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Argatroban

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Contents

Abstract

▲ Argatroban is a direct thrombin inhibitor synthesised to bind to the catalytic site of the thrombin molecule. It binds rapidly and reversibly to both clot-bound and soluble thrombin.

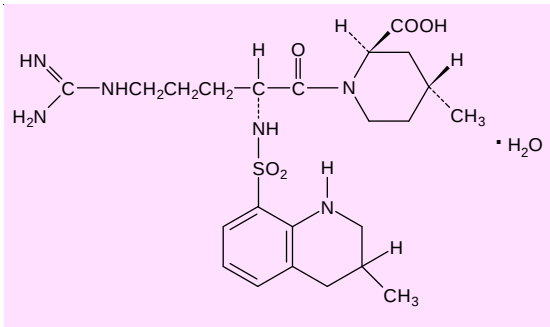
▲ The relatively short elimination half-life of argatroban (39 to 51 minutes) and its reversible binding allow rapid achievement of therapeutic effect on initiation of therapy and rapid restoration of normal haemostasis upon cessation of therapy.

▲ Argatroban produces a predictable dose response that is well correlated with changes in anticoagulant parameters.

▲ Argatroban, given to patients with heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia with thrombosis (HITTS) in a large scale, nonrandomised, prospective trial, reduced a combined end-point of morbidity and mortality when compared with historical controls.

▲ Argatroban was well tolerated in clinical trials of patients with HIT and caused no increase in bleeding risk compared with historical controls.

Features and properties of argatroban (argipidine, MD-805, DK-7419, MCI-9038, OM-805)	
Indications	
Anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT)	
Mechanism of action	
Direct thrombin inhibitor	
Dosage and administration (usual dosage in clinical trials)	
Management of HIT	
Initial dose:	2 μg/kg/min
Maintenance dose: (based on activated partial thromboplastin time 1.5 to 3 times baseline; not >100 sec)	Up to 10 μg/kg/min
Vascular interventional procedures in patients with HIT	350 μg/kg bolus plus 15 to 40 μg/kg/min
Route of administration	Intravenous
Pharmacokinetic profile	
Volume of distribution at steady-state	0.2 L/kg
Total body clearance	0.3 L/h/kg
Elimination half-life	39 to 51 min
Adverse events	
Most frequent	Bleeding, dyspnoea, hypotension



Argatroban

Heparin-induced thrombocytopenia (HIT) is a complication of heparin therapy which manifests in 2 forms.[1] HIT type I is not severe and causes a moderate reduction in platelet count which results from a direct platelet-heparin interaction.[1] HIT type II is a severe, immune-mediated condition, which may be associated with significant morbidity and mortality. Unlike other thrombocytopenias, bleeding is uncommon in HIT type II but there is an increased propensity for the development of venous thrombosis, arterial thrombosis or pulmonary embolism.[1] The frequency of HIT type II varies among published data, largely because of the differences in the following: (i) definition of diagnosis (mainly because of the sensitivity of the methods of serological evaluation); (ii) immunogenic potential of unfractionated versus low molecular weight heparin preparations; and (iii) the dose and duration of heparin treatment.[2] Although less common than HIT type I, HIT type II is a relatively common adverse event and occurs in about 1 to 5% of patients.[1-3] Approximately 20% of patients who develop HIT type II experience a life-threatening thrombotic event with mortality as high as 30% and permanent morbidity, including limb loss, of 20 to 30%.[4,5] Collective studies in this review do not differentiate between HIT type I and type II, but use the diagnosis of HIT to include patients requiring treatment.

Following treatment with heparins, an immune response may be stimulated by the formation of heparin-platelet factor 4 (H-PF4) complexes.[1,2] HIT antibodies react with the H-PF4 complexes resulting in platelet activation and endothelial injury. The recommended treatment of HIT type II includes withdrawal of heparin but continued anticoagulant therapy is usually required. Primary therapy should include an agent that reduces activated thrombin, such as argatroban or hirudin.[2,3]

Argatroban is a small-molecule, synthetic, direct thrombin inhibitor, which competitively binds to the active site of thrombin. It binds rapidly and reversibly to thrombin, thereby inhibiting fibrin formation, the activation of coagulation factors V, VIII and XIII, and the natural anticoagulant protein C.[6] The use of argatroban does not lead to the formation of antiplatelet antibodies or the generation of other antibodies that bind argatroban[7] and it has no structural similarity to heparin.[8]

1. Pharmacodynamic Profile

The pharmacological properties of argatroban (e.g. selective and reversible inhibition of the thrombin catalytic site, rapid onset and short duration of action) offer the potential for significant antithrombotic efficacy and rapid restoration of haemostasis after discontinuation of the drug.[9] Comprehensive reviews of the pharmacodynamic effects of argatroban have been published previously.[9-11] This section highlights representative and key studies.

