



## TREATMENT FOR HEPARIN-INDUCED THROMBOCYTOPENIA

Jisha M Lucca<sup>\*1</sup>, Nathani.Minaz<sup>1</sup>, B.Prasanthi<sup>2</sup>, Venkataramana.M<sup>2</sup>

Asst. Professors, Department of Pharmacy practice and pharmacology, Bharat Institute of Technology-Pharmacy, Hyderabad, AP, India.  
M Pharm students. Department of Pharmacy practice, Bharat Institute of Technology-Pharmacy, Hyderabad, AP, India.

\*Corresponding author's E-mail: [jishajo06@yahoo.co.in](mailto:jishajo06@yahoo.co.in)

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### ABSTRACT

The clinico-pathological syndrome of heparin-induced thrombocytopenia (HIT) can present as isolated thrombocytopenia or in association with a thrombotic event. Management of patients with isolated HIT focuses on the prevention of thrombotic events. Treatment of HIT and associated thrombosis syndrome (HITTS) involves prevention of thrombus extension, and prophylaxis of additional thromboemboli. Both patient groups should be managed with immediate cessation of heparin therapy. Regardless of whether used as treatment or as prophylaxis of thrombosis, alternative anticoagulation is strongly recommended in patients with HIT. When treated with heparin discontinuation alone, the risk for thromboembolic complications (TECs) is more than 50%. Argatroban and lepirudin, are currently approved two direct thrombin inhibitors (DTIs), for the treatment of HIT. Argatroban, is a univalent inhibitor of thrombin, while lepirudin, is a bivalent inhibitor of thrombin.

**Keywords:** Anticoagulants, Argatroban, Danaparoid. Heparin, Lepirudin, Thrombocytopenia.

### INTRODUCTION

Heparin-induced thrombocytopenia is defined as a decrease in platelet count during or shortly following exposure to heparin.<sup>1</sup> Two different types of HIT are recognized. The first, HIT type I (also called heparin-associated thrombocytopenia in the past), is a benign form not associated with an increased risk of thrombosis. The mechanism of HIT type I is still unknown but it is likely to be non-immune, probably related to its platelet proaggregating effect. This form of HIT affects up to 10% of patients under treatment with heparin and is characterized by a mild and transient asymptomatic thrombocytopenia (rarely less than 100,000 platelets/ $\mu$ l) that develops early (usually within the first two days of starting heparin) and disappears quickly once the heparin is withdrawn. The second form is, HIT type II, is immunemediated and associated with a risk of thrombosis. It has recently been proposed that the term "HIT type I" be changed to "non immune heparin associated thrombocytopenia" and that the term "HIT type II" be changed to "HIT" to avoid confusion between the two syndromes.<sup>2</sup>

Unfractionated heparin and low-molecular-weight heparins (LMWHs) are routinely used for thromboprophylaxis or treatment. Despite heparin therapy, patients sometimes have new or recurrent thrombosis if anticoagulation fails or heparin induced thrombocytopenia (HIT) occurs. HIT is a serious, immune-mediated condition in which 38 to 76% of patients acquire thrombotic complications, typically venous thromboembolism (VTE), in the days to weeks after its onset.<sup>3</sup> HIT is caused by the binding of antibodies (most frequently IgG) to a complex of heparin and platelet factor IV.<sup>4</sup> These antibodies activate platelets through their Fc receptors, causing platelet destruction and the

release of prothrombotic platelet-derived microparticles<sup>5</sup> Microparticles in turn promote thrombin generation and contribute to a hypercoagulable state,<sup>6</sup> if VTE is not associated with HIT, heparins are recommended; if VTE is associated with HIT, heparins are contraindicated and alternative anticoagulation is recommended.<sup>7</sup>

