Heliyon 9 (2023) e19811

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Application of nafamostat mesylate for anticoagulation in hemoperfusion therapy in patients with bromadiolone poisoning: Case reports

Weiwei Qian [a,b,1], Chengtong He [a,1], Yan Ren [a], Xiaoyan Xian [a], Zhen Jiang [a], Shuyun Xu [a,*]

[a] Department of Emergency Medicine, Laboratory of Emergency Medicine, West China Hospital, And Disaster Medical Center, Sichuan University, Chengdu, 610041, Sichuan, China
[b] Department of Emergency, Shangjinnanfu Hospital, West China Hospital, Sichuan University, Chengdu, 610044, Sichuan, China

ARTICLE INFO

Keywords:
Nafamostat mesylate
Anticoagulation
Hemoperfusion
Bromadiolone
Poisoning

ABSTRACT

Bromadiolone, as a second-generation coumarin anticoagulant rodenticide, may accidently cause harm to humans and non-target animals when overused or misused due to its high toxicity and long-lasting effects. In some severe cases such as the presence of active bleeding, treatment should involve the administration of hemoperfusion therapy. Nafamostat mesylate is a synthesized protease inhibitor that inhibits most factors in the coagulation process, preventing clotting and ensuring smooth blood flow during the procedure. Nafamostat mesylate helps maintain the efficacy and safety of hemoperfusion treatment. Despite its wide application in Japan, the clinical practice and research of nafamostat mesylate are limited in China, especially for patients undergoing maintenance hemodialysis. This paper reports two cases of bromadiolone poisoning and describes the treatment procedure and therapeutic effect of anticoagulation in hemoperfusion therapy with nafamostat mesylate.

1. Introduction

Bromadiolone is one of the most common insecticides widely used for the prevention and control of rodent pests in households, agriculture, industry, and public places [1]. Pharmacologically, bromadiolone belongs to a second-generation 4-hydroxycoumarin derivative and a vitamin K antagonist, acting as a potent anticoagulant rodenticide (AR), also known as "super warfarin". Bromadiolone shows potent anticoagulant effects and tends to accumulate in the liver of organisms during poisoning, with a half-life of up to 24 days in the human body [2,3]. The symptom of bromadiolone poisoning is internal bleeding, mainly manifested as the extensive bleeding of the skin, mucous membranes, and internal organs. Measures, therefore, should be taken to curtail skin contact and gas inhalation while using. Also, bromadiolone should be properly stored to prevent accidental ingestion and harm to humans and other non-target animals [4]. In daily life, bromadiolone poisoning is often related to accidental ingestion, suicide, and homicide. Exposure to excessive amounts of bromadiolone can cause serious damage to the human nervous and cardiovascular systems [5], and may even

* Corresponding author. Department of Emergency Medicine, Laboratory of Emergency Medicine, West China Hospital, and Disaster Medical Center, Sichuan University, 37 Guoxue Road, Chengdu, 610041, Sichuan, China.
E-mail address: 120xsy@163.com (S. Xu).
[1] They are co-first authors.

https://doi.org/10.1016/j.heliyon.2023.e19811
Received 17 May 2023; Received in revised form 31 August 2023; Accepted 1 September 2023
Available online 5 September 2023

lead to death in the case of severe poisoning. Hence, the treatment of patients with bromadiolone poisoning remains a challenging issue. The selection of therapeutic strategies for bromadiolone poisoning depends on the degree of poisoning and the severity of symptoms. The commonly used therapeutic methods include gastric lavage, symptomatic treatment, and oxygen inhalation. For severe poisoning symptoms, hemodialysis or hemoperfusion may be necessary to remove excessive bromadiolone from the body [6]. However, since both blood purification and bromadiolone poisoning status increase the risk of bleeding, anticoagulants such as unfractionated heparin and low-molecule heparin used for routine blood purification are not the optimal choice.

