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EXPERT REVIEW

Safety and Efficacy of Argatroban in the Management of Heparin-Induced Thrombocytopenia

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Abstract: Heparin-induced thrombocytopenia (HIT) is a life-threatening adverse reaction to heparin therapy that is characterized by thrombocytopenia and an increased risk of venous and arterial thrombosis. According to guidelines, in patients with strongly suspected or confirmed HIT all sources of heparin have to be discontinued and an alternative, nonheparin anticoagulant for HIT treatment must immediately be started. For both the prophylaxis of thrombembolic events in HIT and the treatment of HIT with thrombosis the direct thrombin inhibitor argatroban is approved in the United States. The objective of this review is to describe the mechanism of action and the pharmacokinetic profile of argatroban, to characterize argatroban regarding its safety and therapeutic efficacy and to discuss its place in therapy in HIT.

Keywords: argatroban, heparin-induced thrombocytopenia, anticoagulation

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Introduction

Both unfractionated heparins and low-molecular-weight heparins (LMWH) are very commonly used in hospitalized patients for the prophylaxis of thrombosis, for therapeutic anticoagulation, and as anticoagulant agents during renal replacement therapy.[1–3] Occasionally heparins can lead to a life-threatening adverse reaction that is characterized by thrombocytopenia and an increased risk of venous and arterial thrombosis: Heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis (HITT).[4,5] Historically, it has been differentiated between two types of HIT (HIT type I and HIT type II).[6,7] Since HIT type I (a common, non-immune-mediated decline in platelet count in heparin-treated patients) is self-limiting and not associated with thrombosis, it is usually considered to be of no clinical significance.[7] Therefore, HIT is usually referred to as HIT type II that is an immune-mediated serious prothrombotic disorder.

The use of both unfractionated heparin and LMWH can lead to HIT with a lower incidence of HIT in LMWH-treated patients.[4] In addition to the type of heparin used, the frequency of HIT depends on various other influencing factors including the patient population.[4] The usually reported frequency of HIT is 0.5%–5% of patients exposed to heparins, with the exception of cardiac transplantation patients with an HIT frequency of up to 11%.[4,5,8]

Regarding the pathogenesis of HIT, immunglobuline G-class antibodies bind to a complex formed of heparin and platelet factor 4.[4,6,9–11] This immune complex of "HIT antibodies", heparin, and platelet factor 4 binds to the Fc receptor on platelets inducing activation of platelets and release of "platelet-derived procoagulant microparticles" finally leading to platelet aggregation and consumption and thrombocytopenia.[4,6] In addition, these complexes cause excessive thrombin generation increasing the risk of thrombembolic events.[4,6]

New venous or arterial thrombosis (deep vein thrombosis, pulmonary embolism, myocardial infarction, limb artery occlusion) as clinical signs for HIT occur commonly in patients with HIT (in 38%–76% of patients treated by only stopping heparin exposure) and often lead to the diagnosis of HIT as the first recognized symptom.[4,12–16]

For the diagnosis of HIT clinical and laboratory findings have to be combined: In patients exposed to heparins showing a decline in platelet count to $<150 \times 10^9$/L or of more than 50%, HIT should be considered.[4–6] The decline in platelets can usually be recognized starting 5 to 14 days after the initiation of heparin treatment.[4–6,17] However, besides this "typical-onset" HIT, "rapid-onset" HIT in patients with prior heparin exposure within the previous 100 days and "delayed-onset" HIT characterized by HIT symptoms developing 9 to 40 days after heparin exposure are known.[4,6,17,18]

Since thrombocytopenia is a common finding in many different disorders, a clinical-laboratory test for the assessment of the pretest probability of HIT in patients at risk has been introduced ("4 T's"-Test).[4,6,19]

Laboratory testing for HIT should be performed on clinical suspicion of HIT (decline in platelet count and/or occurrence of thrombosis with typical time course during or after heparin exposure).[4,20] For laboratory confirmation of HIT antigen assays as well as functional assays are available.[4,6]

However, practice guidelines strongly recommend *not* to await the result of the laboratory confirmation test in patients with strongly suspected HIT but to discontinue all sources of heparin immediately *and* to start an alternative, nonheparin anticoagulant for HIT treatment promptly.[4–6]

For both the prophylaxis of thrombembolic events in HIT and the treatment of HITT the direct thrombin inhibitors argatroban and lepirudin are approved in the United States.

