Argatroban in HIT Type II and Acute Coronary Syndrome

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Key Words
Argatroban · Thrombin inhibitor · Heparin antibody · Acute coronary syndrome

Abstract
Prior to initiation of the ARG-911 and ARG-915 clinical trials, there was no optimal replacement for heparin anticoagulation in patients with heparin-induced thrombocytopenia (HIT) type II. These prospective, historical controlled studies were designed to determine the usefulness of argatroban, a direct thrombin inhibitor (DTI) that is not immunogenic and does not interact with heparin antibody, in answering this clinical need. Clinical outcomes (37-day period) for 568 argatroban-treated and 193 control patients demonstrated significantly reduced risks of the primary efficacy composite endpoint (all-cause death, all-cause amputation, new thrombosis) and the secondary endpoints (death due to thrombosis, new thrombosis) with argatroban. Argatroban patients also experienced a more rapid recovery of platelet count. Bleeding events were similar among both groups. It was concluded that argatroban anticoagulation, compared with historical controls, improves clinical outcomes without increasing bleeding risk in patients having HIT with or without thrombosis. Argatroban has since been approved in the US for both prophylaxis and treatment of thrombosis in patients with HIT. Argatroban has been used in percutaneous coronary interventions in patients with and without HIT, for peripheral vascular procedures in both large and small vessels in HIT patients, and as an adjunct to thrombolytic therapy for the treatment of AMI. Treatment success rates and the same or less bleeding was demonstrated with argatroban compared to heparin controls. These pilot studies suggest that argatroban will provide reliable anticoagulation during interventional procedures. A consistent safety profile of argatroban has been demonstrated in all studies to date. The main attributes of argatroban are its rapid onset of action, fast reversibility of its anticoagulant effect, inhibition of clot-bound thrombin, easily monitored by the aPTT and ACT and no dosage adjustment in renal-impaired individuals. These properties make argatroban a predictable and useful anticoagulant for HIT and non-HIT patients.

Introduction
Argatroban is a small molecule direct thrombin inhibitor (DTI). This drug has been used in Japan for the management of thromboembolic disorders for over 10 years. Despite this and a large number of preclinical studies on the pharmacology of argatroban, clinical trials for argatroban in Europe and North America were only initiated in 1993.
Argatroban is of a class of drugs that differs in many respects from heparin, low molecular weight heparins and heparinoids [1–5]. Many of the characteristics common to thrombin inhibitors make argatroban beneficial for use as an anticoagulant in patients with heparin-induced thrombocytopenia (HIT). These attributes include no cross-reactivity with heparin antibody, no potentiation of HIT and absence of antibody formation (tables 1, 2).

The clinical utility of argatroban for the management of patients with HIT-associated thrombosis and in the setting of interventional cardiology will be reviewed.

**Argatroban for HIT**

**Pathophysiology of HIT**

HIT, type II, is a disease spectrum triggered by an immune response to heparin. HIT occurs in approximately 2% of all heparin-treated individuals. The currently accepted hypothesis of the pathophysiology of HIT is based on the development of an IgG antibody to the heparin-PF4 complex that recognizes the FcyRIIa receptor on platelets. Binding of the IgG complex causes platelet activation, aggregation and thrombin generation [6–10]. The antibody is not heparin specific, and has been shown to react with other highly sulfated materials [11, 12]. Other antibodies have been identified.

The IgG antibody binding to heparin-PF4 will also target PF4 bound to endothelial cell heparan sulfate [13–15]. Damaged endothelial cells can act as a starting point for the thrombotic event potentially through exposure of tissue factor that is enhanced by recruited monocytes and further tissue factor release from endothelial cells [13, 15–17]. The release of platelet microparticles rich in phospholipid further contributes to platelet activation, endothelial cell activation and thrombin generation [17, 18]. Evidence of important platelet-leukocyte activation suggests an interaction of hemostatic activation with an inflammatory process in HIT [19, 20].

Thus, the pathophysiological mechanism of HIT is characterized by platelet activation, thrombin generation, endothelial cell activation/injury and leukocyte activation [21].

