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Reducing Harm Associated with Anticoagulation

Practical Considerations of Argatroban Therapy in Heparin-Induced Thrombocytopenia

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Abstract

Argatroban is a hepatically metabolized, direct thrombin inhibitor used for prophylaxis or treatment of thrombosis in heparin-induced thrombocytopenia (HIT) and for patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI). The objective of this review is to summarize practical considerations of argatroban therapy in HIT.

The US FDA-recommended argatroban dose in HIT is 2 μg/kg/min (reduced in patients with hepatic impairment and in paediatric patients), adjusted to achieve activated partial thromboplastin times (aPTTs)

1.5–3 times baseline (not >100 seconds). Contemporary experiences indicate that reduced doses are also needed in patients with conditions associated with hepatic hypoperfusion, e.g. heart failure, yet are unnecessary for renal dysfunction, adult age, sex, race/ethnicity or obesity. Argatroban 0.5–1.2 μg/kg/min typically supports therapeutic aPTTs. The FDA-recommended dose during PCI is 25 μg/kg/min (350 μg/kg initial bolus), adjusted to achieve activated clotting times (ACTs) of 300–450 sec. For PCI, argatroban has not been investigated in hepatically impaired patients; dose adjustment is unnecessary for adult age, sex, race/ethnicity or obesity, and lesser doses may be adequate with concurrent glycoprotein IIb/IIIa inhibition. Argatroban prolongs the International Normalized Ratio, and published approaches for monitoring the argatroban-to-warfarin transition should be followed. Major bleeding with argatroban is 0–10% in the non-interventional setting and 0–5.8% periprocedurally. Argatroban has no specific antidote, and if excessive anticoagulation occurs, argatroban infusion should be stopped or reduced.

Improved familiarity of healthcare professionals with argatroban therapy in HIT, including in special populations and during PCI, may facilitate reduction of harm associated with HIT (e.g. fewer thromboses) or its treatment (e.g. fewer argatroban medication errors).

The Joint Commission's 2008 National Patient Safety Goals in the US call for a reduction in the likelihood of patient harm associated with anticoagulation therapy. Heparin-induced thrombocytopenia (HIT) is a serious adverse condition occurring in approximately 0.5–5% of heparin-treated patients.[1] In HIT, antibodies against heparin-platelet factor 4 complexes induce platelet activation; procoagulant microparticle release, thrombocytopenia, excessive thrombin generation and hypercoagulability result.[2] Thrombosis, often fatal, occurs in 38–76% of affected patients.[3] As stated in guidelines,[4,5] HIT should be suspected whenever the platelet count decreases by 50%, or new thrombosis occurs, typically 5–14 days after heparin initiation. When HIT is strongly suspected, heparin should be stopped immediately and a fast-acting, non-heparin anticoagulant, such as the direct thrombin inhibitor (DTI) argatroban, initiated. Unfortunately, serious gaps exist between guidelines and clinical practice. In one registry,[6] HIT was suspected in only 9% of patients who developed thrombocytopenia after 4 days of heparin therapy, and only 25% of the suspected HIT patients received a DTI, often after significant delay. HIT therefore represents a unique and complex clinical situation whereby harm is caused by heparin anticoagulation. Treatment using non-heparin anticoagulation (which in turn requires proper attention for safe usage) is required, yet frequently not started.

Argatroban is indicated as an anticoagulant for prophylaxis or treatment of thrombosis in HIT (North America, Europe and Japan) and, in the US, for patients with or at risk of HIT undergoing percutaneous coronary intervention (PCI). Marketed in the US since 2000, argatroban is a relatively new anticoagulant. Unfamiliarity of healthcare professionals with argatroban, and less experience with its use, may contribute to poor compliance with HIT treatment guidelines as well as medication errors when it is used.[6-8] In prospective historical controlled studies,[9-11] argatroban improved outcomes in HIT, particularly reducing new thrombosis and mortality due to thrombosis, without increasing bleeding. In patients with or at risk of HIT (i.e. according to study protocol, patients with a documented history of HIT as evidenced by a previous or current clinical diagnosis of HIT or previous or current positive HIT antibody test) undergoing PCI, argatroban also enabled successful procedures, and ischaemic and haemorrhagic

outcomes were comparable with those historically reported for heparin.[12] These studies, while important for initially establishing the safety and efficacy of argatroban therapy in HIT, are not the focus of our review. Rather, we present practical considerations of argatroban usage, including its pharmacology, dosing and monitoring, administration in special populations, drug interactions, and bleeding risk and management – all with implications for maximizing safe, adequate therapy in HIT and minimizing harm associated with anticoagulation.

