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ORIGINAL ARTICLE

# Management of liver transplantation in a patient with a history of heparin-induced thrombocytopenia

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## Summary

Heparin-induced thrombocytopenia (HIT) is an adverse immune-mediated drug reaction in which antibodies are generated usually towards complexes of the soluble platelet protein platelet-factor-4 (PF4) and heparin. The resulting immune complexes activate platelets intravascularly, which increases the generation of thrombin. Therefore, HIT is strongly associated with thrombosis and heparin is thought to be contraindicated. As HIT antibodies decline rapidly in titre, short-term re-exposure to heparin is feasible in special situations. We report an uneventful liver transplantation of a heparinized donor in a patient with a 20-month history of HIT. Before, 2, 5, 12 and 25 days after transplantation, the patient's blood was drawn for analysis of heparin-induced antibodies by a functional assay (HIPA) and by an antigen assay (PF4-heparin/ELISA). Lepirudin was used for postoperative anticoagulation. Apart from hepatic artery bleeding, the clinical course was uncomplicated, neither thrombocytopenia nor thromboembolic complications occurred. Weak heparin-induced platelet activation, caused by pre-existing HIT antibodies was detected before and 12 days after transplantation by the HIPA test; moreover borderline amounts of anti-PF4–heparin antibodies were found. Twenty months after an episode of HIT, a patient may receive an organ from a heparin-treated donor without risk of thrombocytopenia or thromboembolic complications. Avoidance of heparin for postoperative anticoagulation is recommended.

## Introduction

We report a female patient aged 37 years, who suffered from Budd-Chiari syndrome of unknown origin. About 2 months before hospital admission the patient noted oedema in both legs and felt abdominal tension. Hospital admission was necessary because of an acute deterioration of liver function, which was indicated by increased liver enzymes, prolonged prothrombin time, high serum bilirubin levels (185 μmol/l), ascites, hepatosplenomegaly and oesophageal varicosis. Two days after hospital admission Budd-Chiari syndrome was diagnosed by magnetic resonance imaging, which indicated a markedly reduced liver perfusion and a missing regular flow signal in the central veins of the liver.

In hospital the patient received unfractionated heparin for thrombosis prophylaxis and, unfortunately, developed heparin-induced thrombocytopenia (HIT). Platelet counts decreased from 353 000/μl to a minimum of 87 000/μl (Fig. 1) accompanied by severe headache, pain in the left lower limb and a cough. Thrombosis of the superior sagittal sinus and the left transverse sinus (day 16), venous thrombosis in the left lower limb (day 18), and pulmonary embolism (day 22) were objectively demonstrated by computed tomography, sonography and by perfusion scintigraphy respectively. HIT was confirmed by the

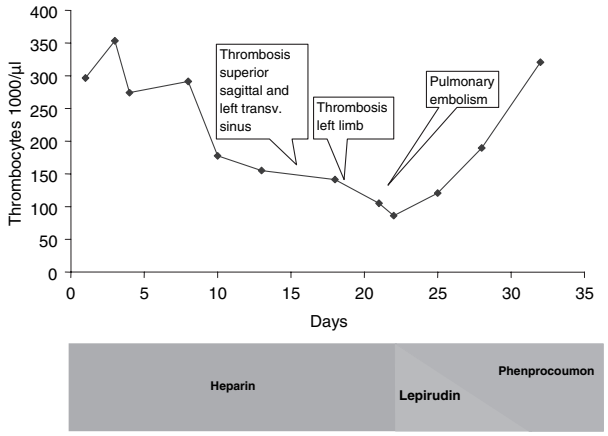


**Figure 1** A 37-year-old woman came to hospital with spontaneous Budd-Chiari syndrome. While receiving unfractionated heparin for thrombosis prophylaxis she developed heparin-induced thrombocytopenia (HIT) with multiple thromboembolic complications including sinus vein thrombosis. After switching anticoagulation to lepirudin, platelet counts increased rapidly and cerebral vessel perfusion normalized. The patient later developed liver failure and was scheduled for liver transplantation. Time course of platelet count during HIT. See text for clinical manifestations of HIT II.

heparin-induced platelet activation test (HIPA) and platelet-factor-4 (PF4)-heparin/ELISA (day 22). A change of the anticoagulatory therapy to i.v. lepirudin (initial bolus 20 mg, followed by 0.6–1.0 mg/h for 9 days) overlapping to phenprocoumon (started at day 22) resulted in normalization of platelet count and recanalization of the intracranial veins (day 26).

