Case Report
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Successful treatment of warfarin overdose with 20% lipid solution: a case report

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Abstract

International Normalized Ratio (INR) value monitoring is important in patients using warfarin, and it is aimed to keep it in the range of 2.5-3.5 in patients with mechanical heart valves. In the light of the management guideline of patients with heart valve disease published by the 2020 AHA/ACC, in the report prepared jointly by the American Society of Cardiology and the college, vitamin K, 4-factor prothrombin complex, administrativecuzumab and andexanet alfa are among the treatment options for reversing anticoagulation. In previous case reports, it has been observed that 20% lipid emulsion causes warfarin resistance and reduces prothrombin time. In this case report, it is aimed to present the successful treatment of a warfarin overdose case using 20% lipid emulsion for the first time in the literature.

Keywords: 20 % lipid solution, warfarin overdose,aortic valve replacement,mitral valve replacement

Introduction

Warfarin is an oral anticoagulant widely used with various indications (1). It is very important to monitor the International Normalized Ratio (INR) value in patients to follow the therapeutic effect of warfarin, and it is aimed to keep it in the range of 2.5-3.5 in patients with mechanical heart valves (2). Among the complications that can be seen are the INR values exceeding the therapeutic upper limit and causing warfarin overdose in patients due to multifactorial factors. If the INR value is above 4.5, the risk of major bleeding increases significantly, and if it is above 6.0, it increases exponentially. Therefore, an INR value of ≥ 6.0 requires rapid reversal of anticoagulation due to the risk of bleeding (3). Vitamin K, 4-factor prothrombin complex, idaricuzumab and andexanet alfa are among the treatment options for reversing anticoagulation (4). In experimental animal studies conducted in rats, 20% lipid emulsion has been shown to reduce the cardiotoxicity of local anesthetic agents, and it can be used in the treatment of some drug intoxications with a high protein binding rate (5). In previous case reports, it has been observed that 20% lipid emulsion causes warfarin resistance and reduces prothrombin time (6-8). However, there are no cases in which 20% lipid emulsion was used for the treatment of warfarin overdose. In this report, a case of warfarin overdose is presented, in which the desired decrease in INR value was achieved with 20% lipid emulsion and resulted in successful treatment.

Case report

An 81-year-old patient with a history of aortic and mitral valve replacement and using warfarin was admitted to the anesthesia intensive care unit for advanced oxygen support due to covid pneumonia. In the patient's labaratory findings, following was detected: International Normalized Ratio (INR) value, 4.15 (0.8-1.2), activated partial thromboplastin time (aPTT): 61.23 second (25.9-36.6), prothrombin time (pT): 37.90 second (10.7-12.9), fibrinogen: 5.58 g/L (1.8-3.5), D-Dimer: 2.43 ug/mL (0-0.55) detected. In the patient who did not receive any other warfarin, anticoagulant or antiaggregant treatment, INR values increased at 6-hour intervals and were found to be 4.48 and 6.31, respectively. Then, treatment was planned for the patient with the diagnosis of warfarin overdose. Considering the unavailability of 4-factor prothrombin complex, idaricuzumab and andexanet alfa in the current hospital, and the INR level may decrease to the recommended range in a long time interval with vitamin K treatment, it was planned to administer a lipid emulsion

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of 20%. After a 1.5 mL/kg IV bolus administration of 20% lipid emulsion, a maintenance infusion of 0.025 ml/kg/min was started. In the follow up of the patient whose lipid emulsion treatment was terminated 10 hours later, hypertension, hemodynamic instability and no change in consciousness were observed. The INR value of the patient was 1.33, 1,24 and 1,19 at the 4th, 16th and 24th hours after the termination of lipid emulsion therapy. Amylase, lipase and lipid plasma values were examined during, at the end and after the treatment, and no increase was found in their values. Since the INR value measured after 48 hours was 1.25, low molecular weight heparin treatment was initiated in the patient. The patient, who received antiviral, steroid and inhaler treatment for Covid pneumonia and whose oxygenation parameters improved, was transferred to the ward from the intensive care unit by taking 6-8lt/min oxygen. Appropriate written informed consent was obtained from the patient for publication of this case report.

