MÆDICA - a Journal of Clinical Medicine

JOURNAL CLUB

Lepirudin as an alternative anticoagulant in heparin induced thrombocytopenia

Claudiu STOICESCU, PhD Fellow
Cardiology Department, University Hospital of Bucharest, Romania

One of the most important and severe complication of heparin treatment is thrombocytopenia. The frequency that it occurs is 0,2% for low molecular weight heparin and 2,6% for unfractionated heparin. Heparin induce antibodies towards a complex formed between platelet factor 4 and heparin which make a prothrombotic state by activating endothelial cells and platelets. The first step when thrombocytopenia occurs is to stop immediately heparin therapy. The second one is to use alternative anticoagulants. One of the most attractive treatments is direct thrombin inhibitors because increased thrombin generation is believed to underlie the marked prothrombotic nature of heparin induced thrombocytopenia (HIT). Lepirudin (Refludan; Pharmion, Cambridge, United Kingdom; Berlex Laboratories, Wayne, NJ) is representative for direct thrombin inhibitors and is approved worldwide for the treatment of patients with heparin induced thrombocytopenia, with or without thrombosis.

Two recent studies have evaluated efficacy and safety of lepirudin in patients with heparin-induced thrombocytopenia. The Heparin-Associated Thrombocytopenia (HAT)-3 study is a prospective, controlled study. Endpoints were new thromboembolic complications, limb amputations, and death and major bleeding. A historical control group (n = 120) was used for comparison. The combined endpoint was reduced (29,7% vs. 52,1%, P = 0,0473), primarily because of reduction in new thromboses (11,9% vs. 32.1%, P = 0,0008), compared with the historical control group (log-rank test). Patients treated with lepirudin have more frequent major bleeding than control group (29,4% vs. 9,1%, P = 0,0148). The mean lepirudin doses were 0,11 mg/kg/h in HIT patients with thrombosis and 0,07 mg/kg/h in patients with asymptomatic HIT.

A second one was a multicenter, retrospective, observational study on 181 patients conducted in France and Switzerland under the auspices of the French group (Groupe d'Etude sur l'Hémostase et la Thrombose [GEHT]). Primary study endpoints were the occurrence of thrombotic and bleeding events during treatment. Data from HAT 3 study or from combined analysis of the all 3 HAT lepirudin studies (HAT 1, HAT 2, and HAT 3) were used for comparison. The mean doses of lepirudin were lower than those reported in HAT 3 study (0,07 and 0,05 mg/kg/h, respectively); despite of this fact the rates of new thrombotic events and amputations after the initiation of lepirudin were comparable (11,9% in HAT 3 study and 13,8% in retrospective study). The incidence

of major bleeding was 20,4% in the upper range of the rates reported in a combined analysis of the all 3 HAT lepirudin studies (HAT 1, HAT 2, HAT 3) (17,6%; 95% CI, 14,0-21,7). The differences are because of the definition of major bleeding used in the studies.

Both studies showed that the mean lepirudin dose was nevertheless not an independent predictive factor for thrombotic complications. In contrast, it was an independent predictive factor for major bleeding (the higher the dose, the higher the bleeding risk).

The results of those two studied provide important information about the lepirudin ability as an alternative treatment for patients with HIT. Patients treated with lepirudin had a lower rate of new thromboembolic complications. The rate of major bleeding might be reduced by reducing the starting dose. For the management of this complex syndrome lower, but still effective, doses of lepirudin may improve the benefit-to-risk ratio of this drug.

Comment on the paper:

Tardy B, Lecompte T, Boelhen F, Tardy-Poncet B, Elalamy I, Morange P, Gruel Y, Wolf M, François D, Racadot E, Camarasa P, Blouch MT, Nguyen F, Doubine S, Dutrillaux F, Alhenc-Gelas M, Martin-Toutain I, Bauters A, Ffrench P, Maistre E, Grunebaum L, Mouton C, Huisse MG, Gouault-Heilmann M, Lucke V, for the GEHT-HIT study group – Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin, *Blood* 2006; 108:1492-1496