Heparin-Induced Thrombocytopenia Association with Impaired Liver Function Tests

Bozulmuş Karaciğer Fonksiyon Testleri ile Heparine Bağlı Trombositopeni Birlikteliği

Heparin-Induced Thrombocytopenia

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Özet

Heparine bağlı trombositopeni son derece prokoagülan bir hastalıktır ve önemli morbidite ve mortalite taşımaktadır. Bununla birlikte, serum transaminaz yüksekliği karakteristik olarak asemptomatiktir ve tedavinin sonlandırılması ile tersine çevrilebilir. Heparine bağlı ciddi karaciğer zararı rapor edilmemiştir fakat hepatosit nekrozu ile beraber ciddi karaciğer hasarı potansiyeli olduğu için karaciğer fonksiyonları yakından izlenmelidir. Bu vaka takdiminde, pulmoner arter bantlama prosedürü sonrasında sol alt ekstremitede arteriyel tromboz gelişen, bir yaşında bir erkek hasta sunmaktayız. Olgumuz antikoagülasyon için fraksiyone olmayan heparin almaktaydı. Heparin tedavisinin üçüncü gününde, rutin kan tahlillerinde hepatik fonksiyon testlerinde bozulma ve trombositopeni saptandı. Standart heparin tedavisi kesildi ve arteriyel tromboz terapötik dozda düşük molekül ağırlıklı heparin ile tedavi edildi. Trombosit sayımı ve karaciğer fonksiyon testleri 2 hafta sonra normale geldi.

Anahtar Kelimeler

Heparine Bağlı Trombositopeni; Karaciğer Hasarı; Arteriyel Tromboz; Çocuk

Abstract

Heparin-induced thrombocytopenia is an intensely procoagulant disorder and carries significant morbidity and mortality. However, the elevations in serum aminotransferases are characteristically asymptomatic and reversible with treatment termination. The serious liver injury due to heparins has not been reported but liver function should be monitored closely since potential severe liver damage with hepatocyte necrosis can occur. In this case report, we present a one-year-old male patient who developed a left lower extremity arterial thrombosis following an pulmonary artery banding procedure. Our case was taking unfractionated heparin for anticoagulation. On the third day of heparin therapy, routine blood analysis revealed deranged hepatic function tests and thrombocytopenia. Unfractionated heparin treatment was discontinued and he was treated with therapeutic doses of low-molecular-weight heparin for arterial thrombosis. His platelet count and liver function tests had normalised 2 weeks later.

Keywords

Heparin-Induced Thrombocytopenia; Liver Damage; Arterial Thrombosis; Children

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Introduction

Unfractionated heparin (UFH) is the traditional anticoagulants used for the prevention and treatment of thromboembolic disease. It is an indirect thrombin inhibitor [1]. Heparin-induced elevations in serum aminotransferases is characteristically asymptomatic and reverse with continued treatment. However, heparin-induced thrombocytopenia is a potentially devastating complication of heparin therapy [2,3]. The best of our knowledge, there are no reported articles on cases of concurrent elevations in serum aminotransferases and thrombocytopenia associated with UFH in children and adolescents. In this report, a one-year-old boy presented with elevations in serum aminotransferases and thrombocytopenia which had been reported to be very rarely seen.

Case Report

A one-year-old, 7-kg boy with secundum atrial septal defect, perimembranous ventricular septal defect and severe pulmonary hypertension underwent pulmonary artery banding procedure. He had left femoral arterial and venous catheters. On the third day of surgery, the developed pallor and loss of pulse his left leg and foot.

He was alert, blood pressure was 90/55 mmHg, body temperature was 36,7°C, heart rate was 118 beats/min , respiratory rate was 42 breaths/min and oxygen saturation was 94%. His breath sounds were normal. Thrombus formation was noted observed in the evaluation of echocardiography. Chest radiographs showed mild cardiomegaly without congestion. Color Doppler ultrasonography (CDU) of the symptomatic leg (left leg) demonstrated no significant colour flow within the common femoral artery, popliteal artery, posterior tibial artery, dorsalis pedis artery, whereas spectral Doppler ultrasonography showed minimal flow within these arteries. Left lower extremity venous CDU were normal. Doppler ultrasonography confirmed a left lower extremity arterial thrombosis. Initial laboratory tests revealed a white blood cell count of 7.680 cells/mL, hemoglobin 12.7 g/dl, platelet count of 240.000 cells/mL, International Normalized Ration (INR) value 1.2 (normal range:1–1.5), and an activated partial thromboplastin time (aPTT) value of 35 s (normal range: 20–40 s). Routine blood biochemistry tests were normal. The thrombus was probably associated with arterial catheter. Treatment with UFH was initiated (70 units/kg intravenous bolus, 20 units/kg per hour continuous infusion, goal aPTT is 60–80 s). Three days after the patient's initial admission and first exposure to heparin, his platelet count had dropped from a baseline of 240.000 to 30.000 cells/mL. Platelet counts for the patient are illustrated in Table 1. There were no other possible causes of the thrombocytopenia. The same time, he was detected to have derangement in liver function tests (LFT). Liver function tests are listed in Table 2. No another drugs known to elevate LFT were given before and after cardiac surgery and all other diagnostic evaluations for liver damage, including viral hepatitis tests and were negative. Ultrasound of the liver was normal. Also, the previous liver function tests from treatment of UFH were normal. Unfractionated heparin was then suspected to be the cause of the derangement in LFT and thrombocytopenia. Therefore, it was stopped. Color Doppler ultrasonography of the left lower extremity show that the disorder was continued. Subcutaneous enoxaparin 0.5 mg/kg every 12 hours was commenced. His LFT and thrombocytopenia started to improve five days after UFH was stopped. The patient was treated with subcutaneous enoxaparin for two weeks. Color Doppler ultrasonography of the left lower extremity was normal on the twelve day of therapy enoksiparin. The LFT and platelet count slowly improved and returned to normal over a period of two weeks.

