Successful heparin desensitization after anaphylactic shock due to heparin

Neriman Defne ALTINTAŞ[1], Melda AYBAR TÜRKOĞLU[1], Bülent BOZKURT[2], Arzu TOPELİ İSKİT[1], Gül KARAKAYA[2], A. Fuat KALYONCU[2]

[1] Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Yoğun Bakım Ünitesi, Ankara
[2] Hacettepe Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Erişkin Allerji Ünitesi, Ankara.

ÖZET

Heparine bağlı anafilaktik şok sonrası başarılı heparin desensitizasyonu

Bu çalışmada, düşük moleküler ağırlıklı heparine bağlı gelişen anafilaktik reaksiyon sonrasında başarılı olmuş bir desensitizasyon protokolü sunulmaktadır. Çoklu ilaç allerjisi ve astımı bilinen 72 yaşındaki bir kadın hasta akut böbrek yetmezliği ile hastaneye kabul edilmişti. Hemodiyaliz seansı sırasında düşük moleküler ağırlıklı heparin ile anafilaktik reaksiyon gelişti. Periton diyalizi yapılamadı. Warfarin ile antikoagülasyon yapılması uygun bir seçenek değildi, diğer antikoagülanlar ise piyasada mevcut değildi. Bu nedenle bir desensitizasyon protokolü planlanarak uygulandı. Seyreltilmiş heparin dozları artırılarak (0.1'den 5000 üniteye), 15 dakikalık aralarla intravenöz olarak uygulandı ve işlemden 8 saat önce desensitizasyon şeması tamamlandı. Bu şekilde, daha sonraki diyaliz seanslarında reaksiyon gelişmeden intravenöz heparin kullanılabildi. Naranjo olasılık skalası bu hastada nadroparine bağlı bir yan etki olasılığına işaret etmektedir. Düşük moleküler ağırlıklı heparinlere bağlı anafilaktik reaksiyon nadiren bildirilmektedir. Olgu, elimizdeki veriler ışığında başarılı heparin desensitizasyonu uygulanmış üçüncü olgudur. Diğer antikoagülanlara ulaşılmadığında ve antikoagülasyondan vazgeçilemediğinde heparin desensitizasyonu bir seçenek olabilir.

Anahtar Kelimeler: *Heparin, anafilaksi, desensitizasyon, hemodiyaliz, düşük moleküler ağırlıklı heparin.*

SUMMARY

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Yazışma Adresi (Address for Correspondence):

Dr. Neriman Defne ALTINTAŞ, Hacettepe Üniversitesi Tıp Fakültesi,
İç Hastalıkları Anabilim Dalı, Yoğun Bakım Ünitesi, Sıhhiye 06100
ANKARA - TURKEY

e-mail: defne98hac@yahoo.com

[1] Medical Intensive Care Unit, Department of Internal Medicine, Faculty of Medicine, Hacettepe University Ankara, Turkey,
[2] Adult Allergy Unit, Department of Chest Diseases, Faculty of Medicine, Hacettepe University, Ankara, Turkey.

A successful desensitization protocol in a patient with low molecular weight heparin induced anaphylactic reaction is being presented. A 72-years-old patient who was known to have multiple drug allergies and asthma was admitted with acute renal insufficiency. She had an anaphylactic reaction with a low molecular weight heparin during a hemodialysis session. Peritoneal dialysis was not feasable. Anticoagulation with warfarin was not considered appropriate; alternative anticoagulants were not available. Therefore a desentization protocol was planned and applied, comprising of IV administration of diluted heparin by gradually increasing doses (0.1 to 5000 units), at 15 minute intervals, completing 8 hours before the procedure. By this way, IV heparin could be administered during the subsequent hemodialysis sessions with no reactions. The Naranjo probability scale revealed a probable adverse reaction associated with nadroparin for this patient. Anaphylactic reaction to low molecular weight heparins is reported rarely in the literature. To the best of our knowledge, this is the third case of successful heparin desensitization. When other anticoagulants are not available and anticoagulation is indispensible, heparin desensitization can be an option.