1. Pharmacology

1.1 Description and Mechanism of Action

Argatroban (molecular weight 527 Da; molecular formula $C_{23}H_{36}N_6O_5S{\cdot}H_2O$) is a parenteral DTI (table I). It is structurally distinct from heparins and therefore neither induces nor cross-reacts with HIT antibodies. Argatroban Injection, marketed by GlaxoSmithKline, comes as a concentrated (100 mg/mL) solution in a 2.5 mL, single-use vial and should be diluted in saline, 5% dextrose, or lactated Ringer's solution to 1 mg/mL, final concentration, before use.[13]

Argatroban reversibly binds freely circulating or clot-bound thrombin,[14,15] blocks access of naturally occurring substrates to the thrombin catalytic site,[16] and thus inhibits thrombin reactions, including activation of various coagulation proteins (e.g. fibrinogen, factor V, factor VIII) and platelet aggregation.[17] Designed to be highly specific for thrombin, argatroban negligibly affects other serine proteases.[18] In thromboelastographic studies, argatroban delays clot formation *in vitro* without significantly reducing clot strength.[19,20]

Table I. Pharmacological and other key features of argatroban

Feature	Argatroban
Drug class	Direct thrombin inhibitor
Description	Synthetic molecule
Molecular weight (Da)	527
Route of administration	Continuous intravenous infusion[a]
Primary route of elimination	Metabolized in the liver; excreted in the faeces
Systemic clearance	5.1 mL/min/kg[b]
Dialytic clearance	<23% of systemic clearance
Elimination half-life	39–51 min[c]
Pharmacodynamic/ pharmacokinetic relationship	Steady-state drug levels increase with dose up to 40 μg/kg/min and correlate well with anticoagulant effects
Routine monitoring	aPTT (ACT at higher doses used in PCI)
INR prolongation	Yes
Antidrug antibody induction	No
Cross-reactivity with HIT antibody	No
Antidote available	No

a Loading bolus also used in patients undergoing PCI.

b Decreased in hepatic impairment.

c Increased in hepatic impairment.

ACT = activated clotting time; **aPTT** = activated partial thromboplastin time; **Da** = Dalton; **HIT** = heparin-induced thrombocytopenia; **INR** = International Normalized Ratio; **PCI** = percutaneous coronary intervention.

1.2 Distribution, Metabolism and Elimination

Argatroban is 54% serum protein-bound, has a steady-state volume of distribution of 174 mL/kg, and is predominantly metabolized in the liver and excreted in faeces.[13,21,22] Of four known metabolites, the major one appears in plasma at 0–20% of the concentration of unchanged drug and 20–33% of the activity. The other metabolites are detected in urine at very low amounts and not in plasma or faeces. Urinary recovery of unchanged drug, relative to total dose, is 16% within 24 hours.[13] In healthy volunteers, argatroban clearance is 5.1 mL/min/kg, and the elimination half-life is 39–51 minutes.[22] In clinical studies, argatroban dialytic clearance is <23%.[23,24] Greater sieving coefficients have been obtained *in vitro* by adapting dialytic technique.[25]

1.3 Pharmacokinetic/Pharmacodynamic Relationship

Plasma argatroban and anticoagulant effects immediately increase upon initiation of intravenous argatroban infusion. Steady-state drug

levels occur after 1–3 hours of continuous infusion (earlier if a loading bolus is given), increase with dose up to 40 μg/kg/min, correlate well with anticoagulant effects and are stable until dose adjustment or drug cessation.[22,26,27] Argatroban prolongs, in a concentration-dependent fashion, various clot-based assays, including the activated partial thromboplastin time (aPTT, used for routine monitoring), activated clotting time (ACT, used for monitoring during PCI), prothrombin time/International Normalized Ratio (INR), thrombin time and ecarin clotting time.[22,26,28-31] After argatroban discontinuation, drug levels and anticoagulant effects jointly return to baseline typically within 2–4 hours (longer if hepatic function is impaired).[22,26,32]

1.4 Differences from Other Direct Thrombin Inhibitors Approved in Heparin-Induced Thrombocytopenia

Two other DTIs are approved for use in HIT: lepirudin in the non-interventional setting (US, Europe) and bivalirudin in the interventional setting (US). Lepirudin is indicated in patients with HIT and associated thromboembolic disease. It is a recombinant protein derived from leech hirudin. In historical controlled studies in HIT,[33] lepirudin reduced the composite of new thrombosis, amputation and death, and the overall major bleeding rate was 18% (mean duration of therapy, 14 days). Lepirudin is primarily renally cleared and doses should be decreased in renal impairment. Lepirudin frequently induces antihirudin antibodies.[34] These sometimes reduce lepirudin clearance, which may cause excessive anticoagulation. Anaphylactic reactions also rarely occur, especially on re-exposure, where the risk is approximately 0.2%.[35] Antibodies to argatroban have not been detected, despite repeated or prolonged drug exposure.[36] Bivalirudin is indicated for patients with, or at risk of, HIT undergoing PCI. It is a 20-amino acid polypeptide with sequence homology to hirudins and is cleared by renal and enzymatic mechanisms. Bivalirudin provided adequate anticoagulation and was well tolerated in 52 patients with or at risk of HIT undergoing PCI,[37] and is also well studied in non-HIT patients undergoing PCI.[38] Reduced doses are needed in renal impairment. In the non-interventional setting in HIT, no controlled studies of bivalirudin are reported, although limited case data are available.[39] Argatroban, lepirudin and bivalirudin have not been prospectively compared. Each lacks an antidote.

