

TREATMENT OF VENOUS THROMBOEMBOLISM WITH ARGATROBAN IN A PATIENT WHO DEVELOPED HIT II – CASE REPORT

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Summary

Representing this patient our intention was to stress the importance of monitoring platelet number in patient on heparin therapy. We have, for the first time, in our hospital used reversible thrombin inhibitor, that showed efficacy in treating HIT II complications. HIT II immunologically caused side-effect of heparin therapy, characterized by decrease in thrombocyte number for more than 50 %, with increased inclination to thromboembolic incidents. The disease most commonly appears 5-10 days after initiation of mainly unfractionated heparin therapy. Application of '4 T score' in clinical judgement for HIT probability, and laboratory investigation for presence of anti-heparin antibodies markedly contribute to in time detection and treatment of this illness. If anti-heparin antibodies are detected, heparin application must be stopped immediately, and must be replaced by some anti-heparin anticoagulant preparation (Fxa inhibitor, heparinoids, or direct inhibitor of thrombin). In time application of substitutional preparation for heparin markedly diminishes the occurrence of thromboembolic complications.

We presented the case of patient hospitalized in our institution by reason of complete thrombosis of left iliac vein, joint femoral vein, deep veins of femoral region, popliteal vein and initial part of great saphenous vein. Treatment started by non-fractionated heparin and continued by warfarin, but the patient developed clinical feature of HIT II, so, current anticoagulant therapy was stopped, and fondaparinux was introduced. Although thrombocyte number increased, D-dimers were in additional rise, and patient developed pulmonary embolism. Reversible thrombin inhibitor argatroban was introduced in therapy in daily dose of 2 µg/kg/min in continual infusion lasting 15 days, followed by continual APTT monitoring, in therapeutic range 1.5-2 times of basic value. Rise in platelet number was monitored, decrease of D-dimer, and local clinical improvement. Marginal recanalization of veins in left femoral region and complete passage of popliteal vein were documented by color doppler.

Further, clinical estimation of HIT II probability using „4T“ graduating system, and laboratory investigation to anti-heparin antibodies, had significant role in diagnosis confirmation, and in selecting suitable substitutional preparation for heparin.

KEYWORDS: *thrombocytopenia, heparin, deep veins thrombosis (DVT), pulmonary embolism (PE), heparin induced thrombocytopenia type II (HIT II), heparin antibodies, fondaparinux, argatroban*

LJEČENJE VENSKE TROMBOEMBOLIJE ARGATROBANOM U BOLESNICE S HEPARINSKOM TROMBOCITOPENIJOM TIPA II (HIT II) - PRIKAZ SLUČAJA

Sažetak

Prikazom smo željeli naglasiti važnost praćenja broja trombocita kod liječenja heparinom. Uporabili smo po prvi puta reverzibilni inhibitor trombina, koji je pokazao učinkovitost u liječenju komplikacija HIT-a II. HIT II je imunološka nuspoja-

va heparinske terapije praćena trombocitopenijom > 50% i povećanom sklonošću tromboemboliji. Najčešće se javlja 5. do 10. dana terapije nefrakcioniranim heparinom. Otkrivanju i lijećenju ove nuspojave značajno pridonosi primjena „4T zbira“ i otkirvanje prisutnosti protutijela na heparin. Ukoliko se protutijela dokažu, heparin se isključuje i nastavlja se ne-heparinskim antikoagulantom (inhibitorom FX-a, heparinoidom ili direktnim inhibitorom trombina), čime se smanjuje rizik tromboembolije. Prikazali smo slučaj bolesnice s kompletnom trombozom lijeve ilijačne vene, zajedničke femoralne vene, dubokih vena natkoljenice, poplitealne vene i početnog dijela velike vene safene. Liječenje je započelo nefrakcioniranim heparinom i nastavljeno varfarinom. Bolesnica je razvila kliničku sliku HIT-a II. Prekinuta se dosadašnja antikoagulantna terapija i uveden je fondaparinux. Broj trombocita je počeo rasti, D-dimeri također. Razvila se plućna embolija. Liječenje je nastavljeno reverzibilnim inhibitorom trombina argatrobanom u dnevnoj dozi od 2 µg/kg/min kontinuiranom infuzijom u trajanju od 15 dana. Pratili smo APTV, čije su vrijednosti bile 1.5-2 puta duže od bazične vrijednosti. Broj trombocita je rastao, koncentracija D-dimera se snizila, nastupilo je lokalno kliničko poboljšanje. Obojeni doppler je pokazao rubnu rekanalizaciju vena lijeve natkoljenice i potpunu prohodnost poplitealne vene. Klinička procjena vjerojatnosti HIT II s „4T“ bodovnim sustava otkrivanja heparinskih protutijela imala je značajnu ulogu u potvrdi dijagnoze i odluci o odabiru odgovarajućeg zamjenskog lijeka za heparin.