The objective of this review is to describe the mechanism of action and the pharmacokinetic profile of argatroban, to characterize argatroban regarding its safety and therapeutic efficacy and to discuss its place in therapy in HIT.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Argatroban is a synthetic low-molecular weight L-arginine derivate (molecular mass 508.7 Da).[21,22] It is a mixture of 21-R and 21-S stereoisomers in a ratio of about 64:36.[21,23,24] Argatroban acts as an anticoagulant by competitive direct thrombin inhibition reducing the thrombin activity.[21] No co-factor is needed for direct inhibition of thrombin by argatroban.[4,25]

Argatroban selectively binds to the active (catalytic) site of both clot-bound and free thrombin forming a reversible complex.[22,26,27] It is classified as a univalent direct thrombin inhibitor since it only binds to the active site of thrombin and not to one of the two "exosites" located at opposite poles of the molecule.[21,28] No binding to platelet factor 4 and no generation of antibody complexes by argatroban has been described.[4,21]

Argatroban is metabolized in the liver by hydroxylation and aromatization of the 3-methyltetrahydroquinolone ring into four metabolites that are mostly inactive.[21,25,29] Although metabolization of argatroban by cytochrome P450 3A4/5 enzymes has been observed in vitro, this elimination pathway seems to be of limited importance in vivo.[25]

A study investigating the pharmacokinetic characteristics of argatroban in healthy volunteers and volunteers with hepatic or renal impairment showed that a two-compartment model with first-order elimination best fitted the observed pharmacokinetic data.[25] Argatroban is characterized by a rapid onset of the anticoagulant effects after starting its administration (steady-state activated partial thromboplastin time (aPTT) target levels are achieved in 1–3 hours) and a fast elimination after cessation of argatroban infusion.[25] The plasma half-life of argatroban is 39–51 minutes.[25] In the study by Swan et al it has been shown that the plasma half-life of argatroban is not altered by renal insufficiency and is not age or sex dependent.[25] However, compared to elderly women, the clearance of argatroban is significantly lower (20%) in elderly men.[25] In patients with impaired hepatic function argatroban clearance is reduced and elimination half-life is longer compared to individuals without liver disease ($P < 0.01$).[25] Anticoagulatory effects of argatroban are well predictable, since plasma drug concentrations of argatroban show a good correlation with anticoagulant effects measured by aPTT and activated clotting time.[25]

Although there is evidence from the study by Swan et al and from other studies investigating this issue, that the argatroban metabolism is not influenced by renal impairment and that argatroban can be used in renal failure and even during renal replacement therapy (RRT),[25,30–35] there are also data suggesting that dose adjustment of argatroban should be considered in patients with renal insufficiency.[30,34,36] The argatroban dose needed to achieve the therapeutic aPTT levels was statistically significantly associated with creatinine clearance in 2 studies investigating patients with renal insufficiency excluding patients with hepatic impairment.[30,36,37]

The recommended initial infusion rate of argatroban in the prophylaxis or treatment of thrombosis in HIT in patients without hepatic impairment is 2 μg/kg/min without an initial bolus.[4,5,21,38] In patients with impaired hepatic function a reduced starting dose of 0.5 μg/kg/min should be used.[5,39] In general, the argatroban dose should be adjusted to achieve a target aPTT level of 1.5 to 3 times the patient's baseline aPTT value.[4,5,21,38] According to consensus guidelines and data from recent trials in certain patient populations (eg, patients with multiple organ dysfunction syndrome or heart failure) markedly lower doses of argatroban are needed to achieve the target aPTT levels.[5,40]