Non-DTI, alternative anticoagulants have also been used in patients with HIT; however, only one, the heparinoid danaparoid sodium, has been well studied and approved in this setting (e.g. in Europe and Canada; unavailable in the US).[4,5]

2. Dosing and Monitoring

2.1 Non-Interventional Setting

For prophylaxis or treatment of thrombosis in adults with HIT, the US FDA-recommended argatroban dose is 2 μg/kg/min, adjusted as clinically indicated, not to exceed 10 μg/kg/min, to achieve a steady-state aPTT 1.5–3 times the baseline value, not to exceed 100 seconds (table II).[13] A reduced dose is required if hepatic impairment is present, with an initial 0.5 μg/kg/min dose recommended for adult patients with moderate hepatic impairment. The aPTT should be checked 2 hours after the infusion is started or adjusted to ensure a therapeutic aPTT. Hospital protocols for argatroban therapy in HIT have been published.[8,40]

Postmarketing, practical experiences indicate that reduced initial doses should be considered in patients with conditions that may indirectly decrease hepatic function, i.e. heart failure, multiple organ dysfunction, anasarca and recent cardiovascular surgery.[32,41-49] In these settings, a 2 μg/kg/min initial dose may result in aPTT overshoot and excessive anticoagulation. Published, contemporary data from single centres as well as a multicentre registry indicate that argatroban 0.5–1.2 μg/kg/min (mean or median dose) typically yields target aPTTs in many hospitalized patients.[47,48,50-55] Some experts suggest initiating argatroban in this dose range for patients

Table II. US FDA recommendations: indications, dosing and monitoring of argatroban in heparin-induced thrombocytopenia (HIT)

Anticoagulant use	Initial dose	Titration
Prophylaxis or treatment of thrombosis in patients with HIT		
Adults		
normal hepatic function	2 μg/kg/min	Adjust, not to exceed 10 μg/kg/min, to achieve aPTTs 1.5–3 times the baseline value, not to exceed 100 sec
impaired hepatic function	Reduced (0.5 μg/kg/min if moderate impairment)	
Seriously ill paediatric patients[a]		
normal hepatic function	0.75 μg/kg/min	Adjust to achieve aPTTs 1.5–3 times the baseline value, not to exceed 100 sec
impaired hepatic function	0.2 μg/kg/min	
Patients with or at risk of HIT undergoing PCI		
Normal hepatic function	25 μg/kg/min, with 350 μg/kg initial bolus	Adjust between 15–40 μg/kg/min, with additional bolus doses of 150 μg/kg bolus allowed, to achieve ACTs of 300–450 sec
Clinically significant hepatic disease or transaminase levels ≥3 times ULN	Avoid; not studied in PCI, and dosing guidance is unavailable	

a Safety and effectiveness of argatroban have not been fully established in paediatric patients.

ACT = activated clotting time; **aPTT** = activated partial thromboplastin time; **PCI** = percutaneous coronary intervention; **ULN** = upper limit of normal.

with conditions that may indirectly decrease hepatic function (table III).[4]

Although argatroban safety and effectiveness are not fully established in paediatric patients, dosing guidance is available for seriously ill paediatric patients, including those with HIT, who require non-heparin anticoagulation (table II). The guidance is based on findings from a multicentre, open-label, prospective study of 18 patients ≤16 years old.[13,58] In seriously ill paediatric patients, continuous argatroban infusion should be initiated at 0.75 μg/kg/min if hepatic function is normal or 0.2 μg/kg/min if hepatic function is impaired. The aPTT should be checked 2 hours later and the dose adjusted to achieve an aPTT 1.5–3 times the baseline value, not to exceed 100 seconds.

Consideration should be given to providing the HIT patient with non-heparin anticoagulation for at least 4 weeks.[65,66] Once a patient is stably anticoagulated on argatroban and the platelet count is $\geq 150 \times 10^9$/L, a vitamin K antagonist, e.g. warfarin, may be initiated at a low, maintenance dose.[4] Because argatroban prolongs the INR, transition from argatroban to warfarin requires careful monitoring (see section 4). Reported mean or median durations of argatroban therapy in HIT range from 5 to 16 days.[9,10,47,48,51-55,59,67]

2.2 Interventional Setting

For patients with or at risk of HIT undergoing PCI, the FDA-recommended starting argatroban dose is a 350 μg/kg bolus (administered over 3–5 minutes) and a 25 μg/kg/min infusion (table II).[13] The ACT should be checked 5–10 minutes after completion of the bolus administration. If the ACT is >300 seconds, PCI may proceed. If the ACT is <300 seconds, an additional 150 μg/kg bolus should be given and the infusion increased to 30 μg/kg/min. If the ACT is >450 seconds, the infusion should be reduced to 15 μg/kg/min. When a therapeutic ACT (300–450 seconds) is achieved, the infusion dose should be maintained. If clinically indicated during the procedure (e.g. impending abrupt closure) or to achieve an ACT >300 seconds, additional 150 μg/kg bolus doses may be administered, and the infusion dose may be increased to 40 μg/kg/min. After any additional bolus or dose adjustment, the ACT should be checked 5–10 minutes later to confirm a therapeutic value. In the prospective studies supporting this dosing regimen,[12] the mean,

Table III. Argatroban anticoagulation in heparin-induced thrombocytopenia (HIT): contemporary clinical experience and use in special populations