KLJUČNE RIJEČI: *trombocitopenija, heparin, duboka venska tromboza (DVT), plućna embolija (PE), heparinska trombocitopenija tip II (HIT II), heparinska protutijela, fondaparinux, argatroban*

INTRODUCTION

Heparin induced thrombocytopenia (HIT) is marked unwilling reaction connected with heparin application, that is most frequently administered anticoagulant preparation (1). HIT is clinically-pathologic syndrome, appearing in two forms: HIT I and HIT II (2). Criteria for diagnosis setting include clinical system of ranging „4 T score“ (thrombocytopenia, timing of platelet count fall, thrombosis, other causes of thrombocytopenia) and laboratory investigation for presence of antiheparin antibodies (3). HIT I is a consequence of non-immune, direct interaction of heparin with thrombocytic surface, characterized by slight and transient thrombocytopenia, without thromboembolic complications. Differently, HIT II is immunologically (antibodies) mediated and characterized by decrease of thrombocytes for more than 50% in relation to value before heparin application, connected with increased inclination to thromboembolic incidents. The disease appears most frequently 5-10 days from beginning of mainly unfractionated heparin therapy. It is a consequence of auto-antibodies appearance, most frequently IgG class, to complex of heparin and thrombocytic factor IV (platelet factor 4, PF4) (4). Antibodies are bond to thrombocytic proteins receptor Fc gamma R II, consequently activation of thrombocytes and emission of procoagulant PF4 takes place. Antibodies bind to endothelial cells and activate coagulation cascade, that leads to formation of thrombine and thromboembolic complications that can have lethal outcome (3,5).

If antiheparin antibodies are detected, heparin use must be immediately suspended, and substituted by some other anti-heparin anticoagulant medicament (FX-a inhibitor, heparinoid, or direct thrombin inhibitor, DTI) (6). It must be taken into account that DTI and fondaparinux can lead to bleeding, and that they have no antidote as heparin, so the laboratory monitoring of preparation efficacy is aggravated; meantime, the effects of argatroban usually quickly disappear after discontinuation of therapy (half time of elimination is 39-51 minutes) (7). Substitutional DTI therapy improves HIT II exit, specially thrombosis and lethal result of thrombosis, without increasing risk of bleeding. Coumarin / warfarin preparations are contraindicated in therapy of acute HIT II (8).

CASE REPORT

A 69 year old female patient after immobilization and reposing because of forearms fractures, was hospitalized in our hospital, due to complete thrombosis of left iliac vein, common femoral vein, deep veins of femoral region, popliteal vein and commencing part of big saphenous vein, that was verified by color doppler and computed tomography (CT) imaging of abdomen and pelvis. The treatment started by continual infusion of unfractionated heparin in dosis of 25.000 i.u. On the third day of therapy besides heparin, warfarin was introduced, in therapeutic range of INR 2-3. Therapy was continued through ten days, but gradual worsening of local clinical finding was