**Clinical Diagnosis of HIT**

The diagnosis of HIT is often not easy or straightforward. Clinical criteria are most important, including platelet count and evidence of unexplained thrombosis. However, HIT can be present even with a normal platelet count [22–24]. Confirmation by specific laboratory tests is optimal but not always possible. Rechallenge with heparin after resolution of the thrombocytopenia to confirm the diagnosis of HIT is dangerous and should not be performed.

**Table 1. Pharmacologic characteristics of argatroban**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Selective, direct inhibitor of thrombin</td>
</tr>
<tr>
<td>Rapid onset of action</td>
</tr>
<tr>
<td>Rapidly reversed</td>
</tr>
<tr>
<td>Short half-life (≈45 min i.v.)</td>
</tr>
<tr>
<td>Clearance through the liver</td>
</tr>
<tr>
<td>No need for dosage adjustment in renal-impaired patients</td>
</tr>
<tr>
<td>Inhibition of clot-bound thrombin</td>
</tr>
<tr>
<td>Not dependent on cofactors (e.g., AT, HCII)</td>
</tr>
<tr>
<td>Easily monitored by aPTT or ACT</td>
</tr>
<tr>
<td>Lesser bleeding risk than other DTIs</td>
</tr>
<tr>
<td>No cross-reactivity with heparin antibody</td>
</tr>
<tr>
<td>Absence of antibody formation that affect pharmacokinetics/ activity</td>
</tr>
</tbody>
</table>

**Table 2. Differences between the two DTIs argatroban and hirudin**

<table>
<thead>
<tr>
<th>Argatroban</th>
<th>Hirudin</th>
</tr>
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<tbody>
<tr>
<td>Shorter half-life</td>
<td>Longer half-life</td>
</tr>
<tr>
<td>Anticoagulant response rapidly reversed</td>
<td>Anticoagulant response slowly reversed</td>
</tr>
<tr>
<td>No antibody formation to argatroban</td>
<td>Antibodies are generated that delay its elimination; antibodies are generated that decrease its anticoagulant activity</td>
</tr>
<tr>
<td>May have less bleeding side effects</td>
<td>May have more bleeding side effect</td>
</tr>
<tr>
<td>Metabolized in the liver</td>
<td>Cleared via the kidney</td>
</tr>
<tr>
<td>Requires dose adjustment in liver disease patients</td>
<td>Requires dose adjustment in renal disease patients</td>
</tr>
<tr>
<td>Effectively monitored by aPTT and ACT</td>
<td>Monitored by aPTT and ACT, but response times are different from argatroban</td>
</tr>
</tbody>
</table>

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Pathophysiol Haemost Thromb
2002;32(suppl 3):46–55

47
The most dramatic clinical expression of HIT is HIT antibody-driven thrombosis. HIT is probably a more common cause of thrombosis than has been appreciated. The majority of cases of HIT are found in medically and surgically treated adults but can also be observed from simple catheter line flush heparin [25], during pregnancy and in children. Postoperative coronary artery bypass patients have a high frequency of venous graft closure. Additionally, outpatients can develop thrombosis in the home setting.

Patients with clinically diagnosed HIT have a 35% probability of developing a clinically significant thrombosis during their hospitalization [22, 26, 27]. Patients with HIT associated thrombosis have a mortality rate of 25–30% and an amputation rate of 25%.

Thrombosis can occur anywhere throughout both the venous and the arterial circulation [22–24, 26]. Recent reports document a higher frequency of venous thrombosis than arterial thrombosis [26]. HIT-associated thrombosis is most commonly associated with deep vein thrombosis and pulmonary embolism, but unusual thromboses, including e.g., mesenteric ischemia, which is commonly overlooked, spinal artery thrombosis, visceral infarctions, cerebral infarction and myocardial infarction are not uncommon. Mesenteric infarction has been seen in 15% of patients, myocardial infarction in 20% and cerebral infarction in 10%.

Laboratory Diagnosis of HIT

There is no highly sensitive and specific laboratory test for HIT [28, 29]. The functional platelet aggregation assay using patient serum (antibody), heparin and donor platelets has several limitations including a high false-negative rate. The serotonin release assay (SRA) using washed donor platelets radiolabeled with 14C-serotonin, patient serum and heparin has a higher sensitivity of 60–80%. Yet there can be patient samples negative by SRA that are positive by the aggregation test. Both the SRA and the aggregation assay are characterized by technical difficulties that require expert lab staff.