Clinical Studies

Prospective clinical studies investigating the efficiency and safety of argatroban as anticoagulant therapy in patients with HIT or HITT were presented by Lewis and co-workers 2001 and 2003 (ARG-911 and ARG-915 study).[14,38] Using a multicenter, nonrandomized, open-label, historically-controlled trial design, the ARG-911 study group investigated 160 patients with HIT and 144 patients with HITT both treated with argatroban (with an initial starting dose of 2 μg/kg/min and dose adjustment to achieve aPTT values of 1.5 to 3 times the baseline aPTT value) compared to patients from a historical control collective with HIT (n = 147) or HITT (n = 46).[38] The patients from the historical control collective had been treated with cessation of heparin therapy and/or oral anticoagulation.[38] Patients were treated with a mean (±SE) argatroban dose of 2.0 ± 0.1 μg/kg/min for 5.3 ± 0.3 days in HIT patients and 1.9 ± 0.1 μg/kg/min for 5.9 ± 0.2 days in HITT patients.[38] Summarizing the results of this trial, argatroban therapy significantly improved the clinical outcomes in the study period of 36 days compared to patients not treated with argatroban in the historical control group (for details see below).[38]

In accordance, the ARG-915 study demonstrated that argatroban therapy—again compared with the same historical control collective investigated in the ARG-911 study—improves clinical outcomes

(especially occurrence of new thrombosis and death due to thrombosis) in patients with HIT.[14] The multicenter prospective ARG-915 study evaluated 189 patients with HIT and 229 patients with HITT treated with the same argatroban dosing protocol used in the ARG-911 study.[14,38]

Safety

Excessive anticoagulation with the risk of bleeding complications is the major risk when using argatroban for prophylaxis or therapy of thrombosis in HIT patients. Major uncontrolled hemorrhage is a contraindication for argatroban therapy.

Among the 304 patients treated with argatroban after enrollment in the ARG-911 study the adverse events coagulopathy (2 patients), anemia (2 patients), gastrointestinal hemorrhage (2 patients) and unspecific hemorrhage (3 patients) were observed.[38] However, major and minor bleeding complications were not statistically significantly different between argatroban-treated patients and historical controls treated with discontinuation of heparin and/or oral anticoagulation (major bleeding: HIT patients, argatroban vs. controls: 3.1% vs. 8.2%, $P = 0.078$; HITT patients, argatroban vs. controls: 11.1% vs. 2.2%, $P = 0.077$).[38] In the argatroban-treated group of patients with HIT and HITT the most common adverse events were diarrhea (11%) and pain (9%). Regarding drug-related adverse events, HIT patients most commonly suffered from rash (2%), unspecific hemorrhage (2%), and purpura (2%), whereas thrombophlebitis was observed as drug-related adverse event in 4% of HITT patients.[38]

According to the results from the ARG-915 study, the incidence of major as well as minor bleeding complications was not different between the patients in the study group treated with argatroban compared to patients in the historic control group (major bleeding: HIT patients, argatroban vs. controls: 5.3% vs. 8.6%, $P = 0.27$; HITT patients, argatroban vs. controls: 6.1% vs. 2.2%, $P = 0.48$).[14]

At present, no antidote for argatroban is available. Therefore, aPTT values should be monitored closely to achieve the target aPTT level of 1.5 to 3 times the baseline aPTT (avoiding an aPTT longer than 100 seconds) in order to avoid excessive anticoagulation and to minimize the risk of bleeding complications during argatroban therapy.[4,5] The recommended starting dose of argatroban in the prophylaxis or treatment of thrombosis in HIT is 2 µg/kg/min (0.5 µg/kg/min in patients with hepatic dysfunction).[4,5,21,38,39] The maximum dose of argatroban in the treatment of HIT patients is 10 µg/kg/min.[21] It has been shown that stepwise dose adjustments of 0.5 µg/kg/min (0.25 µg/kg/min in patients treated with lower doses) according to aPTT values allow appropriate dosage finding.[41]