noticed, with initial skin necrosis bellow the knee. On the tenth day a drop in thrombocyte number from $175 \times 10^9/L$ to $19 \times 10^9/L$ was registered, so the heparin and warfarin therapy was stopped. HIT II was suspected, and laboratory investigation on anti-heparin antibodies was ordered in Croatian Institute for Transfusion Medicine, Zagreb, and heparin was substituted by fondaparinux. Antibodies to PF4 were confirmed by two tests; IgG specific ELISA (OD 2,500) and in partical gel immunoassay (PaGIA). Functional tests of thrombocyte aggregation with heparin supplement (HIPA) and serotoninine SRA-HPLC delivery test were positive, too. On the 10th day fondaparinux was introduced in daily dose of 7,5 mg s.c. Although with a change in therapy, the increase in thrombocyte number from $19 \times 10^9/L$ to $84 \times 10^9/L$, was documented, monitored D-dimers were in continual increase to the value of 35 mg/L fibrinogen equivalent units (FEU). On the 20th day of hospitalization clinical picture of pulmonary embolism emerged. By multi-slice computed tomography (MSCT) angiography of pulmonary artery, riding thrombus in pulmonary artery bifurcation was confirmed. Refractoriness on fondaparinux was suspected due to cross-reactivity of antibodies, that was confirmed in HIPA test with fondaparinux addition. Reversible thrombine inhibitor was introduced in therapy, argatroban, in daily dose of $2 \mu\text{g}/\text{kg}/\text{min}$ in continual infusion lasting 15 days, followed by continual monitoring of APTT, that was in therapeutic range of 1,5-2 x from basic value. The platelet increase from $84 \times 10^9/L$ to $254 \times 10^9/L$ was registered, followed by succesive fall of D-dimer to 16 mg/L FEU, with local clinical improvement. Marginal recanalization of veins in left femoral region was detected by color doppler with complete passability of popliteal vein. Therapy was continued by standard oral anticoagulant therapy. One month after oral anticoagulant therapy, control D-dimers are 1 mg/L FEU.

DISCUSSION

The diagnosis and treatment of patients with HIT are complicated because thrombocytopenia in patients receiving heparin can have many other causes. If there is laboratory evidence of anti-heparin antibodies, heparin should be discontinued

immediatly and replaced by some other non-heparin anticoagulant, such as direct thrombin inhibitor, heparinoid and factor Xa inhibitor. Recently, the most commonly used agent has been fondaparinux, a synthetic and selective factor Xa inhibitor, which rarely causes anti-heparin antibody cross-reactivity (9-11).

Warkentin et al. have reported that oligosaccharide or heparinoid (fondaparinux and danaparoid) show cross-reactivity with HIT antibodies in 10-15% of cases (12). On the contrary to above, the chemical structure of reversible direct thrombin inhibitor argatroban is completely different from the heparin and there is no proven cross-reactivity with HIT antibodies. Argatroban is a small (527 Da) univalent direct thrombin inhibitor (DTI) that non-covalently and reversibly binds to active site on thrombin, it has more predictable anticoagulant effect compared to heparins, because does not bind plasma proteins (13,14).

Considering the above, argatroban is used for prophylaxis or treatment of thrombosis in patients with HIT and for anticoagulation in patients with a history of HIT, or at risk for HIT undergoing percutaneous coronary intervention (PCI) (15). Although there are currently no clear guidelines regarding the dosage and duration of therapy with argatroban, Lewis et al. proposed infusion therapy $2 \mu\text{g}/\text{kg}/\text{min}$ with monitoring and maintaining aPTT in the therapeutic range 1.5-3x from baseline, which should be effective in the treatment of thrombosis and increase the number of platelets, and a tendency not to increase bleeding (16). Steady-plasma concentrations are reached in 10 hours, and the plasma half-life of argatroban elimination is approximately 45 minutes (15). Argatroban is predominantly hepatically metabolized and eliminated in faeces through billiary excretion. Renal elimination is minimal, so dose adjustments are necessary in patients with hepatic but not renal impairment (8, 15).

B. Saugel and colleagues also reported that intensive care unit patients with MODS who developed HIT II can be effectively treated by argatroban, but in those critically ill patients initial dose of argatroban does not support the current recommendation of $2 \mu\text{g}/\text{kg}/\text{min}$ ($0.5 \mu\text{g}/\text{kg}/\text{min}$ for patients with hepatic impairment). To avoid excessive anticoagulation and bleeding complications, they initiated argatroban in a mark-

