our study had a definitive history of exposure to, or contact with toxins. Most had ingested toxins (79 cases). Only one patient was poisoned because they had made contact with toxins (not taken by mouth), while the remaining two patients were poisoned for unknown reasons. For the 70 patients with a confirmed diagnosis of anticoagulant rodenticide poisoning, 50 had bromadiolone poisoning, whereas 20 had brodifacoum poisoning. The specific rodenticide was unknown for 12 patients, but nonetheless they were clinically diagnosed with anticoagulant rodenticide poisoning (Table 1**)**.

Table 1: Patient information; anticoagulant rodenticide poisoning.

Variants	Number of cases	Percentage
How patients got poisoned		
Ingestion	79	96.34%
Contact with toxins	1	1.22%
Unknow reasons	2	2.44%
Toxins that caused the poisoning		
Bromadiolone	50	60.98%
Brodifacoum	20	24.39%
Unknown rodenticides	12	14.63%

4.2. Clinical Manifestations

The main clinical manifestations of anticoagulant rodenticide poisoning are abnormal coagulation functions and systemic bleeding. Bleeding sites for the 32 patients with obvious bleeding at admission included: oral hemorrhage (10 cases), gastrointestinal bleeding (four cases), hematuria (24 cases), skin hemorrhage (four cases) and epistaxis (six cases) (Table 2**)**. The PSS for the 82 patients were: asymptomatic (50 cases), minor (18 cases), moderate (10 cases), severe (four cases) and fatal (0 cases) (Table 3**)**.

Table 2: Bleeding sites in 32 patients with obvious bleeding symptoms at admission.

Bleeding sites	Number of patients	Percentage
Hematuria	24	50%
Oral hemorrhage	10	20.83%
Gastrointestinal bleeding	4	8.33%
Skin hemorrhage	4	8.33%
Epistaxis	6	12.50%

Table 3: PSS for 82 patients with anticoagulant rodenticide poisoning at admission.

PSS	Number of cases	Percentage
0 (asymptomatic)	50	60.98%
1 (minor)	18	21.95%
2 (moderate)	10	12.19%
3 (severe)	4	4.88%
4 (fatal)	0	0

Note: PSS, poisoning severity score.

4.3. Efficacy Assessments

PT, APTT and PT% for the 82 patients at admission were 28.15 ± 55.46 sec, 48.81 ± 32.13 sec and 64.81 ± 55.18%, respectively. PT, APTT and PT% for patients at discharge were 9.69 ± 9.04 sec, 19.10±14.08 sec and 93.42 ± 68.27%, respectively. These results clearly indicate that all patients showed improvements in their coagulation function after vitamin K_1 therapy ($P < 0.05$) (Table 4**)**. Based on vitamin K_1 dosages, the 32 patients were divided into two groups; group A (19 patients who received a 60 mg daily dose of vitamin K_1) and group B (13 patients who received an 80 mg daily dose of vitamin K_1). Patients in group A had slightly longer coagulation function and bleeding symptom recovery times than group B, however, the differences were not statistically significant ($P >0.05$), suggesting both dosing schemes were equally effective (Table 5**)**.

Table 4: Coagulation function test results for the 82 study patients at admission and at discharge.

Coagulation function tests	At admission ($\bar{x}$ ±s)	At discharge ($\bar{x}$ ±s)	t	P
PT (s)	28.15±55.46	9.69±9.04	2.103	0.0386
APTT (s)	48.81±32.13	19.10±14.08	5.42	<0.01
PT% (%)	64.81±55.18	93.42±68.27	2.0869	0.0401

Note: PT, prothrombin time, APTT, activated partial thromboplastin time.

Table 5: Recovery times for coagulation function and bleeding symptom for 32 patients with obvious bleeding symptoms.

Groups	Group A (n=19)	Group B (n=13)	t	P
Recovery time for coagulation function ($\bar{x}$ ±s) (days)	3.053±0.780	2.846±0.801	0.7294	0.4714
Recovery time for bleeding symptoms ($\bar{x}$ ±s) (days)	2.158±0.688	2.077±0.641	0.3361	0.7391

4.4. Correlations between Poisoning Time and Coagulation Function at Admission

Statistically significant differences were observed between the times for patient treatment after poisoning and coagulation function ($P < 0.05$). This result suggested that the longer the poisoning time, the more severe the abnormal coagulation function (Table 6**)**.

Table 6: Correlations between poisoning time and coagulation function at admission.

Test items	At admission	Poisoning time	r	P
PT (s)	9.69±9.04	95.67±164.21	0.57	<0.01
APTT (s)	19.10±14.08	95.67±164.21	0.52	<0.01
PT%	93.42±68.27	95.67±164.21	-0.31	0.014

Note: PT, prothrombin time, APTT, activated partial thromboplastin time.

4.6. Prognosis and Follow-Up

After active treatment, 56 of the 82 patients showed improvements in their symptoms and were discharged from hospital. The remaining 26 patients were discharged at their own or a family members' request. No deaths occurred during hospitalization. All patients were advised to continue vitamin K_1 therapy (maintenance dose = 10 mg/day) for at least three months, and check their coagulation function every 1-2 weeks. One patient died at home from internal bleeding during the three month follow-up period. This patient had discontinued vitamin K_1 treatment after discharge, and did not pay attention to gingival bleeding before death. Another patient also discontinued vitamin K_1 therapy without permission, and were re-admitted to hospital two months after discharge, because of intra-abdominal hemorrhage.