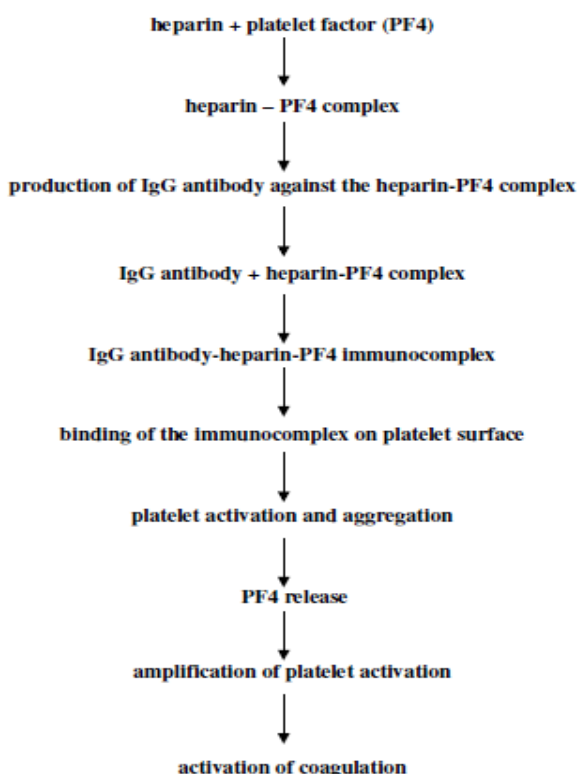
### MECHANISM

The mechanism underlying heparin-induced thrombocytopenia is an immune response.<sup>8,9</sup> The principal antigen is a complex of heparin and platelet factor 4 (PF4). Platelet factor 4 is a small positively charged molecule of uncertain biological function normally found in  $\alpha$ -granules of platelets. When platelets are activated, PF4 is released into the circulation and some of it binds to the platelet surface. Because of opposite charges, heparin and other glycosaminoglycans bind to the PF4 molecules, exposing neoepitopes that act as immunogens leading to antibody production. In fact, patients who develop HIT produce an IgG antibody against the heparin-PF4 complex, which binds to the complex on platelet surface through the Fab region.<sup>10</sup> The Fc portion of the HIT antibody can then bind to the platelet Fc receptor and this interaction triggers activation and aggregation of the platelets. Activated platelets release PF4, thus perpetuating the cycle of heparin-induced platelet activation. In addition, the platelet activation leads to the production of prothrombotic platelet microparticles which promote coagulation. Finally, as a result of the presence of heparin like molecules (heparan sulfate) on the surface of endothelial cells, the HIT antibody-PF4-heparan sulfate complexes formed on the endothelial surface may induce tissue factor expression with further activation of the coagulation cascade and thrombin generation.<sup>11,12</sup> Thrombocytopenia in HIT is largely due to the clearance



of activated platelets and antibody-coated platelets by the reticulo-endothelial system<sup>13</sup>.

**Figure 1**  
Pathophysiology of heparin induced thrombocytopenia.



### Clinical features and diagnosis

The onset of heparin-induced thrombocytopenia may be rapid or delayed. The platelet count in patients with preexisting heparin-PF4 antibodies from a previous exposure and sensitization to heparin may decrease within the first 3 days or even hours after re-exposure to heparin (rapid onset HIT)<sup>14</sup>. However, in patients receiving heparin for the first time, the onset of thrombocytopenia usually occurs 5 to 10 days after the administration of the heparin. Conversely, in delayed-onset HIT, the thrombocytopenia occurs 5 or more days after heparin withdrawal<sup>15</sup>. The thrombocytopenia in HIT is usually moderate in severity, with a median platelet count being between 50 and 80 × 10<sup>9</sup>/L, although the nadir platelet count can remain at a level considered normal (i.e. > 150 × 10<sup>9</sup>/L) but having dropped by 50% or more with respect to the pre-heparin value. The platelet count starts to rise 2 to 3 days after discontinuing heparin and usually returns to normal within 4 to 10 days. The antibody disappears within 2 to 3 months after cessation of heparin therapy<sup>16</sup>. Although HIT does not invariably recur during subsequent re-exposure to heparin, future use of heparin is contraindicated<sup>17</sup>. Despite thrombocytopenia, bleeding is rare<sup>18</sup>. Contrariwise, HIT is strongly associated with thrombosis, which frequently leads to the recognition of HIT<sup>19</sup>. Thrombosis in HIT is associated with a mortality of approximately 20–30%, with an equal percentage of patients becoming permanently disabled by amputation, stroke or other causes<sup>20</sup>. Thromboembolic complications can be venous, arterial, or both and include