Discussion

Warfarin acts by inhibiting the enzymes involved in the formation of a reduced form of vitamin K, which is necessary for the γ-carboxylation of glutamate residues at the amino terminus of coagulation factors II, VII, IX, and X, and the anticoagulant factors protein C and S (1). Unpredictable biological responses, including genetic polymorphisms in warfarin metabolism, can be seen in patients with mechanical valve replacement treated with warfarin, as well as increased INR and bleeding due to multiple interactions of drugs used, foods taken, and other patient-related factors. It is emphasized that if vitamin K is used in cases, it may take a long time for the INR to return to its normal value, and it has been reported that this treatment will not be sufficient in patients with bleeding risk or major bleeding (9). In the studies, it is emphasized that the effect of vitamin K begins after 6 hours, even if it is given as an infusion. The advantage of vitamin K injection is its ease of administration, widespread availability, promoting the formation of factors II, VII, IX, and X in the liver, and a sustained effect in the regulation of coagulopathy. The disadvantages of vitamin K are reported as the risk of developing anaphylaxis, which is thought to be due to the castor oil in the diluent. Warfarin resistance may also develop during vitamin K treatment (10-13). The risk of anaphylaxis has been reported at an estimated rate of 3/100,000, and to avoid these reactions, mixing vitamin K in at least 50 mL of intravenous fluid and giving it at least 30 minutes using an infusion pump are among the recommendations (12, 14). In patients with high INR without bleeding, subcutaneous administration is unreliable and it may take up to 72 hours for INR to reach a normal value (11-13). Intramuscular administration of vitamin K may cause hematoma, and it is emphasized that its consequences are unpredictable (12). Relevant guidelines published by the American College of Cardiology/American Heart Association (ACC/AHA) in 2020 recommended individualization of vitamin K supplementation on a case-by-case basis. The onset of action of vitamin K depends on the route of administration and the dose given, and maintenance therapy is recommended in the presence of active bleeding. In case of life-threatening bleeding, 10 mg intravenous vitamin K is recommended if it is not considered to start a vitamin K antagonist within 1 week (4). In addition, high doses of vitamin K can lead to "warfarin resistance" (up to 3%; 1 week or more) due to the accumulation of vitamin K in the liver, which may require later use of higher doses of warfarin to reach therapeutic INR levels.

In the Fresh Frozen Plasma (FFP) option, the recommended dose is 15 mL/kg infusion (in the range of 10-30 mL/kg), while the average size adult has about 3-4 units of plasma, but the optimal dose is unknown (11-13). The duration of action of FFP is 10 minutes, but a few hours are required for partial reversal and at least 9 hours for a complete reversal of INR (INR<1.5) (10, 13). Other limitations in the use of FFP include fluid overload and acute lung injury due to transfusion. One of the most important reservations about FFP is the risk of viral and bacterial infection (10, 13, 14). In addition, since the plasma is frozen, it must be melted and blood group matched, which leads to a delay in its implementation.

Although FFP is widely used, four-factor prothrombin complex concentrate (PCC) has been noted to have significant benefits over FFP. One of them is that the concentration of clotting factors in PCCs is about 25 times higher than that in FFP, and that the FFP contains an insufficient concentration of factor IX (15, 16). The four-factor prothrombin complex concentrate includes factors II, VII, IX and X. The onset of action is from 5 to 15 minutes, and the duration of action is from 12 to 24 hours. It is a more specific and reliable reversal agent than fresh frozen plasma (4). The main problems limiting the use of PCC are thrombotic complications (approximately 0-7%, mean 2.3%) and the limited availability of these products (12, 14). One cause of PCC-related thrombotic risk is the high level of factor II (relative to other factors) that increases thrombin formation in PCC (15). However, in the presence of life-threatening bleeding, four-factor prothrombin complex concentrate was recommended by the 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (4). Intravenous use of vitamin K is recommended if active bleeding continues despite PCC administration and if vitamin K antagonsite is not started within 7 days (4). For our case, considering the concomitant diseases and COVID-19 pneumonia, although we planned the use of PCC in the foreground due to the long duration of action of vitamin K treatment in translating the effect of warfarin, the risk of infection and the volume burden that FFP may create, we used 20% lipid solution due to the lack of PCC in the local institution where we work.

Recombinant FVIIa provides a rapid and complete biochemical return in INR within 10 minutes, but has a short

half-life of < 1 hour (13). The disadvantage of rFVIIa is that it does not replace all coagulation factors and although the INR is immediately reduced, coagulation may not be reinstituted in vivo. Therefore, repeat infusions are necessary unless used with vitamin K and FFP. In a meta-analysis involving more than 4000 patients, evaluating the use of rFVIIa on the subject, it was shown that thromboembolism developed in 11.1% of the cases (17). Therefore, the most recent guidelines for the management of these patients recommend that rFVIIa be used in the treatment of warfarin-associated bleeding or in the absence of PCC or TDP (15, 18). Idarucizumab (for dabigatran) or andexanet alfa (for anti-Xa agents) is recommended for patients receiving direct oral anticoagulants and those with bioprosthetic valves or annuloplasty rings who require immediate reversal of anticoagulation due to uncontrolled bleeding (Class Of Recommendaiton 2A) (4). Idarucizumab (2.5 mg bolus infusion in two times no longer than 15 minutes) is indicated to reverse the effect of dabigatran. Andexanet alfa is administered as a bolus and 2-hour infusion and is used to reverse the effects of oral anti-Xa agents (4). On the other hand, in a systematic review of the efficacy and safety of vitamin K administration in VKA-treated patients with an INR between 4.5 and 10.0 and without bleeding, the findings suggested that the probability of benefiting from routine vitamin K administration in addition to temporary VKA cessation is low (4).