In patients developing HIT after heparin treatment for coronary artery disease argatroban can be safely and effectively used for anticoagulation according to a study by Jang et al.[42]

Argatroban anticoagulation has been demonstrated to be safe in patients with renal impairment and during RRT according to a literature analysis by Hursting and Murray.[37] A retrospective analysis of patients with HIT and the need for RRT demonstrated that in 6% of patients (3 of 50) major bleeding complications occurred when normal starting doses (2 µg/kg/min in patients without liver impairment) were used.[32] Link and colleagues showed in a prospective dose finding study conducted in a medical and a surgical intensive care unit of a German university hospital that argatroban can provide safe and effective anticoagulation in critically ill patients during continuous RRT.[34] However, a markedly reduced maintenance dose was needed to achieve target anticoagulation levels (mean dose of argatroban 0.7 µg/kg/min).[34]

In addition, there is increasing evidence that special patient populations besides patients with hepatic impairment are at increased risk for excessive anticoagulant effects of argatroban.

Consensus guidelines already recommend a reduced starting dose of argatroban (0.5–1.2 µg/kg/min) for patients with heart failure, multiple organ dysfunction syndrome, severe anasarka, and post-cardiac surgery patients.[5,43–46]

Regarding the treatment of HIT using argatroban in critically ill patients there are contradicting data from previous studies.

Data from an analysis of a subgroup of acutely ill patients taken from the ARG-911 and ARG-915 studies demonstrated that these acutely ill patients can be treated with the normal recommended argatroban doses.[47] In this analysis by Gray and colleagues acute illness was defined as suffering from one or more of 8 ongoing medical conditions (cardiac surgery,

including coronary artery bypass graft surgery, acute myocardial infarction, pulmonary embolism, acute respiratory distress syndrome, acute coronary syndrome, trauma, or ventricular assist device).[47] The mean argatroban dose used in these patients was 1.9 ± 1.2 μg/kg/min for 6.0 ± 5.2 days.[47] Since the frequency of major bleeding did not differ between the study group and the control group (taken from the historical control collective), the authors concluded that no particular dose reduction is needed in the treatment of these acutely ill patients.[47]

In contrast, there are reports that a reduction in argatroban starting doses and maintenance doses is mandatory to avoid supertherapeutic anticoagulant effects and bleeding complications in critically ill patients developing HIT, especially in the setting of multiple organ failure or post-cardiothoracic surgery.[46,48,49]

There is increasing evidence that pharmacokinetics and clearance of argatroban seem to be markedly altered in intensive care unit patients with multiple organ dysfunction syndrome. Beiderlinden et al prospectively investigated 24 patients with multiple organ dysfunction syndrome and HIT who were treated with argatroban to achieve an aPTT target level of 1.5 to 2 times the normal aPTT or an aPTT of 50–60 seconds.[43] To achieve these anticoagulation goals in these critically ill patients, a final mean argatroban maintenance dose of only 0.22 ± 0.15 μg/kg/min was needed.[43] Whereas bleeding complications occurred in patients treated with the recommended dose of 2 μg/kg/min, anticoagulation with a argatroban starting dose of 0.2 μg/kg/min resulted in sufficient anticoagulation without bleeding complications.[43] These data are supported by a retrospective analysis of 12 medical intensive care unit patients with multiple organ dysfunction syndrome and HIT showing that these patients can be effectively treated with argatroban when using markedly reduced doses: to achieve a target aPTT of >60 seconds or 1.5 to 3 times the baseline value, a mean argatroban dose of 0.24 ± 0.16 μg/kg/min was sufficient.[40] Another retrospective analysis of 65 intensive care unit patients also showed that patients with multiple organ failure or heart failure need reduced argatroban doses in the treatment of HIT.[50] The mean argatroban dose of 0.58 ± 0.28 μg/kg/min in patients with heart failure was significantly lower compared to intensive care unit patients without heart failure (P = 0.042).[50] Patients with 3 failed organ systems also needed a markedly lower dose of argatroban (0.58 ± 0.47 μg/kg/min).[50]