Use and patient population	Key findings	References
Prophylaxis or treatment of thrombosis in HIT		
Contemporary clinical experience	Argatroban 0.5–1.2 μg/kg/min (mean or median dose) typically achieves target aPTTs	47,48,50-55
Hepatic impairment	Reduced initial dose required (e.g. 0.5 μg/kg/min if moderate hepatic impairment). Decreased clearance and increased elimination half-life compared with healthy subjects, and longer time may be needed for reaching steady-state levels with argatroban initiation and for full reversal of anticoagulant effects upon its cessation	22,32
Morbidities indirectly affecting hepatic function	Reduced initial dose (e.g. 0.5 μg/kg/min) needed in conditions associated with reduced hepatic perfusion or increased congestion, such as heart failure, multiple organ system failure, severe anasarca and postcardiac surgery. Pharmacokinetic studies remain to be conducted	4,32,41-49
Renal impairment, including failure	No initial dose adjustment required. For each 30 mL/min decrease in creatinine clearance, a reduction of ≈0.1–0.6 μg/kg/min in the aPTT-adjusted, therapeutic dose may occur. Drug levels and anticoagulant effects are stable during dialysis	22-24,45,50,56,57
Elderly patients	No age-related dose adjustment required	9,11,22,54
Paediatric patients	Decreased clearance compared with adults; reduced initial dose needed (e.g. 0.75 μg/kg/min if normal hepatic function; 0.2 μg/kg/min if hepatic impairment). Argatroban was well tolerated and provided adequate anticoagulation in 18 seriously ill paediatric patients requiring non-heparin anticoagulation	13,58
Sex	No sex-related dose adjustment required	22,59
Pregnancy	Use only if clearly needed (very limited data)	13,60
Nursing women	Unknown whether argatroban is excreted in human milk. Discontinue nursing or argatroban, considering the importance of the drug to the mother	13
Race/ethnicity	No racial/ethnicity-related dose adjustment required (limited data)	27
Obesity	No dose adjustment necessary for BMI up to 51 kg/m^2	55
Patients with or at risk of HIT undergoing PCI		
Contemporary clinical experience, including use with GPIIb/IIIa inhibition	Argatroban 18 μg/kg/min with 241 μg/kg initial bolus (mean doses), with or without concurrent GPIIb/IIIa inhibition, supports safe, effective anticoagulation, when ACT is <450 sec	61,62
Age (for adults)	No age-related dose adjustment required; argatroban clearance not significantly affected by age at doses used during PCI	27,63
Sex	No sex-related dose adjustment required; argatroban clearance not significantly affected by sex at doses used during PCI	27,63
Race/ethnicity	No race/ethnicity-related dose adjustment required; argatroban clearance not significantly affected by race at doses used in PCI	27,63
Obesity	No dose adjustment necessary for BMI up to 51 kg/m^2. Clearance increases linearly with patient bodyweight	27,64

ACT = activated clotting time; **aPTT** = activated partial thromboplastin time; **BMI** = body mass index; **GP** = glycoprotein; **PCI** = percutaneous coronary intervention.

ACT-adjusted infusion dose was 23 μg/kg/min. After PCI, argatroban may be continued, if needed, using doses appropriate for the non-interventional setting.

The safety and effectiveness of argatroban in combination with a glycoprotein (GP) IIb/IIIa inhibitor during PCI in patients with or at risk of HIT have not been established. Postmarketing experiences offer some dosing guidance, however, for argatroban when administered with a GPIIb/IIIa inhibitor (table III). In 120 patients with or at risk of HIT undergoing PCI,[62] many

with acute coronary syndrome,[61] argatroban 18 μg/kg/min (initial 241 μg/kg bolus; mean doses), with or without GPIIb/IIIa inhibition, provided adequate anticoagulation with an acceptable bleeding risk, when the ACT was maintained at <450 seconds. Although argatroban is not approved for use in non-HIT patients during PCI or in HIT patients during peripheral intervention, limited published experience exists in these settings, with the argatroban doses generally similar to those reported in post-marketing experiences in HIT patients during PCI.[63,68]

2.3 Dosage Adjustments

When adjusting the argatroban dosage, the target aPTT (or ACT) and the patient's current dose, aPTT (or ACT) and co-morbidity, including hepatic dysfunction, should be considered. In the non-interventional setting, the initial dose of argatroban should be adjusted as clinically indicated (not to exceed 10 μg/kg/min) to attain an aPTT of 1.5–3 times the baseline value (not to exceed 100 seconds). In an historical controlled study of argatroban therapy in HIT, 17% of patients retained their initial dose throughout therapy.[69] When adjustment is needed in the non-interventional setting, consideration should be given to adjustments of dosage in increments of 0.25–0.5 μg/kg/min for adult patients (smaller increments may be required at extremely low doses), 0.1–0.25 μg/kg/min for paediatric patients with normal hepatic function and 0.05 μg/kg/min or less for paediatric patients with impaired hepatic function.[13,69] For adjustment during PCI, consideration should be given to adjustments of dosage in increments of 5 μg/kg/min.[69]

3. Special Populations

Table III summarizes considerations regarding argatroban use in special populations with HIT, plus doses typically used in contemporary practice in non-interventional and interventional settings. Despite the growing literature on argatroban use in special populations, no prospective, controlled studies have evaluated the safety and effectiveness of argatroban therapy in HIT at doses besides those that are FDA-recommended (table II).