There are two Elisa tests for quantitating the antibody titer to the heparin-PF4 complex (Stago, Asnières, France and GTI, Brookfield, Wisc., USA). A minimum critical titer has not been identified that is associated with HIT thrombosis [28]. Heparin or low molecular weight (LMW) heparin treatment alone provokes antibody production that is not accompanied by thrombocytopenia or thrombosis [24, 29–32]. This common finding can lead to inappropriate treatment in patients who do not have HIT. On the other hand, patients clinically positive for HIT do not necessarily have positive Elisa antibody titers [28, 33]. Thus, although the Elisa is easy to perform, it does not provide results that are always clinically relevant.

As yet, there is no single assay that is ideal for diagnosing HIT. Each of the current assays for HIT contributes independent information. None can be used alone with complete confidence to identify a HIT-positive patient. Clinically positive patients could be missed by all assays, and antibody alone (Elisa positive) does not determine clinical HIT. Use of the Elisa method as a stand-alone test or as a rapid, preliminary screening test for HIT with confirmation by a follow-up SRA test should be discouraged. The combination of platelet aggregation, SRA and Elisa testing, with multiple samples, offers the best chance of identifying a positive HIT patient. Clinical observations remain of foremost importance in diagnosing HIT.

Clinical Management of HIT

The apparent paradox of a fall in platelet count with thrombotic rather than hemorrhagic complications is analogous to the syndrome of thrombotic thrombocytopenic purpura [23, 24]. HIT is clinically managed as an allergy to heparin. All heparin is immediately discontinued upon suspicion of the disease with a meticulous search for all sources of exogenous heparin. Due to the high probability of thrombosis, a vigorous search for venous and arterial thrombosis should be undertaken.

Unfortunately, early discontinuation of heparin does not significantly reduce the incidence of morbidity and mortality in patients with HIT [26]. It may be appropriate to use antithrombotic drugs as prophylaxis against thrombosis in this high-risk population. This practice has not been common, but this may relate more to the lack of appropriate prophylactic agents for this patient population than to the medical rationale. Today, use of a DTI can be recommended, initiated at a low level of anticoagulation until the thrombocytopenia resolves for patients with HIT antibody despite no other indication for anticoagulation. For patients with HIT-associated thrombosis, there is an immediate need to treat to avoid propagation of the clot or development of pulmonary embolism.

Other considerations for anticoagulation needs in the patient with HIT include patients with thrombosis for non-HIT-related events, such as myocardial infarction, unstable angina, heart valves and atrial fibrillation. Perhaps the greatest obstacle to overcome in the management of these patients is anticoagulation for coronary revascularization or cardiac surgery. For a short period, heparin has been used in patients who have negative antibody titers, albeit with some risk [23].
Traditional Therapies

The conventional anticoagulants aspirin and dextran are of limited value in the treatment of patients with HIT-associated thrombosis (table 1) [24, 34]. Coumadin derivatives require a loading period that leaves patients without anticoagulant protection for 48–72 h. Coumadin derivatives also inhibit protein C, potentially resulting in a prothrombotic state. Because of this, it is recommended that coumadin derivatives be initiated at low doses only when patients are out of the acute phase of HIT when platelet counts are on the rise [34]. Patients who have limb-threatening or life-threatening thrombosis can be treated with selective thrombolytic infusion, e.g., lower dose for postoperative patients and higher dose for non-postoperative patients [35, 36] until angiographic evidence of complete resolution of thrombus. Surgical thrombectomy remains a reasonable therapy in patients who have dire clinical circumstances and cannot afford the time required for selective thrombolytic infusions [23, 24]. However, the endothelial damage that occurs with thrombectomy, combined with the involvement of HIT antibody on endothelial cells, may explain the limited success with thrombectomy.