Nafamostat mesylate (NM), a synthetic serine protease inhibitor, exerts inhibitory effects on most factors in the coagulation process, which can suppress thrombin, coagulation factors, platelet activation, kallikrein-kinin system, complement system, and lipopolysaccharide-induced nitric oxide production [7]. Due to its short half-life and low risk of bleeding, NM is commonly used as an anticoagulant in continuous renal replacement therapy (CRRT) [8]. Although it has been approved in China since 2022, the clinical application of NM is relatively limited. There are few reports on the safety and effectiveness of NM, especially for patients undergoing hemodialysis. Here we report 2 cases of bromadiolone poisoning who received NM for anticoagulation in hemoperfusion, describe the treatment process and efficacy, and briefly review the current research status of NM.

2. Case presentation

2.1. Case 1

A 47-year-old male was admitted to our department at 9 p.m. on June 28, 2022 due to low back pain, hematuria, and black stool for over a week. A week ago, the patient developed bilateral low back pain (mainly on the right side), urinated bright red hematuria (4–5 times per day, specific amount unknown), and defecated black stool three times, accompanied by dizziness and fatigue. The patient went to the hospital for treatment about 3 days after experiencing symptoms. Coagulation function testing results showed the prothrombin time (PT) of 39.9 s, prothrombin activity (PTA) of 14%, international normalized ratio (INR) of 3.84, activated partial thromboplastin time (APTT) of 49.7 s, and hemoglobin of 62 g/L. The urine routine indicated urine occult blood (3+) and urinary protein (2+). After treatment with acid suppression, hemostasis, blood transfusion, and fluid infusion, the symptoms of hematuria and low back pain were slightly relieved, and the patient sought further medical attention in our hospital. Physical examination on admission showed: heart rate at 89 beats/minute, breathing at 20 breaths/minute, blood pressure at 107/66 mmHg, oxygen saturation (SpO_2) of 98%, clear consciousness, accurate answering, anemic appearance, a small amount of ecchymosis on limbs, no skin or scleral icterus, bilateral pupils of equal size and shape with sensitive reaction to light, symmetric and clear pulmonary respiratory sound, no rhonchi or moist rales, soft abdomen at palpation without tenderness and rebound tenderness, muscle strength of limbs at grade IV, and no edema of both lower extremities.

The medical history was inquired after admission. The patient reported that he dined out about 1–2 times a month and the people

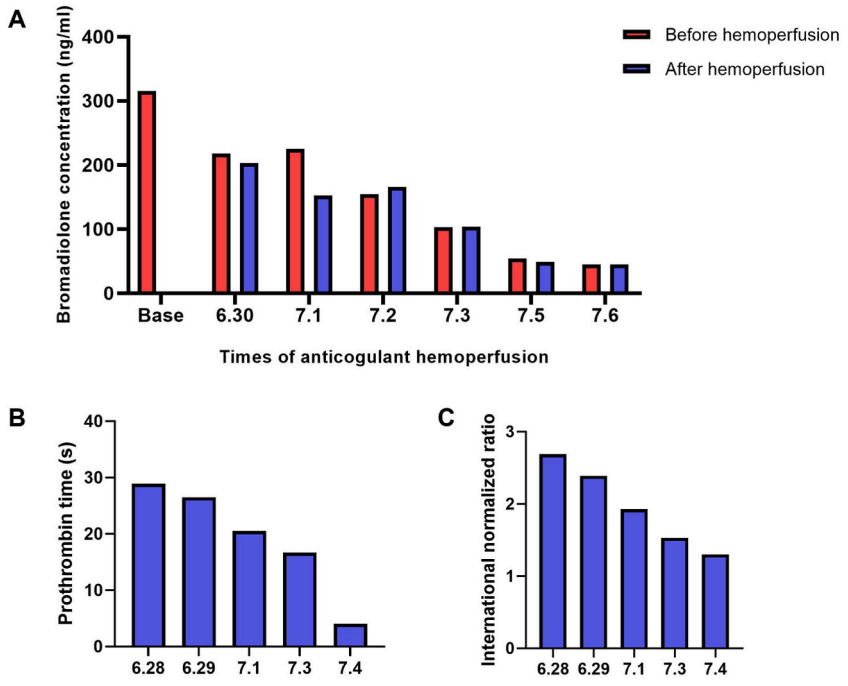

Fig. 1. Laboratory examination results of Case 1. A. Bromadiolone concentration before and after 6 times of hemoperfusion with NM for anticoagulation. The alternation of PT (B) and INR (C) examinations during treatment.

