An unusual case of enoxaparin induced thrombocytopenia in intensive care unit

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OBJECTIVES: *To present a case of heparin induced thrombocytopenia in a patient treated with enoxaparin.*
METHODS: *A case of heparin-induced thrombocytopenia was examinated with a detailed platelet count analysis over the time and with detection of platelets antibodies.*
RESULTS: *The detection of platelet antobodies and the recovery of platelet count after cessation of enoxaparin strongly support the diagnosis of heparin-induced thrombocytopenia (HIT).*
CONCLUSION: *HIT is a severe side effects of heparin administration. It is more frequent in patients treated with unfractionated heparin however can also be induced by low molecular weight heparin. Guideline suggests the cessation of heparin administration and the treatment of patients with fondaparinux.*

KEY WORDS: Enoxaparin, Heparin induced thrombocytopenia, Thrombocytopenia

Introduction

Evidence-based guidelines recommend that heparin-induced thrombocytopenia (HIT) should be suspected whenever a patient in Intensive Care Unit (ICU) develops thrombocytopenia or thrombosis 5 to 14 days after heparin initiation [1,2]. HIT is one of the most important adverse drugs events in intensive care patients [3,4]. It is a life- and limb-threatening immune-mediated, prothrombotic complication that occurs with unfractionated heparin (UFH), rarely with low-molecular-weight heparin (LMWH) and in patients treated with fondaparinux [5,6].
HIT must be distinguished from other causes of platelet count reduction as it often induces new thrombosis. We report an unusual case of suspected heparin-induced thrombocytopenia and thrombosis (HIT/HITT) resulting in acute profound thrombocytopenia occurring in a women with duodenum resection treated with enoxaparin.

Case Report

HISTORY

A 63-year-old woman, with a medical history of schizophrenia undergoing effective medical treatment with olanzapine, was brought to a medical ICU two days after partial duodenum resection due to the presence of a benign neoplasm, because of worsening respiratory failure in an underlying severe pancreatitis (Table I).

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TABLE I - *Lipase and amylase values expressed in U/l over a 7 day period (day 0 is pre-operative, on day 3 the patient was transferred to ICU).*

Days	0	1	2	3	4	5	6	7
Lipase	22	2512	1656	413	169	57	46	n.a.
Amylase	31	2407	2569	1506	963	232	158	105

Orotracheal intubation and positive pressure mechanical ventilation was necessary as pulmonary oedema compromised respiratory gas exchange and a newly documented atrial fibrillation worsened hypotension.
On the eighth day of ICU stay as pancreatitis improved thank to the ongoing somatostatin continuous infusion a new respiratory and hemodynamic equilibrium was achieved the patient was ready to be weaned by mechanical ventilation and transferred to the surgical ward but platelet count started to decrease at a steady rate.

INVESTIGATION

Common causes of platelet reduction were examined: sepsis, wasting (such as DIC or spleen trapping), bone marrow aplasia were ruled out.
A prophylactic anticoagulant regimen had been established soon after the operation, almost ten days earlier, with sodium enoxaparin 4000 IU one daily while no UH had been employed on the patient. Fig. 1 shows platelet count over 12 days of hospital stay. Enoxaparin was switched to fondaparinux 2.5 mg once daily with a prompt platelet count normalization over the next four days.
We tested anti platelet antibodies by using a commercial immunoassay Eliza test (Asserachrom H PF4 ELISA kits, Diagnostica STAGO, Milan, Italy) [2,4]. Anti-platelet antibodies, IgM and IgG, were both positive on the eleventh day of hospital stay, with the latter being only mildly significant. Anti-platelet factor 4 antibodies were screened after 3 months and no evidence of such alteration was found.
After 60 days of ICU stay, due to the emergence of numerous co-pathologies connected to pancreatitis that required intensive treatment, the patient was transferred to a surgical ward and no platelet count deflection was reported.

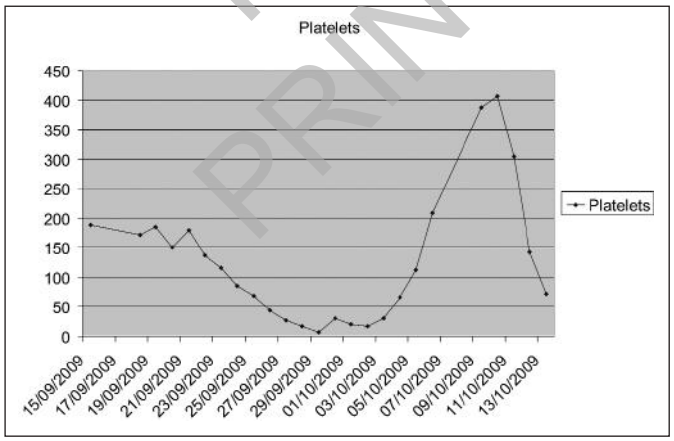

Fig. 1: Platet count over 12 days of hospital stay, on day 10 enoxaparin was switched to fondaparinux.