Anticoagulants other than heparin are necessary for proper treatment of patients with HIT (table 3). The early treatment alternatives have been less than optimal due to high bleeding risk, slow onset of action, long half-life, poor efficacy and lack of an antidote. These options have included the defibrinating agent ancrod (Arvin®; Knoll, Whippany, N.J., USA) [37, 38], and the heparinoid danaparoid (Orgaran®; Organon, Oss, The Netherlands) [39]. It has also been shown that heparin antibodies can cross-react with danaparoid [40]. LMW heparins appear to be less likely than heparin to cause HIT [31]; however, in vitro results unequivocally demonstrate that the heparin antibody recognizes LMW heparin producing platelet aggregation in a heparin-antibody-stimulated system [12, 40, 41]. Thus, LMW heparins should not be administered to patients with known heparin antibody.

Argatroban, a Direct Thrombin Inhibitor

An anticoagulant of a structure different from heparin, that has no ability to cross-react with the HIT antibody, would be the drug of choice for patients with HIT. The most promising class of drugs to date for treatment of patients with HIT are the DTIs. Argatroban (GlaxoSmithKline, Philadelphia, Pa., USA) is approved for the prophylaxis and treatment of HIT thrombosis in the USA. Among other beneficial characteristics, this drug does not cross-react with the heparin antibody as shown by in vitro data and successful treatment of HIT patients (table 1) [12, 19, 42].

The ARG-911 was a multi-center study conducted to evaluate the safety and efficacy of argatroban in patients with HIT (table 4) [42]. Continuous intravenous argatroban was administered at 2 µg/kg/min continuous infusion for an average of 6 days (14 days maximum) to 304 HIT patients. Dosage was adjusted to maintain the activated partial thromboplastin time (aPTT) between 1.5–3.0 × baseline. Because there was no approved alternative agent for use as an active comparator when the studies were conducted, a historical control was used for comparison (n = 193).

Outcomes were assessed during and following therapy (37 days). The primary efficacy composite endpoint (new thrombosis, all-cause amputation, or all-cause death) was reduced significantly in argatroban-treated patients (n = 160) vs. controls (n = 147) with HIT (25.6 vs. 38.8%, p = 0.014). In patients with heparin-induced thrombocytopenia thrombosis syndrome (HITTS), the composite incidence in argatroban-treated patients was 43.8% (n = 144) vs. 56.5% (n = 46), p = 0.131. Significant between-group differences by time-to-event analysis of the com-

### Table 3. Anticoagulants for the treatment of thrombosis in patients with HIT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
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<tbody>
<tr>
<td>Warfarin and dextran</td>
<td>limited efficacy; warfarin can be useful for long-term management after thrombin inhibitor treatment during acute phase</td>
</tr>
<tr>
<td>Selective thrombolytic infusion or surgical thrombectomy</td>
<td>useful for life-threatening thrombosis only</td>
</tr>
<tr>
<td>Ancrod (defibrinating agent)</td>
<td>difficult dosing regimen; slow onset of action; high bleeding risk; no antidote</td>
</tr>
<tr>
<td>Danaparoid (heparinoid)</td>
<td>monitoring not convenient; long half-life; high bleeding risk at high dose; no antidote; may cross-react with heparin antibody</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>drug of choice</td>
</tr>
<tr>
<td>Factor Xa inhibitors</td>
<td>investigational</td>
</tr>
<tr>
<td>Anti-platelet drugs</td>
<td>investigational, alone or in combination with thrombin inhibitors</td>
</tr>
</tbody>
</table>

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Table 4. Summary of the ARG-911 clinical trial of argatroban anticoagulation for patients with HIT and HITTS

<table>
<thead>
<tr>
<th></th>
<th>HIT</th>
<th>HITTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy (p values in favor of argatroban over control)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite endpoint²</td>
<td>0.014</td>
<td>0.131</td>
</tr>
<tr>
<td>Time to event</td>
<td>0.015</td>
<td>0.014</td>
</tr>
<tr>
<td>New thrombosis</td>
<td>&lt;0.001</td>
<td>0.044</td>
</tr>
<tr>
<td>Death</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Safety (p values in favor of argatroban over control)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.078</td>
<td>0.077</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rapid rise in platelet count</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Therapeutic level achieved within 4–5 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ New thrombosis, all-cause amputation, all-cause death [42].

HIT was defined in this study as heparin induced thrombosis without new thrombosis after heparin initiation (latent HIT). HITTS was defined as heparin induced thrombosis complicated by thrombosis that occurred after heparin administration.