3.1 Hepatic Impairment or Morbidities Indirectly Affecting Hepatic Function

Adults with moderate hepatic impairment, compared with healthy subjects, have an approximate 4-fold decrease in argatroban clearance and 3-fold increase in elimination half-life.[22] A reduced initial argatroban dose, e.g. 0.5 μg/kg/min, is needed in adults with HIT and hepatic impairment, as assessed as a Child-Pugh score >6[22] or total serum bilirubin >1.5 mg/dL.[32] Because drug and effect steady-state may be delayed by hepatic impairment, experts advise checking an aPTT 4–5 hours after argatroban initiation or dose change in hepatically impaired patients to confirm the desired level of anticoagulation.[32] After argatroban cessation, normalization of anticoagulant effects may take at least 4 hours, and possibly up to 20 hours.[22,32]

A growing body of literature indicates that reduced argatroban doses are needed in HIT patients with conditions that indirectly affect liver function via reducing perfusion or increasing congestion, e.g. heart failure, multiple organ system failure, severe anasarca and postcardiac surgery.[32,41-49] In one retrospective study,[48] therapeutic doses were significantly lower in patients with, versus without, heart failure (0.6 vs 1.0 μg/kg/min) and decreased as the number of failed organ systems increased from one to two to three or more (i.e. 1.1 to 0.9 to 0.6 μg/kg/min, respectively). Although clinical evidence suggests that argatroban clearance is decreased in such conditions, this remains to be established in pharmacokinetic studies. For patients with morbidities indirectly affecting hepatic function, a reduced initial dose, e.g. 0.5–1.2 μg/kg/min, adjusted according to the patient's aPTT, has been suggested.[4] As with patients with hepatic impairment, delayed achievement of steady-state drug levels may occur following argatroban initiation and a prolonged effect may occur following argatroban discontinuation.

The use of high doses of argatroban during PCI in patients with clinically significant hepatic disease or transaminase levels ≥3 times the upper limit of normal is unstudied and, in the absence of dosing guidance, should be avoided.

3.2 Renal Impairment

No initial dose adjustment is required for renal impairment. In 24 patients with a wide range of creatinine clearance (CL_{CR}) values who were administered argatroban 5 μg/kg/min for 4 hours, no clinically significant effects of renal function on argatroban pharmacokinetics or pharmacodynamics were detected.[22] Temporal plasma argatroban profiles were similar among patients grouped by normal, mildly impaired, moderately impaired or severely impaired (CL_{CR} <30 mL/min) renal function, without differences in systemic clearance (group means: 3.3–4.6 mL/min/kg), volume of distribution (156–164 mL/kg) or elimination half-life (47–64 min). ACT and aPTT responses were similar between groups and demonstrated no or negligible association with CL_{CR}. Comparable argatroban clearance values were reported in 13 non-HIT patients undergoing renal replacement therapy while receiving argatroban 2 μg/kg/min (with or without a 250 μg/kg loading bolus)[23] and in five HIT patients undergoing renal replacement therapy while receiving argatroban 0.5–2 μg/kg/min.[24] Plasma argatroban, aPTTs and ACTs remained stable during dialysis. Stable aPTTs were also demonstrated in cardiovascular surgery patients with HIT who underwent haemodialysis on argatroban.[56] Two studies, each excluding patients with abnormal liver function, evaluated the effect of renal function on the aPTT-adjusted therapeutic argatroban dose in HIT.[50,57] Patients received argatroban 1 μg/kg/min (median), adjusted to achieve aPTTs of 50–70 seconds,[50] or 1.8 μg/kg/min (mean), adjusted to achieve aPTTs 1.5–3 times baseline.[57] Mean, aPTT-adjusted doses were 2.0–2.2 μg/kg/min when CL_{CR} was >60 mL/min and 1.2–1.7 μg/kg/min when CL_{CR} was <30 mL/min, with similar aPTTs achieved. By regression analyses, each 30 mL/min decrease in CL_{CR} corresponded to a decrease in the therapeutic dose of ≈0.1–0.6 μg/kg/min.

Pharmacokinetic data have not yet been reported in patients with renal impairment administered argatroban at doses used during PCI.

3.3 Intensive Care

A retrospective analysis of the prospective, historical controlled studies of argatroban therapy in HIT identified 390 argatroban-treated patients and 98 historical control patients who were acutely ill (defined as having one or more of the following ongoing medical conditions or indications for heparin therapy: cardiac surgery, acute coronary syndrome, pulmonary embolism, respiratory distress syndrome, trauma or ventricular assist device).[70] Argatroban administered at a mean dose of 1.9 μg/kg/min for a mean of 6 days, versus control, reduced the composite endpoint of death due to thrombosis, amputation secondary to ischaemic complications of HIT, or new thrombosis, without increasing bleeding.