edly reduced dose of about one tenth to one eighth of the recommended. Argatroban starting dose was $0.32 \pm 0.25 \mu\text{g}/\text{kg}/\text{min}$ to achieve aPTT of 1.5-3 times the baseline aPTT. Despite the very low starting dose adjustment to aPTT required dose reduction in six patients (4 with renal or hepatic failure), so the final mean dose in this critically ill patients was $0.24 \pm 0.16 \mu\text{g}/\text{kg}/\text{min}$. Argatroban dose was significantly lower in patients with hepatic insufficiency ($0.10 \pm 0.06 \mu\text{g}/\text{kg}/\text{min}$). Patients were treated for a mean time of 5.5 ± 3.3 days (min. 1 day, max. 11 days). They checked aPTT at close intervals after drug initiation (about 2 hours later), daily and 4 hours after any dose adjustment. They had no bleeding or other adverse events during therapy with argatroban. Furthermore, no arterial or venous thromboembolic complications appeared in their 12 patients treated by argatroban (17).

Argatroban lacks a specific antidote. However, argatroban anticoagulant effects generally return to baseline rapidly on drug discontinuation (elimination half-life in healthy individuals is 39-51 minutes). Argatroban therapy improves the outcome of heparin-induced thrombocytopenia, particularly thrombosis and death due to thrombosis, without increasing bleeding risk (16).

The use of warfarin in the acute phase of HIT is contraindicated by reason of it may cause a drop of protein C (8). Warfarin therapy is generally not recommended as there has been association between warfarin and an increased risk of microvascular thrombosis during HIT. If warfarin is used, treatment should be delayed until the platelet count is at least $150 \times 10^9/\text{L}$, and there are no signs of thrombosis (via D-dimers and color doppler) (18).

According to Croatian Society for Haematology and Transfusion Medicine guidelines on the diagnosis and management of HIT, fondaparinux as a replacement for heparin preparation is effective in most patients, except in cases where the anti-heparin antibodies show cross-reactivity with fondaparinux; then direct thrombin inhibitor must be applied (19, 20).

We have presented a case of female patient hospitalized in our institution due to complete thrombosis of left iliac vein, joint femoral vein, deep veins of femoral region, popliteal vein and initial part of great saphenous vein. The treatment started by non-fractional heparin, and continued

by warfarin, but the patient developed clinical picture of HIT, so, the current anticoagulant therapy was stopped, and fondaparinux was introduced. Although the number of platelets rised, D-dimers are in continual rise, and the patient developed pulmonary embolism. By laboratory investigation anti-heparin antibodies to complex of heparin and PF4 were proved; IgG specific ELISA (OD 2.500) and in partial gel immunoassay test (PaGIA). Functional thrombocyte aggregation tests with heparin supplement (HIPA) and test of serotonin liberation SRA-HPLC, were also positive. Reversible thrombin inhibitor argatroban was introduced in therapy in a daily dose of $2 \mu\text{g}/\text{kg}/\text{min}$ in continual infusion lasting 15 days, followed by continued APTT monitoring, that was in therapeutic range from 1.5 -2 times of basic value. Thrombocyte rise, D-dimer fall and local clinical benefit were registered. Marginal recanalization of veins in left femoral region, with complete passage of popliteal vein, were confirmed by Doppler. Therapy was continued by standard oral anticoagulant medication.

One month after oral anticoagulant therapy, control D-dimers are 1 mg/L FEU.

CONCLUSION

Presenting our case we intended to stress the importance of thrombocyte number control in patients on heparin therapy, and laboratory diagnostics for anti-heparin antibodies, in purpose of recognition life-threatening complications of such therapy. Clinical estimation of HIT II probability, selection of methods of laboratory investigation to antiheparin antibodies, and decision upon application of substitutional preparation for heparin, in a great deal alleviates the recommendation of International Society for Thrombosis and Hemostasis in diagnostics- therapeutic proceeding for diagnostics and treatment of thrombocytopenia caused by heparin. National recommendations, if existing, are of great benefit in selection of available and validated methods of laboratory investigation for HIT, as well as, in a case of urgent need to apply the substitutional preparation for heparin, that is on national list of approved medications. We have in our hospital for the first time used reversible thrombin inhibitor, that showed efficacy in treatment of HIT II complications.