deep venous thrombosis, pulmonary embolism, myocardial infarction, thrombotic stroke and occlusion of limb arteries<sup>21</sup>. However, the type and site of thrombosis depends on the patient's clinical profile. For example, deep vein thrombosis and pulmonary embolism occur very frequently in postoperative patients who are already prone to developing venous thromboembolism<sup>22</sup>. In fact, Warkentin and colleagues reported that the incidence of deep vein thrombosis in orthopedic patients who received heparin for thromboprophylaxis was 17.8%, but that this incidence increased dramatically to 88.9% among patients who developed HIT<sup>22</sup>. Similarly, patients with central venous catheters and HIT develop upper limb venous thrombosis more frequently than those without HIT<sup>23</sup>. In some cases thrombosis of the cerebral venous sinuses can occur, giving rise to a clinical picture of severe headache and progressive neurological deficits<sup>24</sup>. In contrast, arterial thrombosis occurs more frequently than venous thrombosis in HIT patients receiving heparin for cardiovascular diseases<sup>25</sup>. Furthermore, areas of necrosis developing at the site of heparin injections can be a manifestation of HIT, and are not necessarily associated with thrombocytopenia. Platelet activation and thrombosis due to heparin-dependent, platelet-activating IgG have been shown to be the underlying pathogenic mechanisms of this complication.<sup>26</sup> In some cases, thrombosis may be generalized leading to a syndrome resembling disseminated intravascular coagulation.<sup>27</sup> Finally, in some patients with HIT resistance to heparin may occur, meaning that an increasing dose of heparin dose is required to maintain the activated partial thromboplastin time (aPTT) within the therapeutic range.<sup>28</sup> The diagnosis of HIT remains a clinical one, supported by confirmatory laboratory testing.<sup>29,30</sup> The criteria include: a) thrombocytopenia (i.e., a drop of the platelet count to below 100 × 10<sup>9</sup>/L or a drop of > 50% from the patient's baseline platelet count); b) the exclusion of other causes of thrombocytopenia; c) the resolution of thrombocytopenia after cessation of heparin.<sup>31</sup> As regards the laboratory tests, HIT-antibodies can be demonstrated *in vitro* by functional tests and immunoassays<sup>32,33</sup>. Functional tests, which measure platelet activity in the presence of the patient's serum and heparin, include heparin-induced platelet aggregation (HIPA) and the serotonin release assay (SRA). Although the HIPA test is easier to perform and thus more commonly used, the SRA is more sensitive, albeit more complex, technically demanding and not readily available in most centers, and is therefore considered the "gold standard"<sup>31</sup>. The immunoassays utilize immunoenzymatic tests (enzyme-linked immunosorbent assay, ELISA) to detect the HIT antibody that binds to the PF4/heparin complex. Immunoassays are technically easier to perform than the functional assays and are also more sensitive<sup>31</sup>. On the other hand, comparative and prospective studies have demonstrated that functional tests are more specific than enzyme immunoassays and thus, being better at detecting the clinically significant HIT antibodies, are more helpful in the diagnosis of HIT<sup>34</sup>.



## TREATMENT

Heparin-induced thrombocytopenia, presenting as isolated thrombocytopenia (HIT) or thrombocytopenia with thrombotic complications (HITTS), is a potentially catastrophic complication of heparin therapy. For treatment of HIT/ HITTS, heparin discontinuation is necessary and also these patients may require continued anticoagulation.<sup>35,36</sup>

Consequently, a safe, effective and rapidly active anticoagulant is needed for use in this setting. At present, Danaparoid, Argatroban, and Lepirudin are approved in a number of countries for the treatment of HIT. These drugs are immediately active and either inhibit thrombin directly or inhibit thrombin generation.

### Danaparoid

Danaparoid is a heparinoid derived from porcine intestinal mucosa, composed of heparin sulfate, with lesser amounts of dermatan sulfate and chondroitin sulfate<sup>37</sup>. Its mechanism of action is the inhibition of factor Xa, with lesser effects on factor IIa. The ratio of anti-factor Xa activity to anti-factor IIa activity is 28:1 (for heparin it is 1:1). It exhibits *in vitro* cross-reactivity with the antibody causing HIT (HIT-IgG) and *in-vivo* cross reactivity is uncommon. A steady state is reached after 4 to 5 days of administration, and 40 to 50% of danaparoid is excreted renally. Danaparoid is primarily indicated as an immediate substitute for heparin in HIT II patients requiring postoperative prophylaxis against venous thromboembolism.

