Review Article

Case Report on Heparin Sodium Injection Associated Skin Necrosis in a Tertiary Care Referral Hospital - Kerala

P. Linu Mohan*, C. Dilip, K. Jaseem Sabith and C. Shinu

Department of Pharmacy Practice, Al Shifa College of Pharmacy, Kizhattur, Poonthavanam Post, Perinthalmanna, Kerala-679 325, India.

ABSTRACT

Heparin Sodium is a widely used injectable anticoagulant to prevent thromboembolism. It is a powerful instantaneously acting nonprothrombopenic injectable anticoagulant which acts indirectly by activating plasma antithrombin III and other similar cofactors. Here we report a case of skin necrosis following the administration of Heparin Sodium. The case was in a 35 year old female patient admitted in Gastroenterology department of the hospital for the treatment of splenic vein thrombosis. During treatment she developed skin necrosis in various body parts (forearm) after administration of heparin sodium injection. Erythematous subcutaneous lesion with skin oedema and pain was the first symptoms, then on day 5 that is converted to necrosis of the skin. The causality of the event assessed as per the WHO-UMC for standardized case causality assessment criteria can be considered as probable. Analyzed by Naranjo's ADR probability scale, the score was 7, which also make it a probable event.

Keywords: Heparin Sodium, Injection, Skin Necrosis.

INTRODUCION

Heparin Sodium is a powerful instantaneously acting nonprothrombopenic injectable anticoagulant which acts indirectly by activating plasma antithrombin III and other similar cofactors.[1,2] Heparin is a non-uniform mixture of straight chain mucopolysaccharides with molecular weight 10,000 to 20,000. It contains polymers of two sulfated disaccharide units of D- glucosamine-L-iduronic acid and D-glucosamine-D-glucuronic acid. The mechanism of action of Heparin is indirect, by activating plasma antithrombin III and may be other similar cofactors. . The Heparin- AT III complex then binds to clotting factors of the intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa, and XIIIa) and inactivates them but not factor VIIa operative in the extrinsic pathway. The anticoagulant action is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin.It has atherogenic activity. It also has anti-inflammatory and anti-allergy actions.[2]

Heparin is a large highly ionized molecule; therefore not absorbed orally. Injected i.v. it acts instantaneously, but after subcutaneous injection anticoagulant effect develops after about 60 min. Bioavailability of subcutaneous heparin is inconsistent. Heparin does not cross blood brain barrier or placenta, which makes it the anticoagulant choice during pregnancy. It is metabolized in liver by heparinase and fragments are excreted in urine. Heparin released from mast cells is degraded by tissue macrophages.

Heparin should not be mixed with penicillin, tetracyclines, hydrocortisone in the same syringe or infusion bottle. Heparinized blood is not suitable for blood counts, fragility testing and complement fixation tests.

Some of the primary clinical applications are the treatment and prevention of pulmonary embolism, prevention of mural thrombosis after myocardial infarction, initial treatment of deep- vein thrombosis, immune thrombocytopenia, and prevention of cerebral thrombosis during evolving stroke and after vascular surgery.[2, 3]

Hypersensitivity and other adverse side effects may occur. Manifestations include bronchospasm, rash, urticarial, pruritus, chills fever, vasospasm, neuropathy with parasthesis, hair loss, thrombocytopenia, irritation, mild pain, hematoma, ulceration, cutaneous or subcutaneous necrosis, 'white clot" syndrome, anaphylactoid reactions[1-4.]

Here we report a rare occurrence of skin necrosis after the administration of heparin sodium intravenous injection.

CASE REPORT

A 35Y old female patient weighing 67kg was admitted to gastroenterology department for presenting with pain in abdomen for 12 days. On examination, the patient was shown to be conscious and well oriented with tenderness in left epigastrium and hypochondria. The laboratory test reports of CT Pancreas showed the presence of thrombosis in splenic vein and multiple collateral vessels in abdomen. The hemoglobin in blood was 12g/dl.

Lab Test	Day 5	Day 6	Day 7
INR	1.11	1.00	1.00
APTT	65s	35s	74s
Pro thrombin Time	15s	14s	14s

She was prescribed with Tramadol 50mg tablet every 8th hourly from days 1 to 9, Bisacodyl 5mg tablet2hs on day1, Polyethylene glycol powder has stat on day1, Aspirin150mg tablet every 24hours on days 2-5, Heparin 6000u iv every 6th hourly on days 4-8, Warfarin 2mg tablet od at 4pm on day 5, Warfarin 4mg tablet od at 4pm on days 6 to 9, Warfarin 5mg tablet od at 4pm on day 10.