Discussion

Many studies demonstrate an inverse relationship between thrombocytopenia, less than 150x109/l, and mortality [7,8]. Thrombocytopenia occurs in 15% to 58% of ICU patients. The incidence varies based on the patient population, the timing of measurement, and the definition of thrombocytopenia. Thrombocytopenia occurring in the ICU is frequently multifactorial, creating challenges in assessment of the cause [9]. In the present case report we rule out all causes of thrombocytopenia i.e. sepsis and we explore the possibility of HIT. The occurrence of severe thrombocytopenia in patients treated with heparin raises several diagnostic possibilities, some of which are potentially associated with thrombotic complications, i.e. HIT [10]. The management of patients who develop thrombocytopenia while requiring heparin presents a double-edged challenge. On one side, HIT should be seriously considered, and patients should be appropriately protected against thromboembolic complications until the diagnosis has been ruled out [1]. In contrast, bleeding is frequent and adversely affects mortality [11]. HIT is an immune-mediated adverse drug reaction that occurs following exposure to UH or LMWH. Whether UFH causes HIT more often than LMWH is controversial [5,12,13].
The most clinically significant form of HIT is type II, caused by IgG antibodies directed against a complex of heparin and platelet factor 4 (PF4). The onset of thrombocytopenia following heparin administration usually occurs 5–10 days after the initial exposure to heparin, however it could varies depending on patient's prior exposure [4]. A rapid reduction of platelet plasmatic levels, often within hours, can occur in patients with a recent exposure to heparin and with high levels of PF4-heparin antibodies.
Relevant data were extracted from the ED charts of 134 patients with venous or arterial thrombosis. Documentation (i.e., notation of positive or negative findings) existed for recent heparin exposure in 7 (5.2%) of 134 charts, recent hospitalization in 33 (24.6%), history of thrombocytopenia in 0 (0%), and history of thrombosis in 62 (45.5%). Of 35 patients administered heparin in the ED, the pre-heparin platelet count was available for 19 (54.3%) and old records for 5 (14.3%). Thus, HIT risk assessment frequently remains undocu-

mented for ED patients with thrombosis, including those administered heparin. [14].

The major limitation of the study was that platelet aggregation test was not performed.It is well known that platelets antibodies test have high sensitivity but a low specificity in diagnosing HIT. Platelet activation assays that use "washed" platelets, such as the serotonin release assay and the heparin-induced platelet activation assay, exclusively detect platelet-activating IgG antibodies [15].

These tests have a much higher specificity for detecting clinically relevant antibodies than the commercially available antigen assays. However, performance of these functional assays requires experienced staff and is restricted to a few reference laboratories [15,16].

The antigen assays such as the PF4- dependent enzyme-linked immunoassays (ELISA) that we used in this case are very sensitive for detecting all antibody classes (IgG, IgA, IgM) but are less specific than functional assays for detecting clinically active antibodies [16].

However HIT is a clinicopathologic syndrome; and the diagnosis is based on one or more clinically evident features (most often, thrombocytopenia with or without thrombosis) and the detection of anti- PF4/heparin antibodies with platelet activating properties. In the present case we found anti-platelets antibodies, this feature together with the recovery of platelets count after the cessation of enoxaparin and the switch to fondaparinux strongly support the diagnosis of HIT. Approaches to increase HIT awareness and facilitate HIT risk assessment and documentation in ICU may be needed.

Riassunto

Scopo dell'articolo è la presentazione di un caso di trombocitopenia indotto dall'eparina in un paziente trattato con enoxaparine. L'osservazione in questione è stata analizzata in dettaglio con ripetute conta delle piastrine e con l'individuazione di anticorpi antipiastrine.

La scoperta degli anticorpi-antipiastrine ed il restauro della conta piastrinica dopo la cessazione della somministrazione dell'enoxaparina è alla base della diagnosi di trombocitopenia indotta dall'eparina.

Questo tipo di trombocitopenia è un grave effetto collaterale della somministrazione di eparina, ed è più frequente nei pazienti trattati con eparina non frazionata, ma può comunque essere provocata dalla somministrazione di eparina a basso peso molecolare.

Le linee guida suggeriscono di sospendere la somministrazione di eparina e di trattare i pazienti con fondaparinux.

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