As previously discussed, reduced argatroban doses are needed in HIT patients with hepatic dysfunction or conditions associated with hepatic hypoperfusion such as heart failure, multiple organ system failure and postcardiac surgery.[22,32,41-49] Such conditions are often present in intensive care patients. A dosing algorithm for argatroban therapy in intensive care patients with HIT has been proposed in which the starting infusion is 0.5 μg/kg/min in patients with hyperbilirubinaemia, low cardiac output or cardiac shock, or risk of reduced liver perfusion, and 1.0 μg/kg/min otherwise – with the dose adjusted to achieved aPTTs 1.3–3 times baseline, but not >100 seconds.[71]

3.4 Elderly Patients

Adults >65 years of age require no age-related adjustment in argatroban therapy. In 40 healthy adults administered a continuous infusion of 2.5 μg/kg/min of 4 hours' duration (125 μg/kg loading bolus), no clinically significant effects of age on argatroban pharmacokinetics or pharmacodynamics were detected; the mean argatroban clearance was 4.3 mL/min/kg in subjects aged

65–80 years and 5.0 mL/min/kg in those aged 18–45 years.[22] Times to, and levels of, steady-state aPTTs and ACTs were comparable between groups.[22] In an HIT registry, age was not a significant factor determining the therapeutic dose (median 1.0 μg/kg/min) or thrombotic risk (8%) in 62 elderly patients.[54] In prospective, historical controlled studies in HIT, argatroban effectiveness was not influenced by age.[9,11]

In 152 patients (mean age 63 years) undergoing PCI using argatroban (250–300 μg/kg bolus followed by a 15 μg/kg/min infusion), pharmacokinetic values were similar to those reported in healthy subjects; age did not significantly affect clearance.[27,63]

3.5 Paediatric Patients

In a multicentre, open-label study of 18 seriously ill patients ≤16 years old who required non-heparin anticoagulation, most often for HIT,[13,58] 13 patients received argatroban as a continuous infusion, typically initiated at 1 μg/kg/min, titrated to achieve aPTTs 1.5–3 times the baseline value. Within a 30-day study period, thrombosis occurred in two patients during therapy and in three patients after argatroban cessation. Major bleeding occurred in two patients, including one with intracranial haemorrhage after 4 days of therapy. Another patient, who continued to receive argatroban after completion of the 14-day treatment period, also experienced intracranial haemorrhage. Pharmacokinetic data from 15 patients showed that argatroban clearance was decreased by 50% compared with healthy adults, and was decreased even more among paediatric patients with elevated serum bilirubin. Based upon pharmacokinetic/pharmacodynamic modelling, an initial dose of 0.75 μg/kg/min (if hepatic function is normal) or 0.2 μg/kg/min (if hepatic function is impaired) is advised to support achievement of aPTTs 1.5–3 times the baseline level and avoidance of aPTTs >100 seconds in seriously ill paediatric patients.[13] Further study of argatroban therapy in paediatric patients appears warranted.

3.6 Sex

Sex-related adjustments in argatroban therapy are unnecessary. In 40 healthy adults (50% male), administered a continuous infusion of 2.5 μg/kg/min (125 μg/kg loading bolus) for 4 hours, no clinically significant differences in argatroban pharmacokinetics or pharmacodynamics were detected between the sexes: argatroban clearance was 5.1 mL/min/kg in females and 4.2 mL/min/kg in males, with aPTT responses being comparable between groups.[22] In a HIT registry, initial and maintenance argatroban doses, duration of therapy and aPTT responses were comparable between 50 males and 42 females.[59] Death, amputation or new thrombosis within 37 days occurred in ten (24%) females and eight (16%) males. Major bleeding occurred in 2% of both males and females.

In 152 adults (70% male) undergoing PCI using argatroban anticoagulation, clearance was unaffected by the sex of the patients.[27,63]

3.7 Pregnant or Nursing Women

Apart from anecdotal case data,[60] argatroban therapy remains unstudied in pregnant or nursing women with HIT. It is unknown whether argatroban is excreted in human milk. The FDA recommends that for pregnant women argatroban be used only if clearly needed (Pregnancy Category B), and for nursing women a decision be made to discontinue either nursing or argatroban, after considering the importance of the drug to the mother.

3.8 Race/Ethnicity

No published data clearly indicate a need for race/ethnicity-related adjustment of argatroban therapy, although data are limited. Among the minority patients in the historical controlled studies of argatroban therapy in HIT, the median aPTT-adjusted dose was less in Asians than in African Americans or Hispanics. However, the groups were small (e.g. 13 Asians and 14 Hispanics) and had some baseline differences. Additional study is needed before clear conclusions can be drawn regarding possible interracial effects

on the therapeutic dose needed.[72] Argatroban clearance was unaffected by race in adults undergoing PCI using argatroban anticoagulation.[27,63]

3.9 Obesity

Dose adjustment is not required for obesity, i.e. body mass index (BMI) up to 51 kg/m^2. In 83 patients with suspected HIT and BMI of 15.5–50.8 kg/m^2,[55] argatroban dosing requirements, aPTT responses and clinical outcomes were similar between obese (BMI >30 kg/m^2) and non-obese patients. No differences in the rate of death, amputation or new thrombosis or major bleeding were detected between groups, and thrombotic risk was not predicted by BMI.

The effect of BMI and obesity on argatroban therapy during PCI was investigated in 225 patients (85 obese) with a BMI of 16.3–50.9 kg/m^2.[64] After receiving an initial loading bolus of 350 μg/kg (HIT group) or 300 or 250 μg/kg (non-HIT group), patients were administered argatroban 25–30 μg/kg/min (adjusted to achieve ACTs 300–450 seconds, HIT group) or 15 μg/kg/min (target ACTs 275–325 seconds, non-HIT group) during PCI, with additional 150 μg/kg boluses allowed if needed. No association was detected between BMI and the first ACT after bolus administration, mean infusion dose, need for additional boluses, or time to ACTs ≤160 seconds after argatroban cessation. No differences were detected in ischaemic or haemorrhagic complications between obese and non-obese patients.