Table 1. Platelet Counts of the Patient

	PLT (cells/mL)
Baseline PLT (cells/mL)	240.000
PLT 3 Days after UFH Treatment	30.000
PLT 24 h after Stopping UFH	42.000
PLT 1 Week after Stopping UFH	97.000
PLT 2 Week after Stopping UFH	281.000

PLT: Platelet counts

Discussion

Central venous and arterial catheters (CVAC) are used in critically ill children and in children with chronic diseases for the administration of fluids, medications, total parenteral nutrition or blood products. But, despite their many benefits, CVACs are not innocuous and are associated with important complications [4]. Arterial and venous thromboembolism are significant because they are difficult to detect, increase the cost of care, and are potentially life-threatening adverse events [5]. The main stays of anticoagulant therapy for children with thrombus are UFH, low molecular weight heparin, and warfarin. Unfractionated heparin is often the anticoagulant of choice in children because of its efficacy, reversibility, ease of monitoring and clinical experience is extensive [6]. Also, we started initially UFH to our patient. The UFH doses are age dependent,with infants (up to 2 months corrected for gestational age) having the highest requirements (average 28 U/kg/h) and children over 1 year of age having lower requirements (average 20U/kg/h) [3,6].

The major complications of UFH therapy are thrombocytopenia,

Table 2. Serial Liver Function of the Patient

LFT	Baseline LFT	LFT 3 Days after UFH Treatment	LFT 24 h after Stopping UFH	LFT 1 Week after Stopping UFH	LFT 2 Week after Stopping UFH
AST (U/L)	32	10600	2466	197	39
ALT (U/L)	46	7580	5140	1446	39
ALP (U/L	101	112			107
GGT (U/L)	61	121	83		64
LDH (U/L)	214	497	304		221
Total bilirubin (mg/dl)	1.2	1.3			1.2

LFT, liver function tests; AST, aspartate transferase; ALT, alanine transferase; ALP, alkaline phosphatase; GGT, glutamyl transpeptidase; LDH, lactate dehydrogenase; UFH, unfractionated heparin.

bleeding, osteoporosis, elevations in serum aminotransferases, skin necrosis and skin lesions [1,7]. Heparin-induced thrombocytopenia (HIT) is a life-threatening, severe, immunological drug reaction that carries a high risk of morbidity and mortality. The frequency is reported to be 2.3% to 3.7% with a 1% to 3% prevalence in children undergoing cardiac surgery with the use of UFH [3]. It is generally suspected in cases of unexplained acute thrombocytopenia; generally more than 50% fall in absolute platelet count from the baseline, in a patient that has been on heparin for 4–14 days. The diagnosis of HIT initially is clinical. The awareness of the syndrome is necessary to suggest HIT in cases of unexplained thrombocytopenia during heparin exposure [3]. We have excluded other causes of thrombocytopenia and the patients was defined as HIT. Drug-induced liver injury is a major concern for the physicians. Almost one thousand medicines used in clinical practice have been shown to induce hepatotoxicity. in medical literature. Several medication are lipophilic substances and their transformation into hydrophilic compounds by the cytochrome P-450 system results in production of toxic metabolites. The necrotic death follows antioxidant consumption and oxidation of intracellular proteins, which determine increased permeability of mitochondrial membranes, loss of potential, decreased ATP synthesis, inhibition of calcium-dependent ATPase, reduced capability to sequester calcium within mitochondria, and membrane bleb formation. The activation of nucleases and energetic participation of mitochondria are the main intracellular mechanisms that lead to apoptosis. Non-parenchymal hepatic cells are inducers of hepatocellular injury and targets for damage [8]. The exact pathogenesis of distorted liver function tests induced by heparin is so far unknown. The serious liver injury due to heparins has not been reported. It is characteristically asymptomatic and reverse with continued treatment [2,9]. Unfractionated heparin-associated hepatotoxicity is generally detected within the first week of therapy and resolves upon discontinuation of the offending agent. In our patient, the aminotransferase elevation was beginning at 3 days after the initiation of dosing UFH treatment and ıt was returning to normal values within 2 week of discontinuing treatment of UFH. But, some studies showed drug-induced toxic centrilobular hepatocellular balloon degeneration in a patient with high liver enzymes (>3000 U/L) [10,11]. Therefore, should be noted that develop toxic liver necrosis in patients with liver enzymes especially more than 3000 U/L.

In conclusion, anticoagulation therapy in the hospital is widespread and many patients will be exposed to heparin at some time during their hospitalization. Unfractionated heparin is used ubiquitously for the treatment and prevention of thrombosis. However, proper medication use requires an understanding of the medication's indications and side effects.

Competing interests

The authors declare that they have no competing interests.

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