who ate with him did not have similar symptoms, and he denied having a feud with others. The relevant examinations were completed after admission. The plasma concentration of bromadiolone was 315.6 ng/mL on June 29, 2022. Then the diagnosis of "bromadiolone poisoning" was made when its plasma concentration was higher than 0.5 ng/mL. Preoperative coagulation routine: PT 35.6 s, INR 3.30, and APTT 36.7 s. After admission, the patient was given symptomatic treatments including oral administration of 10mg eprazole enteric-coated tablets once a day for 1 week, intravenous transfusion of 60mg sodium carbonate once a day for 1 week, and intramuscular injection of 20mg vitamin K1 every 12 hours for 8 days, accompanied with oral administration of 20mg vitamin K1 once a day for 6 months. Afterward, 6 times of hemoperfusion (velocity of blood flow: 150cm/s) with NM with an initial dose of 20mg and a maintenance dose of 20mg/hr for anticoagulation were performed by the blood purification machine (Diapact CRRT, Braun, Germany) and hemoperfusion machine for 4 hours (HA280, JAFRON Biotechnology Co., Ltd, China) on June 30, July 1, July 2, July 3, July 5, and July 6, respectively. No adverse events during the treatment have been observed. The blood coagulation function indicators and bromadiolone concentration were measured before hemoperfusion and after hemoperfusion. The concentration of bromadiolone before and after 6 times of hemoperfusion therapy is shown in Fig. 1(A- C). The plasma concentration of bromadiolone on July 6, 2022 was 45.3 ng/mL. On July 8, 2022, the PT, INR, and APTT was 12.6 s, 1.17, and 25.6 s, respectively. The patient was discharged from the hospital on July 9, 2022. On October 25, 2022, the latest outpatient follow-up examination showed a PT of 10.9 s, an INR of 1.06, and an APTT of 24.1 s.

2.2. Case 2

A 51-year-old female was admitted to our department at 4 p.m. on June 6, 2022 due to the accidental consumption of rodenticide 4 days ago. The patient mistakenly took rodenticide (the specific dose and name were unknown) 4 days ago and did not have symptoms of nausea, vomiting, or skin mucosal bleeding. Physical examination on admission: heart rate at 92 beats/minute, breathing at 21 breaths/minute, blood pressure at 112/75 mmHg, oxygen saturation (SpO_2) of 97%, clear consciousness, accurate answers to the point, no abnormalities in the skin and sclera, equal size and roundness of both pupils, sensitive light reflex, smooth breathing, normal heart sounds, regular rhythm, no murmurs in various valves of the heart, symmetric and clear bilateral lung breathing sounds, no rales heard, slight tenderness in the entire abdomen at palpation, no rebound tenderness or muscle tension, normal bowel sounds, negative pathological signs, negative meningeal stimulation signs, muscle strength of the limbs graded V, and no edema in both lower limbs. Routine examination of disseminated intravascular coagulation on June 6, 2022 indicated a PT of 75.4 s, INR of 6.55, and APTT of 36.2 s. The plasma concentration of bromadiolone on June 6, 2022 was 526.9 ng/mL. Then the diagnosis of "bromadiolone poisoning" was made when its plasma concentration was higher than 0.5 ng/mL. The patient received symptomatic treatments including hemostasis, plasma infusion, and correction of blood coagulation. Hemoperfusion with NM with an initial dose of 20mg and a maintenance dose of 20mg/hr for anticoagulation was given 5 times on June 7, June 8, June 9, June 10, and June 11, respectively, and blood coagulation function indicators and bromadiolone concentration were measured before hemoperfusion and after hemoperfusion. No adverse