Currently, various pharmacokinetic and pharmacodynamic mechanisms have been proposed for the application of intravenous lipid emulsion as an antidote (19). Theories put forward about the mechanism of action of ILE; 1) it is the "lipid sink" theory, which assumes that it improves myocardial performance, 2) that the toxic compound is held in a lipid compartment in the bloodstream, 3) the ion channel modulation theory (5). Lipid Sink Theory describes the beneficial effects of intravenous lipid emulsion in cases of lipophilic drug toxicity, known as lipid or pharmacological "sink"; It is explained by the formation of "a lipid compartment where circulating lipophilic drugs are held" and is thought to be diffused into the new compartment by separating lipophilic toxins from the target tissues (20). With a better understanding of lipid resuscitation, intravenous liposomes have been reported as a lipid shuttle or a capture/release mechanism to transport a drug, not as a compartment for capturing and isolating the drug (21). In this regard, exogenous lipid metabolism is thought to be similar to chylomicrons (20).

In addition to its primary purpose of use, parental feeding can be used as an antidote in local anesthetic toxicity and for various purposes, including the treatment of drug overdoses (22). Significant clinical improvement in local anesthetic toxicity achieved in the treatment of poisoning with intravenous lipid emulsions and some lipophilic drugs after its use has been identified. Advantages such as the relatively easy application and low cost have led to an increase in the off-label use of lipid emulsions and paved the way for their use in the treatment of poisoning. Drug toxications that respond to treatment with lipid emulsions are bupivakain, clomipramine, verapamil, bupropion, mepivakain, ropivacaine, haloperidol, quetiapine, doxepine, carvedilol, carbamazepine, flekany, hydrochloroquine, amlodipine, propanolol and moxidectin (5).

On the other hand, some studies have suggested that lipid solutions may play a role in warfarin resistance. MacLaren et al. (6) gave 30 mg of warfarin per day to a case under propofol infusion containing 10% soybeans, but no anticoagulation was achieved (6). After the termination of propofol therapy, it was seen that after they reached effective anticoagulation, the anticoagulation was reversed when they supplemented the patient with 20% lipid solution (6). Lutomski et al. (7) described a patient with short bowel syndrome and recurrent thrombotic episodes requiring both intravenous lipid and anticoagulation. They showed that continuous infusion of a soybean oil emulsion (Intralipid) in parenteral nutrient solution interferes with the anticoagulant effect of warfarin. They achieved the desired coagulation goal by discontinuing lipid infusion and re-administration of warfarin (7).

Cotto et al. (8) added lipid infusion at varying rates to the blood samples of 23 cases with anticoagulated and prothrombin time > (1.3-2.0 x control). Lipid-free plasma and prothrombin time from lipid-containing plasma samples were compared. Average decrease in prothrombin durations; It was 0.29 seconds at 50 micrograms/ml, 0.23 seconds at 100 micrograms/ml and 0.29 seconds at 200 micrograms/ml. All concentrations showed a statistically significant decrease compared with control with the Scheffe test. This study supported the idea that lipid emulsions reduced prothrombin times in patients using anticoagulants (8). Studies conducted to date show that; patients taking lipid emulsion may have difficulty and resistance to achieving the anticoagulation target with warfarin. Most studies in the literature have pointed out that warfarin resistance develops with lipid therapy (8). In the study conducted by looking at this mechanism in reverse, a decrease in prothrombin values was detected by administering lipid emulsion (8). Warfarin binds to albumin at a rate of 98% (23) Thus, considering that it has lipophilic properties, the 'lipid sink' theory and its transport by intravenous lipid emulsion can be explained in this way.

In our hospital, due to local conditions, vitamin K was available as a therapeutic agent that could be given due to the lack of four-factor prothrombin complex, idarucizumab and andexanet alpha. We did not choose vitamin K because its effect would appear in a long time.

Considering the current cost prices of the agents used in warfarin overdose treatment, approximately; PCC was €152.2, idarucizumab €515.8, andexanet alfa €20.000, TDP €12.37,.The cost price of 20% lipid emulsion was 23.9 € and it seemed more economical than other agents. Intravenous

lipid emulsion had advantages such as faster duration of action and easy access. Although FFP is cheaper than lipid emulsion, we did not prefer it because infectious and non-infectious complications may develop.Since other agents were not available in our hospital, we considered and applied lipid emulsion as an alternative treatment.

In our case, prothrombin and INR values reached the desired value with 20% lipid emulsion and warfarin overdose treatment completed without any complications. 20% lipid emulsion, in cases of warfarin overdose can be considered as an alternative treatment option in limited geographies where the supply of first choice prothrombin complex, darucizumab and andexanet alfa is difficult. As a result, in cases of warfarin overdose or intoxication, 20% lipid emulsion can be used as an alternative treatment in socio-economically selected geographies and cases, although it is not recommended for routine treatment yet. More work is needed on this subject.

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