According to the mentioned studies and to consensus guidelines in certain critically ill patients with HIT (eg, patients with multiple organ dysfunction syndrome or heart failure) markedly lower starting and maintenance doses of argatroban are usually sufficient to achieve the target aPTT levels probably because of the reduced hepatic perfusion in these patients.[5,39,40,43,51]

Efficacy

Argatroban has been shown to be effective in the prophylaxis and therapy of thrombosis in HIT in several patient collectives.

The elementary efficacy data were obtained in the before alluded trials ARG-911 and ARG-915.[14,38] In these 2 multicentric and prospective trials efficacy of argatroban in the treatment of HIT and HITT was compared to the historic control collective treated by cessation of argatroban and/or oral anticoagulation.[14,38] In both studies the recommended initial dose of 2 μg/kg/min was used (lower doses were used in patients with hepatic impairment).[14,38] The maintenance dose was adjusted in order to achieve a target aPTT value 1.5 to 3 times the patient's baseline aPTT.[14,38] In each study, the study groups (304 patients in ARG-911, 418 patients in ARG-915) were assigned to the HIT or HITT study arm.[14,38]

Results regarding efficacy of argatroban in the ARG-911 study can be summarized as follows: In patients with HIT, the primary efficacy endpoint (a composite endpoint of all-cause death, all-case amputation, or new thrombosis) was statistically significantly reduced in patients treated with argatroban compared to patients from the historical control group (25.6% vs. 38.8%; P = 0.014).[38] In HITT patients the reduction in this composite incidence did not reach statistic significance (43.8% vs. 56.5%; P = 0.131).[38] Whereas, the incidence all-cause death and all-cause amputation was not significantly different between the study group and the control collective in both study arms (HIT and HITT), the incidence of new thrombosis and death caused by thrombosis was significantly reduced in both HIT and HITT patients treated with argatroban compared to patients from the historical control group.[38] Adequate anticoagulation (defined by a aPTT target

value of 1.5 times the baseline aPTT) was achieved in 83% (HIT) and 94% (HITT) of argatroban-treated patients and in about 4–5 hours after starting the argatroban infusion in 76% (HIT) and 81% (HITT) of patients, respectively.[38] The median daily aPTT values during the study period were 52.2 to 62.6 seconds (HIT patients) and 52.4 to 68.0 seconds (HITT patients).[38]

In the ARG-915 study the same control collective from the ARG-911 study was compared to argatroban-treated patients with HIT (n = 189) and HITT (n = 229).[14] The same composite primary efficacy outcome endpoint used in ARG-911 was analyzed in ARG-915: The composite primary endpoint occurred in 28.0% of HIT patients (38.8% in controls; $P = 0.04$) and 41.5% of HITT patients (56.5% in controls; $P = 0.07$).[14] Again, as already observed in the ARG-911 study, the rate of new thrombosis ($P < 0.001$ for both study arms) was significantly lower in patients treated with argatroban.[14] Compared to controls, the secondary efficacy endpoint death caused by thrombosis occurred significantly less often in argatroban treated patients with both HIT and HITT ($P = 0.04$ and $P = 0.002$, respectively).[14]

Time-to-event analysis performed for the composite primary efficacy endpoint for both studies (ARG-911 and ARG-915) statistically significantly favored the use of argatroban in both HIT and HITT patients ($P < 0.02$).[4,14,38]