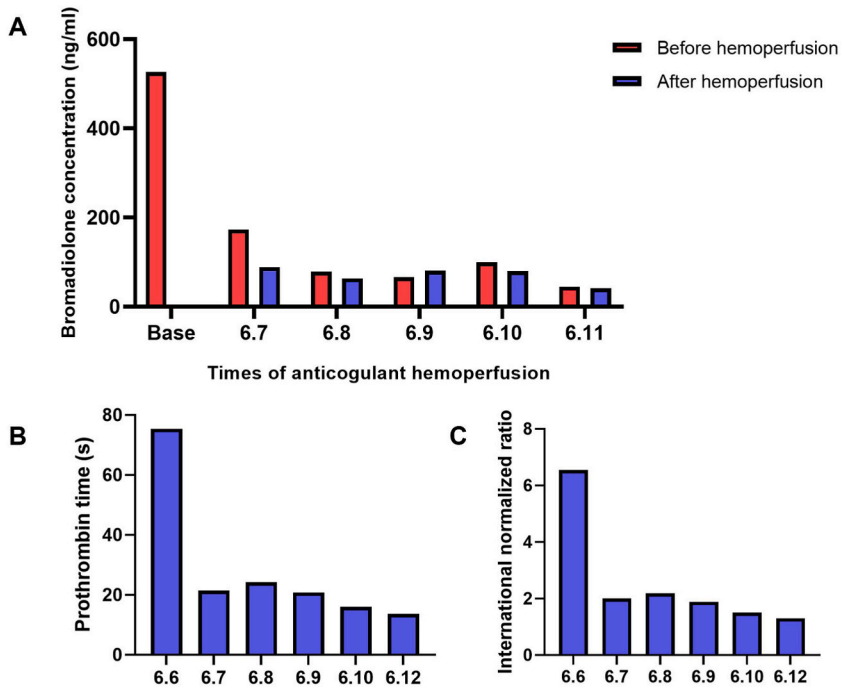

Fig. 2. Laboratory examination results of Case 2. A. Bromadiolone concentration before and after 5 times of hemoperfusion with NM for anticoagulation. The alternation of PT (B) and INR (C) examinations during treatment.

events during the treatment were observed. The concentration of bromadiolone before and after 5 times of hemoperfusion is shown in Fig. 2(A-C). Following 5 times of treatments, the plasma concentration of bromadiolone on June 12, 2022 was 41.4 ng/mL; the PT was 13.7 s; the INR was 1.3, and the APTT was 1.35 s. The patient was discharged from the hospital on June 12, 2022. On June 29, 2022, a further consultation was made in the outpatient department: a PT of 10.4 s, INR of 0.93, and APTT of 23.7 s. The latest outpatient follow-up examination on November 3, 2022 showed a PT of 9.8 s, INR of 0.99, and APTT of 26.1 s.

3. Discussion

This paper reports two cases of bromadiolone poisoning who received NM for anticoagulation in hemoperfusion. Blood purification uses specific equipment and technology to remove toxins and wastes from the body of patients, thereby improving physical function and treating certain diseases. Currently, the most commonly used anticoagulants in blood purification therapy are local citrate anticoagulation and general heparin anticoagulation, but they have certain contraindications and side effects [9]. Particularly, most patients receiving continuous blood purification have severer disease conditions and more complications. NM is a novel serine-protease inhibitor used for the treatment of pancreatitis and shows inhibitory effects on most coagulation factors, with a significantly shorter half-life than heparin [7,10]. In addition to inhibiting prothrombin, NM can also inhibit platelet aggregation and thereby impede the process of microthrombosis formation [11]. Both the APTT and TT of hemodialysis patients can be prolonged by 2 times after NM anticoagulation treatment, while ordinary heparin anticoagulation can prolong the APTT and TT of patients even by more than 2 times [12]. Here, we did not notice the occurrence of adverse events such as bleeding during the treatment. Hence, it is indicated that anticoagulation with NM may be safer, especially for patients with active bleeding or bleeding tendencies. NM has been commonly used as an anticoagulant during CRRT [13]. In the absence of an anticoagulant, the life span of filter in CRRT cannot achieve a satisfactory service life of 12 hours. NM for anticoagulation may be an ideal alternative to reducing the number of filters used [14]. During extracorporeal membrane oxygenation (ECMO), NM anticoagulation can reduce adverse events such as bleeding, blood transfusion, and thrombosis compared with ordinary heparin anticoagulation, thereby prolonging the duration of ECMO. However, the anticoagulant effect of NM in CRRT combined with ECMO is still unclear [15].