Key Words: *Heparin, anaphylaxis, desensitization, hemodialysis, low molecular weight heparin.*

Heparin is commonly used for anticoagulation of thromboembolic patients, hemodialysis patients and cardiac and arterial surgery patients. Although, most commonly observed side effect is bleeding, immune mediated reactions like heparin-associated thrombocytopenia, skin necrosis and eczema can also frequently occur (1). Heparin induced acute hypersensitivity reactions and anaphylaxis are rarely reported. There have been recent reports of heparin related allergic reactions, and ways to manage patients with heparin allergies (1-6). Low molecular weight heparins (LMWH) were even less frequently reported to be allergic (5-8). We are presenting a case of anaphylactic reaction due to LMWH administered during a hemodialysis session and the successful heparin desensitization of the patient.

CASE REPORT

A 72-years-old woman was admitted to the hospital with acute renal insufficiency with the tentative diagnosis of rapidly progressive glomerulonephritis. She had perennial allergic rhinitis and conjunctivitis since 50 years. She was diagnosed with asthma 15 years ago. She was known to have allergies to multiple drugs and food additives. She had history of skin rash with acetylsalicylate; angioedema with an antitussive preparation (ephedrin and guaifenesin) and famotidine on separate occasions; bronchospasm with clopidogrel and a test dose of verapamil on separate occasions. She had tested positive for penicillin skin test. She did not report any new recent drugs. While the diagnostic tests were being performed for the cause of acute renal failure, hemodialysis was needed. She was administered her usual medications that included lansoprazole, salmeterol/fluticasone propionate combination inhaler, montelukast, budesonide/formoterol combination inhaler and amino acid supplements. Hemodialysis sessions were started without anticoagulation in an attempt to minimize medications administered, but due to persistent clotting, anticoagulation was needed. Starting from the fourth hemodialysis session, LMWHs which are known to be less allergenic were used. They were administered only during the hemodialysis which was performed every other day. In the third hemodialysis session with anticoagulation (7^{th} day after start of therapy), within minutes after IV nadroparin calcium (Fraxiparine®, Glaxosmithkline) administration, the patient had severe bronchospasm and shock necessitating mechanical ventilation, and subsequently myocardial infarction. High dose steroids, intravenous fluids and vasopressors were administered. She was promptly intubated and admitted to the intensive care unit with the diagnosis of severe bronchospasm, angioedema and acute myocardial infarction. Membrane hypersensitivity was

not considered since no reactions were observed during the previous hemodialysis sessions. The Naranjo probability scale revealed a probable adverse reaction associated with nadroparin for this patient with a score of 7 (9). Anticoagulant and antiaggregant treatment for myocardial infarction could not be administered because of her allergies. Thrombocyte count which was 326.000/mL upon admission to the hospital had decreased gradually to 110.000/mL. During her stay in the intensive care unit, marked thrombocytopenia developed over a few days, with levels as low as 34.000/mL. In the days following the incident, she still required hemodialysis and had to be anticoagulated, since hemodialysis without anticoagulation was ineffective due to clotting. Peritoneal dialysis was not an option because of a recent laparotomy. Anticoagulation with warfarin was not considered appropriate and alternative anticoagulants such as danaparoid were not available in Turkey.

There were two reported cases of successful heparin desensitization, one for coronary artery bypass surgery and one for aortic valve replacement (2,3). A scheme was planned based on the protocol used in the latter one, and applied 10 days after the incident, after informed consent was obtained. The desensitization protocol comprised of IV administration of diluted heparin by gradually increasing doses, at 15 minute intervals, completed 8 hours before the dialysis (Table 1). Seven hours before the hemodialysis session 40 mg prednisolone, one hour before the session 40 mg prednisolone, 50 mg ranitidine and 50 mg pheniramin IV were administered. After the first session of hemodialysis after desensitization ranitidine and pheniramin were discontinued. However 40 mg/day prednisolone was continued because of bronchospasm. Heparin was administered (5000 units bid SC) daily, even when the patient did not have a hemodialysis session. By this way, IV heparin could be administered during the subsequent hemodialysis sessions with no reactions. However, the patient was lost a month later because of sepsis.