During the following months, liver function deteriorated (Child-Pugh A) and the patient was scheduled for elective, orthotopic liver transplantation about 3 months after the episode of HIT. HIT antibodies had not been tested during the following waiting time before liver transplantation. In a blood sample drawn immediately before transplantation no relevant amount of HIT antibodies could be detected (Table 1).

Twenty months after the episode of acute HIT, during June 2003, a compatible organ became available. During explantation of the liver, the donor had received a bolus of unfractionated heparin (25 000 IU) 9 min before clamping of liver vessels. The University of Wisconsin solution (Viaspan; Bristol-Myers Squibb, Brussels, Belgium) was used for organ preservation. Orthotopic transplantation was intraoperatively uncomplicated. The patient received packed red blood cells (3.3 l) and fresh frozen plasma (4.8 l). No enhanced clotting was observed. Before transplantation and 2, 5, 12 and 25 days after transplantation, blood was drawn for HIPA test and ELISA.

Six hours after transplantation lepirudin was started (bolus 0.1 mg/kg b.w., followed by 0.08–0.12 mg/kg b.w./h, adjusted to twofold prolongation of the normal laboratory aPTT). Two days after transplantation the patient had to be re-operated for hepatic artery bleeding. Eight days after transplantation phenprocoumon was started. Standard triple therapy immunosuppression was used with steroids (prednisolone), cyclosporin and mycophenolate mofetil. Liver enzymes normalized within 2 weeks. The patient was discharged from the intensive care unit 7 days after surgery and was discharged home at day 36. The course of platelet counts and HIT antibody test results are presented in Table 1.

## Discussion

Heparin-induced thrombocytopenia is an adverse immune-mediated drug reaction which is induced by an antigenic complex of heparin and PF4. Patients susceptible to HIT develop antibodies against these complexes. The resulting immune complexes cause intravascular platelet activation. Therefore, HIT is usually associated with a rapid decline of platelet counts starting typically from 5 to 14 days after start of heparin. The resulting microparticles catalyse the generation of thrombin. As a result, despite heparin treatment (generation of antigen) and low platelet counts (intravascular activation), patients are at a high risk of developing new thromboembolic complications.

Thrombosis in HIT is still associated with a mortality of about 10% with an equal number of patients being permanently disabled by amputation or stroke. The course of the patient during first admission with deep

**Table 1.** Laboratory results before (0), 2, 5, 12 and 25 days after liver transplantation.

| Day | AST (U/l) | ALT (U/l) | LDH (U/l) | Bilirubin (µmol/l) | Platelet count (1/µl) | HIPA | ELISA |
|---|---|---|---|---|---|---|---|
| 0 | 19 | 27 | 118 | 10.2 | 203 | + | 0.540 |
| 2 | 119 | 120 | 255 | 20.4 | 232 | Neg. | 0.347 |
| 5 | 72 | 143 | 218 | 20.4 | 223 | Neg. | 0.522 |
| 12 | 8 | 30 | 156 | 13.6 | 450 | + | 0.460 |
| 25 | 16 | 33 | 142 | 11.9 | 864 | Neg. | 0.497 |

Serum levels of aspartate transaminase (AST; U/l), alanin aminotransferase (ALT; U/l), lactate dehydrogenase (LDH, U/l) and bilirubin (µmol/l), platelet count (1/µl) and results of HIPA test (intensity of platelet activation, range from + to ++++) and PF4-heparin/ELISA (OD).

vein thrombosis and sinus vein thrombosis is a typical presentation of severe HIT.

In patients with acute HIT and circulating HIT antibodies, even small amounts of heparin such as line flushers or heparin-coated catheters can provoke the syndrome. Therefore, heparin has been thought to be contraindicated in patients with a history of HIT. Whereas there are alternative anticoagulants available, e.g. for thrombosis prophylaxis in these patients, in certain clinical scenarios such as liver transplantation in which the donor had been treated with heparin, heparin reexposure to the patient cannot be avoided.

The titre of HIT antibodies declines rapidly within a few weeks after cessation of heparin. After 100 days they are usually below the detection levels. After this time interval, patients with a history of HIT who are shortly re-exposed to heparin are usually not at risk of developing early-onset HIT (<5 days) [1,2].

Usually it lasts several days after boosting, until B cells produce sufficient amounts of antibodies relevant for inducing clinical HIT. Therefore, patients with a history of HIT have been successfully re-exposed to heparin during cardiopulmonary bypass surgery when HIT antibodies cannot be detected [3,4]. In fact, this procedure is currently considered to be the most appropriate approach in patients with a history of HIT requiring cardiopulmonary bypass surgery [5].