Thrombin Binding and Inhibition

- Argatroban binds rapidly at a diffusion-controlled rate to the catalytic site domain of thrombin.[11] Unlike hirudin and bivalirudin the interaction is fully reversible. It has an inhibition constant of 3.9×10^{-8} mol/L for human thrombin.[10]

- Argatroban is an effective inhibitor of thrombin bound to fibrin clots as well as thrombin free in solution. In contrast, heparin and hirudin are less potent in inhibiting bound versus soluble thrombin.[12] *In vitro* the plasma argatroban concentrations required to inhibit by 50% (IC_{50}) the activity of soluble, fibrin-bound and clot-bound thrombin were, respectively, 1.1, 2.8 and 2.4 μmol/L.[12] Heparin and hirudin each showed over 1000-fold

decreases in inhibitory potency for clot-bound versus soluble thrombin.[9,12]

• Argatroban is an effective inhibitor of thrombin bound to aged fibrin clots and of thrombin bound to fibrin clots already treated with streptokinase or alteplase.[13] Blood clots formed *in vitro* from the blood of healthy adults were aged and some were treated with streptokinase or alteplase. In a clot permeation model, the IC_{50} of argatroban for clots aged 3 hours was 2.7 μmol/L, which was not significantly different from those aged 6 hours (3.4 μmol/L). Argatroban inhibited approximately 85% of the thrombin activity present in these aged fibrin clots. In clots treated with streptokinase or alteplase, a saturating argatroban concentration inhibited thrombin by approximately 70%.[13]

Anticoagulant Effects

• In several animal models the antithrombotic effect (e.g. reduction in mean thrombus weight, increase in duration of postlesion vessel patency) of argatroban was similar to that of heparin; however, argatroban was associated with less systemic anticoagulation of haemorrhagic potential [e.g. increase in activated partial thromboplastin time (aPTT) or bleeding time] (reviewed by Hursting et al.[9]).

• The effect half-life for argatroban, given by continuous infusion at 4 escalating dose levels of 1.25, 2.5, 5 or 10 μg/kg/min, with or without a bolus-loading dose of 250 μg/kg, was approximately 18 to 40 minutes and was similar for both aPTT and activated clotting time (ACT). In contrast, the effect half-life for heparin (0.15, 0.20, 0.25 or 0.30 U/kg/min, with or without a bolus-loading dose of 125 U/kg), was somewhat longer than argatroban and was different for aPTT and ACT.[14] When argatroban was administered by continuous infusion alone in healthy volunteers, steady-state anticoagulant effects were achieved within 1 to 3 hours.[14]

• Studies in healthy volunteers have demonstrated that argatroban, with or without a bolus dose, increases the ratios of coagulation parameters (ACT and aPTT) in a similar, dose- and concentration-dependent manner (fig. 1) with a pre-