Heparin sodium is a globally used anticoagulant to prevent blood clotting. It is the main anticoagulant used in extracorporeal circuits, but it may cause massive bleeding and heparin-induced thrombocytopenia [7]. Other anticoagulants used during extracorporeal circuit treatment include NM. According to the data provided by the Japanese Pharmaceuticals and Medical Devices Agency, there are also certain side effects in the anticoagulant treatment of NM. During the period 2004–2019, a total of 2008 cases of side effects caused by NM occurred, including 1072 cases (53.4%) of allergic reactions, 45 cases (2.2%) of leukocytosis/reduction or thrombocytopenia, and 43 cases (2.1%) of fever [16]. Other side effects of NM such as hyperkalemia and agranulocytosis have also been reported [17]. Therefore, the vital signs, electrolytes, and blood routine of patients should be closely monitored in the application of anticoagulant therapy with NM. In the event of adverse reactions, NM anticoagulation should be stopped immediately, and symptomatic support treatment should be performed as soon as possible.

The high cost also limits the wide application of NM. The original patented drug Fusan (Torii Co., Japan) costs about $40/50mg. If the dosage of NM is 30mg/h, the cost of anticoagulation alone is close to $600 per day. Although the current cost of generic drugs is already 1/5 of the original drug, the cost of NM is still higher than that of ordinary heparin. The price of NM is about 5 times that of ordinary heparin, and the daily anticoagulation cost of ordinary heparin does not exceed $5 [18]. However, the use of ordinary heparin for anticoagulation may increase the risk of bleeding. Without anticoagulation treatment, the filters may need to be frequently replaced and blood transfusions may be required, which also eventually increases the cost of treatment.

4. Conclusion

To sum up, this paper discusses the use of NM for anticoagulation in hemoperfusion therapy in two cases of bromadiolone poisoning. The therapeutic process and efficacy suggest that NM may serve as an effective alternative anticoagulant in blood purification, which can help especially avoid the occurrence of coagulation events in the external circulation circuit in the absence of anticoagulation and prolong the ideal treatment duration. However, blood perfusion is an invasive therapy, and it is necessary to closely monitor the potential side effects while using NM for anticoagulation and take into account the patient's economic conditions. Hence, we need to take cautious consideration about the indications during the application in clinical practice, such as coagulation disorders and thrombosis conditions, allergy considerations, and intractable bleeding disorders. This case report provides a preliminary sketch for the application of NM for anticoagulation in hemoperfusion therapy in bromadiolone poisoning, further study with larger subjects is needed to weigh the potential benefits and risks of hemoperfusion therapy with NM, thus making optimal treatment for patients with bromadiolone poisoning.

Ethics statement

This study was designed in accordance with the Declaration of Helsinki and approved by the ethics committee of Laboratory of Emergency Medicine, West China Hospital, and Disaster Medical Center, Sichuan University. Informed consent was obtained from all subjects involved in the study.

Author contribution

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

This work was supported by Early diagnosis of venom-induced ventricular fascia syndrome based on high frequency ultrasound and shear wave elastography [grant numbers 2021YFS0189, Shuyun Xu]; Effect and mechanism of adiponectin regulating oxidative stress on astrocyte injury after glufosinate-ammonium poisoning [grant number 2022NSFSC0669, Zhen Jiang].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We would like to acknowledge the reviewers for their helpful comments on this paper.

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