Recently, this concept has been expanded by re-exposing patients with a history of HIT >3 months to heparin in case of emergency cardiac surgery even without prior HIT antibody testing [6] and by re-exposing patients with weak HIT antibody titres (OD < 0.7) to heparin.

The present case demonstrates and expands the usefulness of this concept in a patient with liver transplantation.

According to standard protocol the organ donor was anticoagulated with heparin and a bolus of 400 IU heparin per kg body weight was given before organ explantation to avoid macrothrombi and microthrombi [7]. Although the portal vein was rinsed with an organ preservation solution, sufficient amounts of heparin might have remained, e.g. bound to the endothelial surface, to activate platelets and to induce intravascular thrombosis. In patients with HIT even small amounts of heparin as released from heparin-coated devices [8] used for blocking of peripheral catheters or administered with a prothrombin complex concentrate [9] are able to induce clinical complications. Therefore, in patients with a history of HIT who are scheduled for organ transplantation, a major concern is loss of the organ because of spontaneous clotting as has recently been described for a bone marrow preparation obtained from a patient with recent (<3 months) HIT to which heparin was added during the preparation process [10].

In the present case organ transplantation, however, was not complicated by HIT, because the titre of HIT antibodies had declined to a minimum within 20 months after the HIT episode, and the re-exposure to heparin was restricted to a short time period, i.e. the reperfusion of the transplant.

For anticoagulatory therapy and for thrombosis prophylaxis in patients with a history of HIT, heparin should be avoided and alternative anticoagulants such as danaparoid [11], lepirudin [12] and argatroban [13] should be used. However, for none of these new anticoagulants an antidote is available which limits their use in very high concentrations as needed during cardiopulmonary bypass surgery. In other situations, like in organ transplantation, no experience exists with these new drugs. In the present case, the reason for the Budd-Chiari syndrome could not be identified, implying an immanent risk of small venous thrombosis. Therefore, postoperative anticoagulation was initiated with lepirudin and continued with phenprocoumon.

The present case of liver transplantation in a patient with a history of HIT has three important implications:
**1** Similar to the experiences in heart surgery, a patient with a history of HIT, >3 months, can be re-exposed safely for a short period of time to heparin during organ transplantation.
**2** An organ, which is taken from a donor treated with heparin, can be transplanted safely to a patient with a history of HIT at least 3 months before transplantation.
**3** Very low titres of HIT antibodies (OD < 0.7 in the PF4-heparin/ELISA) or a long lag time (>35 min) in the HIPA test are not prohibitive for using a heparin-rinsed organ.

Patients with a history of HIT should therefore not be excluded from the waiting list, once the HIT antibody titres have fallen to a low level.

## References

1. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001; **344**: 1286.
2. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. *Chest* 2002; **122**: 37.
3. Pötzsch B, Klovekorn WP, Madlener K. Use of heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia. *N Engl J Med* 2000; **343**: 515.
4. Pötzsch B, Madlener K. Management of cardiopulmonary bypass anticoagulation in patients with heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-induced Thrombocytopenia*. New York: Marcel Dekker, 2003: 531–551.

5. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg* 2003; **76**: 2121.
6. Selleng S, Lubenow N, Wollert H-G, Mülleians B, Greinacher A. Emergency cardiopulmonary bypass in a bilaterally nephrectomized patient with a history of heparin-induced thrombocytopenia: successful reexposure to heparin. *Ann Thorac Surg* 2000; **71**: 1041.
7. Bodenham A, Park GR. Care of the multiple organ donor. *Intens Care Med* 1989; **15**: 340.
8. Laster JL, Nichols WK, Silver D. Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. *Arch Intern Med* 1989; **149**: 2285.
9. Bowers MJ, Jones FG. Thrombus in harvested marrow from a patient with recent heparin-induced thrombocytopenia. *Br J Haematol* 2002; **119**: 294.
10. Greinacher A, Michels I, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: the antibody is not heparin specific. *Thromb Haemost* 1992; **67**: 545.
11. Chong BH, Magnani HN. Danaparoid in heparin induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-induced Thrombocytopenia*. New York: Marcel Dekker, 2003: 371–396.
12. Greinacher A. Lepirudin in heparin induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-induced Thrombocytopenia*. New York: Marcel Dekker, 2003: 397–436.
13. Lewis BE, Hurstin M. Argatroban in heparin induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-induced Thrombocytopenia*. New York: Marcel Dekker, 2003: 437–474.