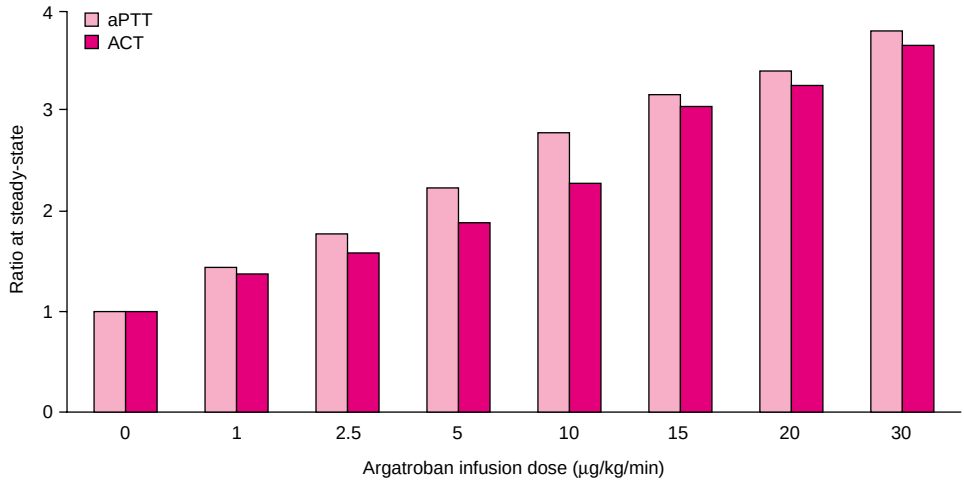


Fig. 1. Dose-response effects of argatroban (continuous intravenous infusion of 4-hour duration following a 250 μg/kg bolus) on steady-state ratios for activated partial thromboplastin time (aPTT) and activated clotting time (ACT) in 9 healthy volunteers. Values are presented as aPTT ratio and ACT ratio, determined by response obtained after 4 hours of intravenous infusion relative to that obtained before medication.[9]

dictable temporal response and a plateau between 1 and 3 hours.[9,14,15] When argatroban is discontinued, the ACT and aPTT values rapidly return to baseline values.[9]

• The plasma concentration of argatroban correlates well with the pharmacodynamic effects measured by aPTT[6] or ACT.[6,16,17] In 10 patients with HIT undergoing cardiovascular interventional procedures, a bolus of argatroban 350 μg/kg was given followed by a 25 μg/kg/min intravenous infusion during the procedure. The mean ACT during the infusion was 412 seconds which corresponded to a mean plasma argatroban concentration of 5.2 mg/L. Two hours after the procedure the mean ACT was 237 seconds with a mean plasma argatroban concentration of 2.3 mg/L.[16] Argatroban has not been extensively evaluated in patients receiving platelet glycoprotein IIb/IIIa inhibitors.

Effects on Vascular Smooth Muscle

• A 2-week placebo-controlled study of 20 patients with peripheral arterial obstructive disease evaluated the effect of daily argatroban infusion therapy on the plasma levels of endothelial-derived nitrous oxide (NO) and nitrosyl-haemoglobin (HbNO). Patients treated with argatroban 5 μg/kg/day (administered over 1 hour) had significantly increased plasma levels of NO and HbNO in venous blood together with an increased blood flow, evidenced by an increase in the temperature of the affected limbs.[18]

• In canine coronary arteries the concentration of argatroban required to inhibit the vasoconstrictive effects of thrombin by 50% (ED_{50}) was 0.3 μmol/L.[19] In the presence of an intact endothelium, argatroban did not inhibit relaxation dependent on the endothelium-derived relaxing factor induced by trypsin, acetylcholine or the calcium ionophore A23187. In segments stripped of endothelium, argatroban partially inhibited the vasoconstrictive effects of thrombin.[19]

• In rat aortic smooth muscle cells argatroban significantly suppressed the thrombin-induced proliferation of cells in a concentration-dependent manner. The mean inhibition rates of 6 experiments were calculated as 26% for argatroban 1 μmol/L and 76% for 10 μmol/L.[20]

2. Pharmacokinetic Profile

• In 110 patients with HIT, a constant infusion of argatroban up to 10 μg/kg/min for periods up to 14 days achieved mean steady-state plasma concentrations of 1.9 mg/L.[16,21]

• Argatroban is approximately 54% bound to plasma protein in humans (20% to albumin and 34% to glycoprotein).[22] Pharmacokinetic studies in healthy volunteers indicate that the drug has a volume of distribution of 0.2 L/kg, total body clearance of 0.3 L/h/kg (5 ml/min/kg) and an elimination half-life of 39 to 51 minutes.[6] Age, gender and renal function had little or no effect on pharmacokinetic parameters.[6]

• Argatroban is extensively metabolised in the liver to at least 4 metabolites.[23,24] M1 is the major metabolite and its antithrombin potency is about 30% that of the parent compound.[23] Plasma concentrations of M1 were markedly lower than those of the parent compound in healthy volunteers receiving short duration low doses of argatroban and in HIT patients undergoing coronary angioplasty receiving relatively high doses for short duration.[23] However, in patients with HIT on prolonged argatroban therapy M1 plasma concentrations were 2- to 8-fold higher than those of the parent compound.[23]