In addition, a study combining the results of the ARG-911 study and the ARG-915 study revealed that the use of argatroban in the study group significantly reduced the incidence of new stroke ($P = 0.041$) and stroke-related mortality ($P = 0.039$).[52]

As aforementioned when discussing safety of argatroban, argatroban can be efficiently used in patients with HIT and renal impairment as well as during RRT.[37] Data obtained in a retrospective analysis demonstrated that argatroban provided sufficient anticoagulation during RRT in patients with HIT when using the doses recommended by the manufacturer.[32] The aPTT ratio (achieved aPTT relative to baseline aPTT) was 2.2 (1.6–3.6) and 2.0 (1.4–4.1) for patients without and with hepatic impairment, respectively.[32] In a prospective study in critically ill patients with HIT and the need for continuous RRT argatroban was administered as a bolus of 100 µg/kg followed by an infusion rate of 1 µg/kg/min providing effect anticoagulation during continuous RRT.[34] After adjustment of the argatroban maintenance infusion dose to the target aPTT (median duration till aPTT target of 70–90 seconds was achieved: 5 hours), the infusion rate was kept stable during the continuous RRT treatment period without signs of reduced argatroban effects during continuous RRT.[34] As mentioned before, in this patient population a reduced mean dose of argatroban (0.7 µg/kg/min) was sufficient.[34]

As described above, argatroban can be used efficiently in intensive care unit patients with multiple organ dysfunction syndrome. According to the few studies investigating argatroban therapy for HIT in these critically ill patients sufficient anticoagulatory effects are observed even with markedly lower doses of argatroban than usually recommended.[5,39,40,43,50,51]

Argatroban is FDA-approved in patients with contraindications for heparin undergoing percutaneous coronary intervention (PCI).[5] Three prospective, multicenter studies, ARG-216, ARD-310, and ARG-311 that were combined in a pooled analysis investigated the efficacy and safety of argatroban in HIT patients undergoing PCI.[53] In these studies, patients received oral aspirin (325 mg) 2–24 hours before PCI and a bolus of argatroban of 350 µg/kg followed by continuous argatroban infusion at a rate of 25 µg/kg/min or 30 µg/kg/min (ARD-310 and ARG-311 or ARG-216, respectively).[53] The infusion rate was adjusted to achieve a target activated clotting time of 300–450 seconds.[53] The mean infusion dose was 23.1 ± 7.0 µg/kg/min in the group of patients undergoing initial PCI and 22.1 ± 4.5 µg/kg/min in the group of patients undergoing repeated PCI.[53] At the discretion of the investigator, argatroban infusion was continued after PCI at a reduced dose of <10 µg/kg/min adjusted to achieve aPTTs of 1.5 to 3 times the value before PCI.[53] In 91 HIT patients a total of 112 PCIs were performed using argatroban anticoagulation.[53] In 94.5% of patients undergoing initial PCI the primary endpoint (subjective assessment of the attainment of a satisfactory outcome of the procedure) was achieved (100% in the repeat group).[53] In addition, in 97.8% of patients in this group adequate anticoagulation during PCI (subjective assessment by the investigator) was observed (100% in the group of patients undergoing repeated PCI).[53] Major acute

complications (myocardial infarction in four patients, revascularization at 24 hours after PCI in four patients) occurred in 7.7% of patients overall.[53] In only one of the 91 patients undergoing initial PCI a major bleeding complication (non-fatal retroperitoneal hemorrhage) was observed.[53]

There is very limited data on the anticoagulant effectiveness (and safety) of argatroban in patients treated with extracorporeal lung-assist devices. Data on this clinical setting are limited to case reports describing the use of argatroban in patients with HIT and acute respiratory distress syndrome treated with venovenous extracorporeal membrane oxygenation.[54,55] There is one case report describing an "off-label use" of argatroban in a patient with HIT treated with the arteriovenous interventional lung-assist device (although HIT is considered a contraindication since the membrane of the interventional lung-assist device is heparin-coated).[56]