REFERENCES

1. Warkentin T.E, Levine M.N, Hirsh J, et al. Heparin-induced thrombocytopenia low-molecular weight heparin or unfractionated heparin. *N Engl J Med* 2007;356:891-3.
2. Franchini M. Heparin-induced thrombocytopenia: an update, *Thromb J* 2005;3:14.
3. Fabris F, Ahmad S, Cella G, Jeske W.P, Walenga JM, Fareed J. Pathophysiology of heparin-induced thrombocytopenia. Clinical and diagnostic implications – a review. *Arch Pathol Lab Med* 2000;124(11):1657-66.
4. Rauova L, Ponez M, McKenzie S.E, et al. Ultralage complexes pathogenesis of heparin-induced thrombocytopenia. *Blood* 2005;105:131-8.
5. Chong BH, Berndt M.C, Heparin-induced thrombocytopenia. *Blut* 1989;58:53-7.
6. Kannam M, Saxena R, Adiguzel C, Fareed J. An update on a prevalence and characterization of H-PF4 antibodies in Asian-Indian patients. *Semin Thromb Haemost* 2009;35(3):337-43.
7. Keeling D, Davidson S, Watson H. Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology. The management of heparin-induced thrombocytopenia. *Br J Hamatol* 2006;133(3):259-69.
8. Swan S.K, Hursting M.J. The pharmacokinetics and pharmacodynamics of argatroban: effects of age, gender, and hepatic or renal dysfunction. *Pharmacotherapy* 2000;20(7):756-70.
9. Grouzi E, Kyriaoku E, Panagou I, Spillotopoulou I. Fondaparinux for the treatment of acute heparin – induced thrombocytopenia: a single centre experience. *Clin Appl Thromb Hemost* 2010;16(6):663-7.
10. Sun J, Teoh K.H, Sheth T, Landry D, Jung H, Warkentin T.E, Yusuf S, Lamy A, Eikelboom J.W. Randomized trail of fondaparinux versus heparin to prevent graft failure after coronary artery bypass grafting: the Fonda CABG study. *J Thromb Thrombolysis* 2011;32(3): 378-85.
11. Blackmer A.B, Oertel M.D, Valgus J.M. Fondaparinux and the management of heparin – induced thrombocytopenia: the journey continues. *Ann Pharmacother* 2009; 43(10):1636-46.
12. Warkentin T.E, Chong B.H, Greinacher A. Heparin-induced thrombocytopenia: toward consensus. *Thromb Haemost* 1998;79:1-7
13. Alban S. Pharmacological strategies for inhibition of thrombin activity. *Curr Pharm Des* 2008;14:1152–75.
14. Weitz J.I, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest* 1990;86:385–91.
15. Lee C.J, Ansell J.E. Direct thrombin inhibitors, *BJCP* 2011;72(4):581-92.
16. Lewis B.E, Wallis D.E, Leya F, Hursting M.J, Kelton J.G. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. *Arch Intern Med* 2003;163:1849–56. doi: 10.1001/archinte.163.15.1849.
17. Saugel B, Phillip V, Moessmer G, Schmid R.M, Huber W. Argatroban therapy for heparin-induced thrombocytopenia in ICU patients with multiple organ dysfunction syndrome: a retrospective study. *Crit Care* 2010; 14(3): R90, doi: 10.1186/cc9024
18. Lancaster C, Tobias J.D. Why Is the Platelet Count Low: Should I Be Concerned About Heparin-Induced Thrombocytopenia? *J Pediatr Pharmacol Ther* 2012;17(1): 2–6. doi: 10.5863/1551-6776-17.1.2
19. Bošnjak B, Čuljak-Aleksić M, Gojčeta K, Golubić-Čepulić B, Debeljak Ž, Dodig J, Kogler-Majerić V, Mesarić J, Peraica-Planinc A, Prinčić M, Rode B, Skorić B, Stančić V, Suvić-Križanić V, Šturm D, Tomičić M. Croatian Society for Haematology and Transfusion Medicine Guidelines on the diagnosis and management of heparin induced thrombocytopenia (HIT). *Liječ Vjesn* 2012;134:253–58.
20. Brayant A, Low J, Austin S, Joseph J.E. Timely diagnosis and management of heparin-induced thrombocytopenia in a frequent request, low incidence single centre using clinical 4T'score and particle gel immunoassay. *Br J Haematol* 2008; 143(5):721-6

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