DISCUSSION

Heparin is a mucopolysaccharide that may cause different immunologic reactions such as urticaria, asthma, anaphylaxis, delayed cutaneous eruptions, and heparin associated thrombocytopenia type II, which is mediated by IgG formed against platelet factor 4 (PF4) and is modified by heparin (4). Type I thrombocytopenia, commonly observed with heparin administration, is not immunologically mediated, is mild and reverts upon discontinuation of the drug. Delayed cutaneous reactions may be observed and are related to skin eruptions at injection sites. Although this type of reactions are reported less frequently with LMWH, it is well known that they cross react with heparin. After any type of a reaction, replacement of heparin therapy with other anticoagulants (other than LMWH, such as warfarin, danaparoid) is recommended (1,4). However oral anticoagulation is not feasible for hemodialysis patients and cardiopulmonary bypass surgery patients.

Multiple drug allergy syndrome is defined as presence of hypersensitivity reactions with multiple different classes of drugs. The presence of this condition is known to create a tendency for future hypersensitivity reactions. Since the patient had a history of reactions with acetylsalicylate, clopidogrel, famotidine, penicillin and verapamil; heparin sensitivity might have been a part of this syndrome.

Since a hypersensitivity reaction with any drug was possible for this patient, LMWH, which se-

Table 1. Heparin desensitization scheme.

Time to HD*	45´	30´	15´	-12 hrs	45´	30´	15´	-11 hrs	45´	30´
Heparin (units)	0.1	0.1	0.2	0.4	0.8	1	2	4	8	10
Time to HD*	15´	-10 hrs	45´	30´	15´	-9 hrs	45´	30´	15´	-8 hrs
Heparin (units)	20	40	80	100	200	400	800	1000	2000	5000

* Time left to hemodialysis session; heparin administration ends 8 hours before the hemodialysis session.

ems to be less allergenic was preferred for anticoagulation. Yet an anaphylactic shock was observed within 2 minutes after administration of the drug for the third time. There was a report of four pregnant patients with severe reactions to IV heparin and the authors suggested heparin induced thrombocytopenia might predict a severe reaction (5). As well, acute cardiorespiratory reactions have been defined in patients, who were not atopic, with heparin-induced thrombocytopenia (10,11). In those patients, eosinophilia and IgE antibodies to heparin were missing, but ELISA test for antibodies to PF4 was positive. It was postulated that antibodies to PF4 could cross-react with PF4 bound to pulmonary endothelial cells and directly activate microvascular endothelial cells. Another mechanism could be temporary blocking of pulmonary microvasculature by platelet aggregates (11). What ever the mechanism is, this potentially fatal complication can be prevented, if heparin associated thrombocytopenia is timely diagnosed and therapy is discontinued.

Our patient had decreasing platelet counts over the few days (320.000/mL to 171.000/mL) but was not thrombocytopenic at the time of the event. There was a dramatic decrease in the platelet count after the incident. Tendency in the platelets to decrease might have been a clue for the immunologic process, but the lack of clinical signs of thrombosis and clinically insignificant decrease in the number led to the assumption that this might be a type I thrombocytopenia prior to the event. However, after the incident considering the clinical progress, this could as well have been an immunologically mediated process.

Naranjo probability scale is frequently used to assess whether an adverse event during drug administration is related to a drug (9). It consists of ten questions related to previous reports of the reaction, time relation of the event with the drug, drug causality and presence of objective evidence. Presence of previous reports on this reaction, appearance of reaction after heparin administration and resolution after discontinuation, absence of alternative causes for the reaction, confirmation of the reaction with objective evidence confers a score of 7, which is interpreted as a probable drug reaction.