Place in Therapy

HIT is a transient prothrombotic adverse event of heparin therapy. After cessation of heparin, thrombocytopenia resolves within days or weeks and the HIT antibodies disappear within weeks or a few months.[5,17] Therefore, during this relatively short period the benefits of an anticoagulant therapy exceed its potential risks and immediately starting an anti-thrombotic therapy is of crucial importance in the management of HIT patients.[5]

Before the platelet count is recovered (usually above 150×10^9/L) and therefore vitamin K antagonist therapy can be initiated, an alternative nonheparin anticoagulant has immediately to be started.[5]

In the United States three alternative anticoagulants are approved for the treatment of HIT: the direct thrombin inhibitors lepirudin, argatroban and bivalirudin (the latter one only for patients undergoing percutaneous transluminal coronary angioplasty).[5] The factor Xa inhibitor danaparoid was withdrawn from the United States market in 2002.[5]

Even practice guidelines state that the optimal management strategy for HIT remains uncertain.[5] However, for patients with strongly suspected (or confirmed) HIT or HITT the use of an alternative nonheparin anticoagulant is recommended with a Grade 1B recommendation for danaparoid (that has been withdrawn from the United States market) and a Grade C recommendation for the other direct thrombin inhibitors lepirudin and argatroban.[5] Regarding direct thrombin inhibitors, the physicians can therefore choose between lepirudin and argatroban in the prophylaxis and therapy of thrombosis in HIT.[5] In contrast to argatroban, that is primarily metabolized by the liver with an elimination half life of about 45 minutes, lepirudin is renaly eliminated with an elimination half life of about 80 minutes.[5] According to practice guidelines for both direct thrombin inhibitors the recommended doses are lower compared to the recommendations in the package insert.[5] The infusion rate of lepirudin needs to be adjusted to different degrees of renal insufficiency.[5] For argatroban, a reduced initial dose of 0.5 μg/kg/min instead of 2 μg/kg/min is recommended for patients with hepatic impairment.[5]

Conclusions

Argatroban is a direct thrombin inhibitor.[21] Argatroban is primarily hepatically metabolized.[21,25,29] The plasma half-life of argatroban in healthy subjects is about 45 minutes.[25]

The recommended initial infusion rate of argatroban in the prophylaxis or treatment of thrombosis in HIT in patients without hepatic impairment is 2 μg/kg/min without an initial bolus.[4,5,21,38] In patients with impaired hepatic function a reduced starting dose of 0.5 μg/kg/min should be used.[5,39] In general, the argatroban dose should be adjusted to achieve a target aPTT level of 1.5 to 3 times the patient's baseline aPTT value.[4,5,21,38]

The safety and efficacy of argatroban in the treatment of HIT patients has been demonstrated in 2 prospective, multicenter, nonrandomized, open-label, historically-controlled trials (ARG-911 and ARG-915 study).[14,38] In both studies, argatroban therapy significantly improved the clinical outcomes (especially the occurrence of new thrombosis and death due to thrombosis) without increasing the risk of bleeding complications.[14,38]

Argatroban anticoagulation has been demonstrated to be safe in patients with renal impairment and during RRT.[37]

In certain critically ill patients with HIT (eg, patients with multiple organ dysfunction syndrome or heart failure) markedly lower starting and maintenance doses of argatroban are usually

sufficient to achieve the target aPTT levels probably because of the reduced hepatic perfusion in these patients.[5,39,40,43,51]

Argatroban can be used in patients with HIT undergoing PCI.[5,53]

As a conclusion, argatroban can be used as an effective and relatively safe anticoagulant in patients with HIT with or without thrombosis (according to practice guidelines Grade C recommendation).[5] Since argatroban is primarily metabolized by the liver, in patients with impaired liver function and patients with reduced hepatic perfusion recommended doses need to be markedly reduced in order to avoid excessive anticoagulant effects.[5]

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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