### Argatroban

Argatroban and lepirudin are direct thrombin inhibitors. Both are active against soluble and clotbound thrombin, with lepirudin having a higher thrombin-binding affinity than argatroban. Argatroban is a small (molecular weight, 526.6 Da) synthetic peptide derived from L-arginine. It has a half-life of about 45 minutes, with clearance primarily through the liver and minimal renal clearance. At a dosage of 2 µg/kg per minute, most patients quickly achieve therapeutic blood levels as measured by 1.5 to 3 times the baseline activated partial thromboplastin time<sup>38</sup>. Its anticoagulant effects are rapidly reversible<sup>39</sup> because it does not cross-react with HIT antibody. Furthermore, being small and synthetic, argatroban does not induce formation of antibodies that can alter its clearance.

The efficacy and tolerability of argatroban in HIT were established in a prospective, multicenter, nonrandomized, open-label trial. As no other approved anticoagulant agent was available for comparison, and a placebo control was considered to be unethical, a historical control was applied ( $n = 193$ ). A total of 304 patients participated in this trial, grouped into two treatment arms: those with isolated HIT ( $n = 160$ ) and those with HITTS ( $n = 144$ )<sup>40</sup>. Argatroban was administered intravenously at an initial dose of 2 µg/kg/min with dose adjustment to maintain the

activated partial thromboplastin time (aPTT) at 1.5 to 3.0 times baseline.

### Lepirudin

Lepirudin is a 65–amino acid peptide with a molecular weight of approximately 7000 Da, Originally extracted from leeches, lepirudin is now produced as a recombinant polypeptide.<sup>41-43</sup> It is given intravenously as a bolus dose followed by a constant infusion dosage of 0.15 mg/kg per hour adjusted to prolong the activated partial thromboplastin time ratio to 2 to 3. The recommended dosage is two doses of 750 antifactor Xa units daily subcutaneously for prophylaxis and a bolus of 1,500 U IV followed by 1,500 U subcutaneously twice a day for therapeutic reasons and 2,500 U as a bolus IV followed by 400 U/h for 4 h, then 300 U for 4 h, and finally 150 to 200 U/h for parenteral anticoagulation to maintain antifactor Xa activity at 0.5 to 0.8 U/ml. Therapy can be monitored by quantifying anti-factor Xa activity (in an assay with danaparoid as a standard)<sup>44</sup>. Monitoring is mandatory in patients with severe renal impairment, extremely low or high body weight, or thromboembolic or bleeding complications during therapy. There is no specific antidote available. Cross-reacting PF4/heparin complex antibodies can be detected in 7 to 50% of patients, but two retrospective studies showed no difference between patients treated with danaparoid independently of the presence of cross-reacting antibodies.<sup>45</sup>

### Management of acute HIT II in particular clinical settings

#### HIT II in pregnancy and childhood.

Danaparoid has been successfully used during pregnancy, and there is no evidence for crossing of the placental barrier or appearance in breast milk<sup>46</sup>. Hirudin should be administered cautiously in pregnancy, because embryotoxic effects have been demonstrated in rabbits after administration of high concentrations of hirudin<sup>47</sup>. Hirudin is not secreted into the breast milk<sup>48</sup>. For the application of argatroban in pregnancy, no data are available.

#### HIT II in the intensive care unit.

Thrombin-specific inhibitors are perfectly suited for patients in the intensive care unit due to their short half-lives. Since antidotes are lacking, in cases of severe bleeding under therapy with these inhibitors the infusion of recombinant factor VIIa should be considered. If danaparoid is administered in doses greater than those used for prophylactic purposes, monitoring assays should be readily available.<sup>49</sup>

#### HIT II in dialysis patients.

For dialysis patients argatroban is the ideal alternative to heparin, since it is not excreted renally and therefore does not require dose adjustment<sup>50</sup>. The half-life of lepirudin in patients undergoing dialysis is 52 h. It has been successfully used to maintain anticoagulation during dialysis when given as a single bolus prior to dialysis at a dose of 0.08mg/kg<sup>51</sup>. Danaparoid was administered to



patients undergoing hemofiltration with an initial bolus of 2,500U followed by an infusion of 200 to 600 U/h.<sup>52</sup>

### CONCLUSION

HIT is an uncommon and challenging complication of heparin therapy. Early recognition of the disorder and prompt discontinuation of heparin are important first step in management. In patients who require ongoing anticoagulation, several approaches have been tried with success. The low molecular weight heparinoid, danaparoid, and the thrombin specific inhibitors, lepirudin and argatroban, have been shown to be effective in HIT patients. Direct antithrombin therapy with lepirudin has been approved by the FDA for this condition and may help to limit complications. However, devising the best strategy for treatment of HIT is an evolving process.

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