Argatroban was a rapid onset of action, and it is rapidly dissociated from thrombin [2, 3, 45–48]. Argatroban has a shorter half-life than that of hirudin. The shorter half-life of argatroban seems to provide for easy clinical administration of the drug (‘turn on-turn off’) which seems to be reflected in a wider safety net (lesser bleeding) than that of hirudin. Argatroban is cleared through the liver; hirudin is cleared through the kidney. Hirudin is a protein and can generate antibodies that increase its anticoagulant activity by prolonging the half-life or antibodies that decrease its anticoagulant effect [49]. Argatroban does not induce antibody generation [50].

Argatroban in Comparison to Hirudin

Hirudin (lepirudin, Refludan®; Berlex, Wayne, N.J., USA) is another direct thrombin inhibitor. It is approved for treatment of HIT-associated thrombosis in the USA and Europe [43, 44], as DTIs hirudin and argatroban are similar. However, there are several pharmacologic characteristics that differ between the two drugs (table 2). Argatroban has a rapid onset of action, and it is rapidly dissociated from thrombin [2, 3, 45–48]. Argatroban has a shorter half-life than that of hirudin. The shorter half-life of argatroban seems to provide for easy clinical administration of the drug (‘turn on-turn off’) which seems to be reflected in a wider safety net (lesser bleeding) than that of hirudin. Argatroban is cleared through the liver; hirudin is cleared through the kidney. Hirudin is a protein and can generate antibodies that increase its anticoagulant activity by prolonging the half-life or antibodies that decrease its anticoagulant effect [49]. Argatroban does not induce antibody generation [50].

Argatroban with Coumadin Derivatives

For documented clinical thrombosis associated with HIT, patients should be treated with a DTI at therapeutic aPTT levels for 7–10 days. For patients with HIT and an underlying hypercoagulable state, mechanical prosthetic valves or atrial fibrillation, the ideal management strategy would be to initiate oral anticoagulation while maintaining a therapeutic level of anticoagulation with an intravenous DTI. To avoid skin necrosis, full anticoagulation with coumadin should not be achieved until platelet counts exceed 100,000/µl [34]. Once the INR for coumadin is stable in the therapeutic range, the intravenous DTI can be tapered off then discontinued. Low dose aspirin can be added to the regimen once coumadin is therapeutic.

Argatroban is easily monitored by the aPTT [1, 42, 46, 51, 52]. But one should be aware that the prothrombin time (PT)/International Normalized Ratio (INR) is also affected by DTIs [51, 53, 54]. Higher than expected INR values will be obtained for patients on a combination of DTI and coumadin but without the same relationship between INR and bleeding risk. A nomogram is available that can be used to help direct dosing. A practical recommendation is to co-administer the drugs until an INR of 4 is achieved. Argatroban can then be withdrawn and the INR reassessed. Another recommendation is to utilize the short half-life of argatroban. If clinically practical, blood for the INR assessment can be drawn after the argatroban infusion has been interrupted for 2 h.
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Argatroban with Anti-Platelet Drugs

Despite the potent anticoagulant effect of DTIs as seen in the clinical trials, there remains an unacceptable level of thrombosis-related morbidity and mortality in HIT patients. The glycoprotein (GP) IIb/IIIa platelet receptor inhibitors (abciximab, eptifibatide and tirofiban) and the ADP platelet receptor inhibitor (clopidogrel) have been shown to inhibit the in vitro platelet activation and aggregation responses induced by HIT serum and heparin [15, 17, 19, 55]. This includes inhibition of the formation of thrombogenic platelet microparticles. The DTIs were not effective in suppressing this platelet activation.

Limited clinical experience suggests that a GPIIb/IIa inhibitor as an adjunct to a DTI is effective at reducing thrombus that is resistant to DTI treatment alone [19]. A standard dose of a GPIIb/IIa inhibitor can be administered with a reduced dose of the DTI. In a small group of HIT patients treated as such, there was no overt bleeding that required intervention and all patients exhibited clinical improvement or full recovery. Although promising, optimal dosing for this combination regimen has not yet been established.