4. Drug Interactions and Compatibility

Drug interaction or compatibility studies have been conducted between argatroban and many frequently used medications (table IV). Because of a lack of pharmacokinetic and pharmacodynamic interactions, argatroban coadministered with aspirin (acetylsalicylic acid), erythromycin, paracetamol (acetaminophen), digoxin or lidocaine (lignocaine) should require no dose adjustments.[75,77,79] Compatibility studies support the simultaneous intravenous administration via Y-site injection of argatroban and various medications, with the exceptions of amiodarone (precipitation may occur) and possibly furosemide, nesiritide, sodium nitroprusside and total parenteral nutrition (where further study is needed).[73,76,78] Concomitant use of argatroban with antiplatelet agents, thrombolytics or other anticoagulants may increase the risk of bleeding.[13,62,81]

Although argatroban and warfarin lack pharmacokinetic interactions,[80] their co-therapy prolongs the INR more than with warfarin monotherapy.[29,82] This occurs without an additional effect on factor X levels.[29] While prolongation of the INR is a DTI class effect, it is particularly profound for argatroban.[83] In HIT patients, INRs >5 commonly occur without bleeding during argatroban therapy with or without concurrent warfarin.[84] In HIT patients with INRs >4 while receiving argatroban and warfarin co-therapy, a greater risk exists for thrombosis than for major bleeding.[85] Practice guidelines suggest using factor X levels measured by chromogenic assay for monitoring the effects of a vitamin K antagonist, such as warfarin, during the transition from argatroban.[86] Factor X levels ≤45% during co-therapy are predictive of INRs >2 in the absence of argatroban effects.[87] Additionally, an algorithm for interpreting the INR during the transition from argatroban to warfarin (or to other vitamin K antagonists, i.e. phenprocoumon or acenocoumarol) has been published.[29,74] In brief, argatroban is temporarily stopped when the co-therapy INR is >4, and if a warfarin monotherapy INR >2 is confirmed 4–6 hours later, argatroban is discontinued. In HIT patients, irrespective of the monitoring method used during the transition, warfarin should be started at a low maintenance dose and only after the platelet count has recovered to at least 150×10^9/L. Argatroban and warfarin should be coadministered for at least 5 days and until the warfarin effects are therapeutic for at least 2 days.[4]

5. Bleeding Risk and Management

Table V presents the clinically significant or major bleeding risk associated with argatroban therapy in HIT in the prospective, safety and

Table IV. Drug interaction and compatibility studies with argatroban

Drug	Interaction/compatibility with argatroban	References
Abciximab	Physically/visually compatible	73
Acenocoumarol	PD interaction detected	74
Paracetamol (acetaminophen)	No PK or PD interaction detected	75
Amiodarone hydrochloride	Physically/visually incompatible (precipitation may occur)	76
Aspirin	No PK or PD interaction detected	77
Atropine sulphate	Physically/visually compatible	78
Digoxin	No PK or PD interaction detected	75
Diltiazem hydrochloride	Physically/visually compatible	78
Diphenhydramine hydrochloride	Physically/visually compatible	78
Dobutamine hydrochloride	Physically/visually compatible	78
Dopamine hydrochloride	Physically/visually compatible	78
Eptifibatide	Physically and chemically compatible	73
Erythromycin	No PK or PD interaction detected	79
Fenoldopam mesylate	Physically/visually compatible	76
Fentanyl citrate	Physically/visually compatible	78
Furosemide	Limited physical/visual incompatibility; more study suggested	76
Hydrocortisone sodium succinate	Physically/visually compatible	78
Lidocaine hydrochloride	No PK or PD interaction detected; physically/visually compatible	75,76
Metoprolol tartrate	Physically/visually compatible	78
Midazolam hydrochloride	Physically/visually compatible	78
Milrinone lactate	Physically/visually compatible	76
Morphine sulphate	Physically/visually compatible	78
Nesiritide	Limited physical/visual incompatibility; more study suggested	78
Nitroglycerin	Physically/visually compatible	76
Noradrenaline (norepinephrine) bitartrate	Physically/visually compatible	78
Phenprocoumon	PD interaction detected	74
Phenylephrine hydrochloride	Physically/visually compatible	78
Sodium nitroprusside	Limited physical/visual incompatibility; more study suggested	78
Tirofiban hydrochloride	Physically and chemically compatible	73
Total parenteral nutrition solution	Physical incompatibility after 8 hours	78
Vasopressin	Physically/visually compatible	76
Verapamil hydrochloride	Physically/visually compatible	78
Warfarin sodium	PD, but no PK, interaction detected	29,80

PD = pharmacodynamic; **PK** = pharmacokinetic.