5. Discussion

Patients with anticoagulant rodenticide poisoning are likely to experience coagulation disorders. The second generation of anticoagulant rodenticides are more potent and effective against rodent populations that have become resistant to first generation anticoagulants. Bromadiolone (i.e., super-warfarin) and brodifacoum are now widely used [5]. In our study, 50 patients were poisoned by bromadiolone, compared with 20 patients by brodifacoum (60.98% versus 24.39%). The widespread use of bromadiolone in China may have led to this prevalence of bromadiolone poisoning. A study of anticoagulant rodenticide poisoning in Hong Kong also found that bromadiolone poisoning was the most common poisoning in this jurisdiction [6]. Most adult patients with anticoagulant rodenticide poisoning can recall their exposure to toxins, while most children are unsure how they ingested or came into contact with the toxin. The youngest subject in our study was 15 years old. As most subjects in our study were adults, 80 patients (97.56%) provided definitive histories of exposure to the toxin. In fact, a very high proportion of patients had attempted suicide by swallowing the rodenticides in question. Anticoagulant rodenticides act as antagonists of vitamin K, thus, they indirectly block the synthesis of coagulation factors II, VII, IX and X in the liver; however, they have no effects on coagulation factors already in the body. As coagulation disorders only appear after the gradual depletion of functional coagulation factors, the incubation period for this type of poisoning is 3-5 days. Systemic bleeding can occur after poisoning and affects the urinary system (hematuria), skin (petechiae), mouth (gingival bleeding), digestive tract (hematemesis or black stools), respiratory system (epistaxis or hemoptysis) and the genital tract (vaginal bleeding). In our study, 18 patients had bleeding at one site, while 14 patients had multi-site bleeding. The locations of bleeding were: oral hemorrhage (10 cases), gastrointestinal bleeding (four cases), hematuria (24 cases), skin hemorrhage (four cases) and epistaxis (six cases). The top three bleeding symptoms were hematuria, oral hemorrhage and epistaxis. PSS was first proposed by EAPCCT in 1990 and was available for clinical use in 1994, after the completion of testing and revision processes [4]. The approach is to have a standardized and generally applicable scheme for grading the severity of different forms of poisoning, regardless of the toxins involved. With a simple scoring system, the scheme is widely used in assessing poisoning severity [7-9]. For those 32 patients with obvious bleeding, 18 had a PSS score of one (minor); 10 had a PSS of two (moderate) and four had a PSS of three (severe).

After an anticoagulant rodenticide poisoning diagnosis has been confirmed, vitamin K_1 should be immediately given as the antidote, in addition to routine poisoning treatments. Studies have found that a daily dose of vitamin K_1, at 15–50 mg has strong antidotal effects, but a 10-20 mg daily dose is also effective, with the maximum dose being 800 mg/d [10-11]. However, a dosing scheme of 100–400 mg/d is also recommended [12]. As there is no standardized consensus, a 40 mg daily dose is usually given while referring to dosage in the package insert of vitamin K_1. However, for patients with severe poisoning and obvious bleeding caused by abnormal blood coagulation, the dosage and duration of vitamin K_1 therapy should be increased to improve therapeutic efficacy [13]. On the whole, long-term therapy with large dosages of vitamin K_1 is warranted for treating anticoagulant rodenticide poisoning [14]. The vitamin K_1 dosage was 30–80 mg/day for patients in this study. Specific dosages were adjusted based on individual patient poisoning severity. Most patients, with abnormal coagulation function at admission recover after 1-5 days of treatment. We further divided the 32 patients, with obvious bleeding, into two groups (group A and B), and gave them two different dosing regimens (60 mg/d for group A versus 80 mg/d for group B). We then observed that group A had slightly longer recovery times for the disappearance of bleeding and recovery of coagulation function, but these differences were not statistically significant. This result showed that both dosing schemes were equally effective in treating patients with anticoagulant rodenticide poisoning and obvious bleeding. For patients with a short poisoning time and no obvious abnormalities in coagulation function at admission, and for those who showed normal blood clotting while they were still in hospital during maintenance therapy, their treatment efficacy was satisfactory. After ingestion, anticoagulant rodenticides accumulate in fat and liver, as they are fat soluble. As a result, they are difficult to break down in the human body; it can take a long time for bromadiolone (half-life, 24.2 days) and brodifacoum (half-life, 56 days) to be completely eliminated from the body. Thus, patients need continuous vitamin K_1 therapy (10 mg via intramuscular injection per day) for at least three months after recovery of coagulation function and the disappearance of bleeding. Given the psychological and physical pain caused by long-term intramuscular injections, maintenance therapy with oral vitamin K_1 is also recommended [15-16]. All patients in this study were instructed to continue to take a 10 mg daily dose of vitamin K_1 for three months after hospital discharge. Those patients who adhered to these instructions reported no bleeding during follow-up. One patient died at home and had gingival bleeding before death. We speculate the cause of death was bleeding from internal organs. Another patient was re-admitted to hospital for intra-abdominal bleeding two months after discharge. Neither patient had continued vitamin K_1 treatment as required. In conclusion, vitamin K_1 should be immediately given to patients with a definitive diagnosis of or highly suspected anticoagulant rodenticide poisoning. A daily dose of vitamin K_1, at 30-80 mg was given to all subjects in this study. Most achieved good treatment outcomes. For patients with obvious bleeding, there were no efficacy differences between a 60 mg daily dose of vitamin K_1 and an 80 mg daily dose of vitamin K_1. We recommend initiating a 60 mg daily dose of vitamin K_1

therapy for such patients. However, the sample size in our study was small, therefore, further research is required to verify our observations. During follow-up, one patient died and one patient had intra-abdominal hemorrhaging, because they discontinued vitamin K_1 therapy. These cases highlight the importance of continuing with vitamin K_1 therapy after hospital discharge. Efforts should be made to educate patients on the importance of adhering to prescribed treatment regimens and having regular coagulation function tests after hospital discharge to improve prognosis.

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