Argatroban for Acute Coronary Syndrome

Percutaneous Coronary and Peripheral Intervention

Frequently, patients with HIT require coronary interventional procedures. The feasibility of using argatroban in this patient population was established several years ago [56–58]. Subsequently, two trials (ARG216 and ARG310/311) assessed the safety and efficacy of argatroban as anticoagulant therapy for percutaneous coronary interventional (PCI) procedures, including percutaneous transluminal coronary angioplasty, stent implantation or rotational atherectomy, on HIT patients (table 5) [59].

Patients (n = 91; 112 PCIs) were given 350 μg/kg bolus argatroban followed by a 25 μg/kg/min infusion. Efficacy of anticoagulation for argatroban-treated PCI HIT patients was measured by comparison to the Cleveland Clinic PCI angioplasty registry of heparin-treated non-HIT patients during the concordant time of patient enrollment. Safety of argatroban for PCIs was assessed by comparing the bleeding rate with argatroban to the heparin only arm of the EPILOG trial, which was also conducted during the same time period as patient enrollment in the argatroban PCI trials.

Table 5. Summary of the pilot cardiology studies of argatroban

<table>
<thead>
<tr>
<th>Table 5. Summary of the pilot cardiology studies of argatroban</th>
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<tbody>
<tr>
<td>a  Angioplasty: ARG-216/310/311</td>
</tr>
<tr>
<td>Acute procedural success, %</td>
</tr>
<tr>
<td>Major bleeding, %</td>
</tr>
<tr>
<td>b  Acute myocardial infarction: MINT; ARGAMI</td>
</tr>
<tr>
<td>Acute procedural success, patients presenting within 6 h, %</td>
</tr>
<tr>
<td>Acute procedural success, patients presenting within 3 h, %</td>
</tr>
<tr>
<td>Composite endpoint at 30 days, %</td>
</tr>
<tr>
<td>Major bleeding, %</td>
</tr>
</tbody>
</table>

Argatroban achieved adequate anticoagulation within 10 min of initiation.

*p = 0.03.

1 350 μg/kg bolus plus 25 μg/kg/min infusion.

2 100 μg/kg bolus plus 1 μg/kg/min infusion for 48–72 h.

3 100 μg/kg bolus plus 3 μg/kg/min infusion for 48–72 h.
The 94.5% acute procedural success rate with argatroban compared favorably with the 94.0% procedural success rate with heparin in patients undergoing their initial PCI with argatroban. No unsatisfactory outcomes occurred during repeat PCIs with argatroban (n = 21). Only 1 patient experienced major peri-procedural bleeding. The safety of argatroban during PCI was at least equivalent to that of heparin during PCI (1.1% major bleed rate with argatroban vs 3.1% with heparin).

Adequate anticoagulation as measured by the activated clotting time (ACT) was achieved in 97.8% of argatroban-treated patients after the initial argatroban bolus. The target ACT for PCI of 300–450 s was achieved within 10 min of initiation of argatroban [57]. An ACT of >300 s was maintained throughout the interventional procedure in over 80% of the argatroban-treated patients. A repeat argatroban bolus of 150 µg/kg generally re-established a therapeutic ACT. An ACT of 200–250 s is recommended when argatroban is used in conjunction with a GPIIb/IIIa inhibitor.

Argatroban has also been used for PCI in a limited number of non-HIT patients [1, 60–62]. Three studies reported procedural success in all patients. Argatroban produced predictable anticoagulation and was generally safe and well tolerated.

Although the data are promising for the use of argatroban in PCI in HIT and non-HIT patients, the registry style control data collection used in some of these studies could have introduced observational bias due to the non-blinded nature of the study design. Argatroban is indicated as an anticoagulant in patients with or at risk for HIT undergoing PCI. (Source: Argatroban US prescribing information leaflet, April 2002.)

The use of argatroban for peripheral vascular procedures including carotid and renal arteries as well as cerebral vessels has not been formally studied; however, a number of case reports provide some information regarding the feasibility of argatroban in these situations [58, 63, 64]. Small vessel interventions on tibial and peroneal arteries or intracranial vessels can probably be safely performed using coronary argatroban dosing strategies (350 µg/kg bolus followed by 25 µg/kg/min infusion). Larger vessels such as iliac and renal arteries can probably be treated with lesser argatroban doses (250 µg/kg bolus followed by 10 µg/kg/min infusion).