• The formation of each of the 4 predominantly inactive metabolites of argatroban (M1 to M4) is catalysed *in vitro* by human liver microsomal cytochrome P450 (CYP) 3A4/5 isoenzymes. However, the lack of effect of erythromycin, a potent CYP3A4/5 inhibitor, on argatroban pharmacokinetics suggests that CYP3A4/5-mediated metabolism is not an important elimination pathway *in vivo*.[25]

• Volunteers with normal (n = 12) or impaired (n = 5) hepatic function were given argatroban via intravenous infusion (2.5 μg/kg/min for most individuals) over 4 hours.[6] Argatroban produced

predictable temporal pharmacokinetic/pharmacodynamic profiles, regardless of the degree of hepatic function. However, immediately before cessation of the infusion, hepatically impaired patients demonstrated up to a 2-fold increase, relative to healthy controls, in mean argatroban plasma concentrations and anticoagulant effect (aPTT: 108 *vs* 71 seconds; ACT: 356 *vs* 165 seconds). Hepatically impaired patients also demonstrated over 2.5- to 4.5-fold differences, relative to healthy controls, in argatroban clearance and elimination half-life.[6] It is recommended that the dose of argatroban is reduced in patients with hepatic dysfunction.

• Volunteers with varying degrees of renal function (n = 24), ranging from normal to severe impairment, received an intravenous infusion of argatroban 5 μg/kg/min over 4 hours.[6] No differences were detected across the groups with respect to argatroban clearance, steady-state plasma concentration, steady-state volume of distribution, or elimination half-life.[6]

• Three randomised, crossover studies in healthy adults (n = 35) examined the potential for drug interaction between argatroban and 3 frequently prescribed medications; paracetamol (acetaminophen), lidocaine and digoxin.[26] No pharmacokinetic interaction, as defined for each individual study, was demonstrated.[26]

3. Therapeutic Trials

• A phase III, prospective, nonrandomised clinical trial assessed the efficacy of argatroban in 304 patients with HIT.[27] Continuous intravenous argatroban was administered, starting at 2 μg/kg/min for an average of 6 days. Two study arms were defined; one included patients with HIT alone (n = 160) and the other included patients with heparin induced thrombocytopenia with thrombosis (HITTS) [n = 144]. Dosage was adjusted to maintain aPTT at 1.5 to 3 times the baseline value. Clinical outcomes were compared after a 37-day trial period with those of 193 historical control patients (147 with HIT and 46 with HITTS). The incidence of the primary efficacy end-point, a composite of all-cause death, all-cause amputation or new thrombosis, was significantly reduced in patients treated with argatroban versus historical controls in the HIT arm (25.6 *vs* 38.8%, p = 0.014) [fig. 2], with a trend to reduction in the HITTS arm (43.8 *vs* 56.5%).[27]

• In the same clinical trial[27] a time-to-event analysis of the composite end-point between groups also significantly favoured argatroban ($p < 0.05$) in both the HIT arm and HITTS arm. Relative to historical controls argatroban also significantly reduced new thrombosis and death due to thrombosis in both study arms. Argatroban-treated patients rapidly achieved adequate anticoagulation and relative to controls had a significantly improved platelet count.[27]

• In a single-centre study, mortality in patients with HIT or HITTS was 32% in untreated historical control patients (n = 44) and 18% in argatroban recipients (n = 33). Amputations were 21 and 7% and new clot formation was 38 and 11%.[28] Patients were treated with argatroban infusion from 2 to 10 μg/kg/min maintaining aPTT at 1.5 to 3 times the control value (not to exceed an aPTT of 100 seconds), until thrombocytopenia was resolved. No p-values were given.[28]

• A combined analysis of 3 multicentre trials, presented in abstracts, has examined the clinical outcomes of 91 patients receiving argatroban for the treatment of HIT while undergoing percutaneous coronary intervention (PCI), including angioplasty, stent implantation and atherectomy.[29,30] (Data have been published previously for the first 50 of these patients.[31]) Outcomes for patients having multiple interventions were assessed separately at each procedure. Comparisons were made between outcomes after first PCI (n = 91) and subsequent PCI (n = 21). Patients were given an initial bolus of argatroban 350 μg/kg followed by a continuous infusion of 15 to 40 μg/kg/min. Mean argatroban infusion dosage was 23.1 and 22.1 μg/kg/min, respectively, for the initial and repeat groups. Procedural satisfaction and adequate anticoagulation (primary efficacy end-points as per investigator's