On the days of therapy she developed skin necrosis in various body parts, especially in hands (forearm). Erythematous subcutaneous lesion with skin oedema and pain was the first symptoms, then on day 5 that is converted to necrosis of the skin. This is suspected to be the adverse reaction of Heparin as it has a very high incident rate. The drug was immediately withdrawn,and the patient got relief from the symptoms.

The causality of the event, assessed as per WHO-UMC system for standard case causality assessment criteria can be considered as probable. Analyzed by Naranjo's ADR probability scale6 the score was 7, which also make it a probable adverse drug reaction.

DISCUSSION

There have been many adverse drug reaction reported with Heparin injection. Reported adverse reaction includes ecchymoses, itching and burning, elevation of serum AST and ALT levels, suppression of renal function, transient alopecia, headache, chest pain, hypertension, arthralgia, white clot syndrome, allergic vasospatic reactions, hematoma, ulceration, cutaneous and subcutaneous necrosis, Osteoporosis and spontaneous fractures of the vertebral column,hypersensitivity reactions, anaphylactoid reactions including shock.[1-4]

Here in this patient the first symptom of the localized skin necrosis were erythematous subcutaneous lesion with oedema and pain and this was severe on the arm. The proposed mechanism which induces skin necrosis by Heparin are, immunologically mediated aggregation of platelets or an arthus-type reaction due to formation of antigen-antibody complexes in cutaneous blood vesselsor an incorrect technique of injection[9].

The condition is managed with the withdrawal of the drug and the patient got relief from the symptoms.Discontinuance of the heparin injections promptly leads to recovery. Wound care involves cleaning and dressing the areas of skin loss, with appropriate pain relief.If anticoagulation is still required for the patient for his condition, then an alternative drug should be used, and this may include aspirin, warfarin, hirudins, or unfractionated heparin, depending on the cause of the heparin necrosis[8].

A similar case was reported by Manousos-GeorgiosPramateftakis that is skin necrosis induced by subcutaneous administration of nadroparine in a 53 Year old female.According to the report she underwent a high anterior resection and she received pre- and postoperative antithrombotic prophylaxis with subcutaneous nadroparine on a daily basis. On the 6th and 7th postoperative days, two skin necroses occurred at two injection sites[10].

The drug was reported for thrombocytopenia in a 65 year old woman after prosthetic knee replacement.[6] A case on hyperkalemia induced by Heparin was also reported in a 55 year old Asian woman presented with unstable angina, hypercholesterolemia, hypertension and had a history of anterior myocardial infarction 9 months ago. It was observed during a low dose heparin infusion as prophylaxis for balloon pump and the patient was having increased potassium level 71µmol/L.[7] The drug was also reported for cerebral venous thrombosis due to Heparin induced thrombocytopenia in a 63 year old woman who presented with Polycythemia Vera. The patient was treated with Heparin for superficial septic thrombophlebitis, developed heparin induced thrombocytopenia and cerebral venous thrombosis with superior sagittal sinus occlusion 11 days after the institution of heparin therapy.[8]

CONCLUSION

Heparin induced Skin necrosis is rare but potentially devastating. Heparin is a powerful and instantaneously acting anticoagulant used for prevention and treatment of thromboembolic diseases and doctors

prescribing them should be aware of the condition, as failure to recognize it may increase morbidity and early recognition of the condition is vital as continued treatment with heparin may precipitate life-threatening complications in other organ systems.

Fig. I: Appearance of skin necrosis on the 5th day of Heparin administration

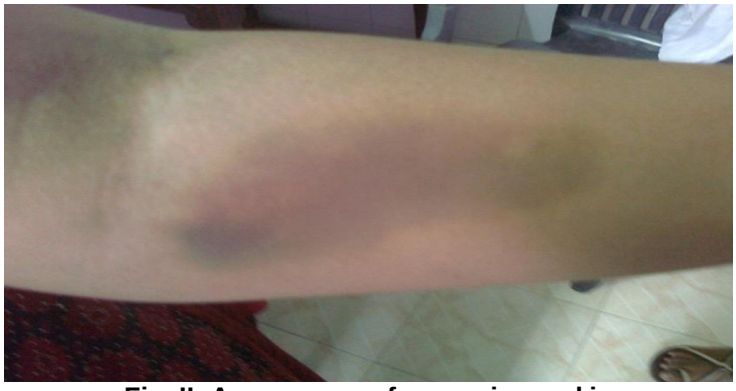

Fig. II: Appearance of necrosis on skin

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