**Acute Myocardial Infarction**

The investigation of argatroban as adjunct therapy to thrombolytics for patients with acute ST elevation myocardial infarction (MI) was performed in a three-arm clinical study, the MINT trial (Myocardial Infarction with Novastan and tPA) [65]. Patients, within 6 h of onset of symptoms for AMI, were randomized to low-dose argatroban (100 µg/kg bolus plus 1 µg/kg/min infusion for 48–72 h), high-dose (100 µg/kg bolus plus 3 µg/kg/min infusion for 48–72 h) argatroban or heparin as adjunct therapy to tPA (n = 125).

The primary efficacy outcome (rate of TIMI grade 3 flow at 90 min) was achieved in 42.1% of heparin, 56.8% of low-dose argatroban (p = 0.20 vs. heparin) and 58.7% of high-dose argatroban patients (p = 0.13 vs. heparin) (table 5). In patients presenting after 3 h, TIMI grade 3 flow was significantly more frequent in high-dose argatroban than heparin patients (57.1 vs. 20.0%; p = 0.03). Major bleeding was observed in 10.0% of heparin, and in 2.6 and 4.3% of low-dose and high-dose argatroban patients. The composite endpoint (death, recurrent MI, cardiogenic shock, congestive heart failure, revascularization, recurrent ischemia at 30 days) occurred in 37.5% of heparin, 32.0% of low-dose and 25.5% of high-dose argatroban patients (p = 0.23).

A second study was conducted which compared argatroban to heparin as adjunct therapy to alteplase (tPA) for the treatment of acute MI [66]. The ARGAMI (Argatroban in Acute Myocardial Infarction) study was an open dose-finding study (n = 35), followed by a placebo-controlled study with a double-dummy technique and a 2:1 (argatroban, n = 82;heparin, n = 45) randomization. An argatroban dose of 100 µg/kg bolus plus 3 µg/kg/min infusion for 72 h was selected for the randomized study. TIMI grade 2 or 3 flow after 90 min, not different between treatment groups, was obtained in 76% of the argatroban patients and in 82% of the heparin patients (not significant). Coronary angiography after 24 h and at 5–10 days showed similar low reocclusion rates in both groups. Bleeding complications, similar in both groups, were observed in 19.5% of the argatroban and in 20.0% of the heparin patients.

**Summary**

The introduction of direct thrombin inhibitor drugs, such as argatroban, has added a new dimension to the management of thrombosis (table 6). These drugs offer a unique substitute for anticoagulation in patients who are heparin compromised, a position we have not had prior to now. Based on clinical studies that have demonstrated the efficacy in patients with HIT, argatroban has been approved in the US for both prophylaxis and treatment of thrombosis in patients with HIT.
The use of DTIs in acute coronary syndrome represents a new application of this class of drugs. Pooled data from the OASIS, TIMI and GUSTO clinical studies showed a significant reduction in cardiac events using hirudin compared to heparin. But unfortunately, it also showed a significant increase in bleeding. Treatment with the shorter-acting hirudin derivative, hirulog, was shown to be associated with both a lower incidence of ischemia and unstable angina and a decreased bleeding rate compared to heparin. Data from the CACHET trial showed a decrease in combined endpoints using DTIs during coronary intervention.

Limited studies suggest that argatroban will provide reliable anticoagulation during PCI and during peripheral vascular interventions in both large and small vessels in HIT patients. In patients with and without HIT procedural success rates similar to that of heparin were demonstrated. Argatroban has also been used in HIT patients with unstable angina and for the treatment of AMI as an adjunct to thrombolysis. Similar clinical outcomes to heparin-treated patients and no significant differences for major hemorrhage were observed with argatroban.

The main attributes of argatroban are its rapid onset of action, the fast reversibility of its anticoagulant effect, inhibition of clot-bound thrombin and no need for dosage adjustment in patients with renal impairment (tables 1, 2). Argatroban is easily monitored by the aPTT for low doses and the ACT for high doses. These properties make argatroban a predictable, safe, easy to dose anticoagulant. Argatroban will continue to be studied as an antithrombotic agent in additional clinical settings such as ischemic and thrombotic stroke and as an adjunct anticoagulant for various indications.

References