Clinically, diagnosis of heparin hypersensitivity can be confirmed by skin testing, in vitro testing, or a re-introduction test (5). However, skin testing is not reliable for predicting immediate-type hypersensitivity reactions (4,6). Additionally, skin testing was not considered, since the patient was on steroids throughout her stay in the intensive care unit, for treatment of concomitant asthma. Some in vitro studies such as lymphoblastic transformation, histamine release test can be performed. Yet, they gather supportive evidence, and are not considered diagnostic tools for heparin allergy. Berkun et al, had confirmed heparin allergy by measuring tryptase levels, which is proposed to be a reliable marker of human mast cell degranulation, by inadvertently reintroducing the drug during hemodialysis sessions and by skin testing in their case series (1). Tryptase testing was not available to us at the time, so it could not be performed. Re-introduction test that is suggested for milder allergic reactions was not appropriate for our patient. Diagnosis was made based on the clinical grounds only. Therefore allergy to the excipient could not be ruled out. Anaphylactoid side effects of hemodialysis are well recognized, as well anaphylactic reactions during hemodialysis (12). One recent example is the recent warning issued by Centers for Disease Control and Prevention in the US, for increased incidences of acute allergic reactions among patients undergoing hemodialysis possibly related to multidose vials of heparin (13). However, a hemodialysis related hypersensitivity reaction was not considered a possibility since no reactions were observed during the 5 prior hemodialysis sessions and the following sessions after heparin desensitization. Although the exact mechanism of acute drug desensitization is unclear, it results in decreased sensitivity. Acute desensitization is accomplished by administering very small amounts of antigen at short intervals (15 min) and gradually increasing the dose. Antigen-IgE complexes are formed but at too small amounts to cause a clinically significant reaction. A refractory period is produced during which the drug can be administered. But after a period of days to weeks the hypersensitivity is restored if drug administration

is discontinued. This was also why we continued the heparin doses even if the patient did not have a dialysis session. On the other hand, chronic desensitization involves long term administration of antigen to produce IgG blocking antibodies to prevent antigens from reaching IgE on mast cells. Acute desensitization was preferred for our patient since the condition was urgent (14).

Patriarca et al, had reported the first acute rapid heparin desensitization in a 55-years-old patient with mitral stenosis and insufficiency, and tricuspid and aortic insufficiency who had urticaria with heparin treatment (15). A pseudoallergic intolerance was diagnosed, because skin testing was negative. Since a mitral valve replacement surgery with the extracorporeal circulation method was planned, a heparin rush desensitization together with antihistaminics were administered. After which the surgery was performed and heparin administered with no reactions.

Berkun et al, had reported successful use of danaparoid in an end-stage renal failure patient, who needed hemodialysis but was allergic to heparin (1). Al-Eryani et al, has reported successful heparin desensitization after heparin-induced shock in a patient with unstable angina before coronary bypass surgery (2).

There was a recent report of a heparin desensitization in a patient requring cardiopulmonary bypass for aortic valve replacement (3). He was a hemodialysis patient who had to start peritoneal dialysis because of heparin allergy. A total of 10.000 units of heparin was administered over a 5 hour period, with pretreatment with steroids and antihistaminics prior to the surgery. Subsequently heparin could be administered and the surgery was completed uneventfully. Since other anticoagulants were not available, a desensitization program based on this scheme was planned for our patient and completed uneventfully.

In conclusion, anaphylactic reactions, although very rare, can occur with LMWH. Upon such a serious adverse reaction withdrawal of the therapy and use of alternative anticoagulants is the safest choice. Yet when the use of heparin is indispensable heparin desensitization may become an option. To the best of our knowledge, this case is the third reported case of successful heparin desensitization.

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