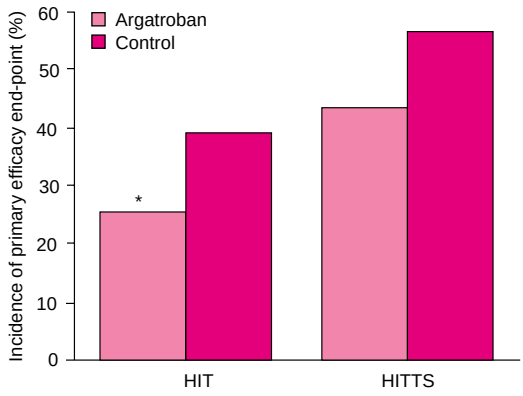


Fig. 2. The incidence of the primary efficacy end-point (a composite of all-cause death, all-cause amputation or new thrombosis), in a prospective nonrandomised study of 304 patients with heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), treated with argatroban and compared with 193 historical controls. Argatroban dosage was adjusted to maintain the activated partial thromboplastin time at 1.5 to 3 times the baseline value. Mean duration of argatroban treatment was 6 days and clinical outcomes were evaluated during a 37-day study period.[27] * p = 0.014 *vs* control.

assessment, not defined) occurred in 94.5 and 97.8% of patients, respectively, at initial PCI and 100% for both end-points at repeat intervention.[29,30]

• Argatroban was used to successfully treat 2 patients with HIT and HITTS who underwent stent implants for vascular lesions in carotid and renal arteries.[32,33] The patients were given an initial bolus dose of argatroban 350 μg/kg followed by a continuous infusion of 25 μg/kg/min and 30 μg/kg/min, respectively. The dose was adjusted in response to ACT results obtained throughout the procedures. The implant procedure was successful in both cases with no evidence of associated thrombosis.[32,33]

• Argatroban was used as a substitute for heparin in 6 patients who developed a clot in the extracorporeal circuit in association with HIT while being haemodialysed for renal failure. In all patients dialysis continued with no further problem. One patient required acetylsalicylic acid (aspirin) as well as argatroban.[34,35]

4. Tolerability

• Argatroban given via continuous intravenous infusion, starting at 2 μg/kg/min (aPTT maintained at 1.5 to 3 times baseline) for an average of 6 days, to 304 patients with HIT or HITTS caused no increase in bleeding risk compared with historical controls.[27]

• Patients with HIT undergoing PCI on 1 or more occasions (n = 91) were treated with argatroban 350 μg/kg bolus plus 25 μg/kg/min intravenous infusion titrated to achieve an ACT of 300 to 450 seconds. Major bleeding occurred in 2 patients (2.2%) compared with 3.1% reported historically for heparin use during PCI.[29]

• According to safety information from the manufacturer based on 568 patients treated with argatroban, the most frequent adverse reactions were minor haemorrhagic events, dyspnoea and hypotension.[36]

• In 3 studies comparing argatroban (n = 46) and heparin (n = 36) in healthy volunteers, the most common adverse events were headache, dizziness and pain at injection/infusion site. The frequency was 30.4, 19.6 and 10.9%, respectively, among subjects receiving argatroban and 11.1, 5.6 and 8.3% among those who received heparin. There were no serious adverse events and no withdrawals due to adverse events with either argatroban or heparin.[14]

5. Argatroban: Current Status

Argatroban is a direct thrombin inhibitor that has received recent approval for use in the US as an anticoagulant for the prophylaxis or treatment of thrombosis in patients with HIT and HITTS. Argatroban was approved in Japan for treatment of arterial thrombosis in 1990, acute cerebral thrombosis (1996) and anticoagulation of antithrombin III deficient patients undergoing haemodialysis (1996). Ongoing multinational phase II and III

trials are further evaluating the clinical efficacy of argatroban in these and other indications. Clinical trials show argatroban to be an effective and well tolerated anticoagulant.

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