efficacy studies and contemporary practice, in the non-interventional and interventional settings. In historical controlled studies in HIT, the major bleeding rate was 6% with argatroban (7% with control therapies), and no intracranial haemorrhage occurred during argatroban therapy (mean duration of therapy, 5–7 days).[12] Contemporary practice indicates clinically significant or major bleeding rates of 0–10% in the non-interventional setting.[47,48,51-55,59] In patients with or at risk of HIT undergoing PCI, periprocedural major bleeding rates of 0–1.1% with argatroban therapy

Table V. Bleeding risk with argatroban in patients with (or at risk of) heparin-induced thrombocytopenia (HIT)

Setting	Percentage of patients with major or clinically significant bleeding	References
Non-interventional setting		
Safety and efficacy (registrational) studies	6[a]	11
Contemporary experience	0–10[b]	47,48,51-55,59
Interventional setting		
Safety and efficacy (registrational) studies	0–1.1[c]	12
Contemporary experience	None without GPIIb/IIIa inhibition[d]	61
	5.8 with GPIIb/IIIa inhibition[d]	

a Bleeding that was overt and associated with a haemoglobin decrease ≥2 g/dL and a transfusion of ≥2 units, or that was intracranial, retroperitoneal, or into a major prosthetic joint.

b Acute bleeding causing haemodynamic instability, a need for the transfusion of blood products, or a decrease in haemoglobin of >3 g/dL;[52] bleeding that was overt and associated with any of the following: haemoglobin decrease of ≥2 g/dL; transfusion requirements of ≥2 units of packed red blood cells or fresh-frozen plasma; or an intracranial, retroperitoneal or prosthetic joint bleed;[51] bleeding during therapy for which a transfusion was administered;[53] bleeding that was overt and associated with a haemoglobin decrease ≥2 g/dL and a transfusion of ≥2 units, or that was intracranial, retroperitoneal or into a major prosthetic joint;[54,55,59] haemorrhagic stroke, a transfusion of ≥2 units of packed red blood cells or a ≥2 g/dL decrease in haemoglobin in a 24-hour period, or other bleeding deemed significant by the treating physician;[47] or bleeding during therapy associated with a haemoglobin drop of ≥2 g/dL and a transfusion of ≥2 units of red blood cells on the same day.[48]

c Bleeding that was overt and associated with a haemoglobin decrease ≥5 g/dL, that led to a transfusion of ≥2 units, or that was intracranial, retroperitoneal or into a prosthetic joint.

d Intracranial haemorrhage or a decrease in haemoglobin ≥5 g/dL (or haematocrit decrease at least 15%).

GP = glycoprotein.

(compared with 1.9–3.7% historically reported for heparin) and 5.8% with argatroban in combination with GPIIb/IIIa inhibition therapy are reported.[12,61] The risk of major bleeding is significantly increased for patients with an aPTT >100 seconds in the non-interventional setting[81] or an ACT >450 seconds during PCI.[62]

Argatroban has no antidote. Excessive anticoagulation, with or without bleeding, in an argatroban-treated patient may be controlled by infusion cessation (or dose reduction). Anticoagulant parameters generally return to baseline (or a lower steady-state level) within 2–4 hours in patients with normal hepatic function, or longer in patients with hepatic impairment or morbidities that indirectly affect hepatic function.[4,22,32] Anticoagulation should be stopped immediately if life-threatening bleeding occurs, and symptomatic and supportive care provided.[88] Anecdotal reports describe the use, with variable success, of recombinant factor VIIa or fresh-frozen plasma for severe bleeding, overdose or supratherapeutic aPTTs with argatroban therapy.[43,49,89-91] The likelihood of overdosing (or underdosing) argatroban may be reduced by the use of smart infusion technology pumps that intercept keypad-entered doses beyond preset, allowable limits.[92]

6. Conclusions

The FDA-recommended argatroban dose for prophylaxis or treatment of thrombosis in adults with HIT is 2 μg/kg/min, adjusted to achieve aPTTs 1.5–3 times baseline; initial dose reductions are required in hepatically impaired patients and paediatric patients. Clinical data indicate that reduced doses are also needed in patients with morbidities that indirectly affect hepatic function, but reduced doses are unnecessary on the basis of renal function, adult age, sex, race/ethnicity or BMI. In contemporary practice, argatroban 0.5–1.2 μg/kg/min typically supports therapeutic aPTTs in many patients. The FDA-recommended dose for patients with or at risk of HIT undergoing PCI is 25 μg/kg/min (350 μg/kg initial bolus), adjusted to achieve ACTs of 300–450 seconds. For PCI, argatroban dosing

guidance is lacking for hepatically impaired patients, and initial dose adjustment is unnecessary for adult age, sex, race/ethnicity or BMI. Contemporary experience suggests that when administered with concurrent GPIIb/IIIa inhibition, argatroban at somewhat lesser doses may support safe, effective anticoagulation in PCI. Argatroban lacks drug-drug interactions and is compatible with many commonly used medications. An exception is that argatroban and warfarin exert a combined effect on the INR, and careful monitoring of the argatroban-to-warfarin transition is needed. There is no antidote for argatroban and excessive anticoagulation should be controlled by cessation or reduction of the infusion rate. Clinically significant or major bleeding rates are 0–10% in the non-interventional setting and 0–5.8% in the interventional setting. Increased familiarity of healthcare professionals with the use of argatroban therapy in HIT may increase compliance with treatment guidelines and reduce harm from possible medication errors.

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