

An Overview of the Direct Thrombin Inhibitor Argatroban

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Key Words

Argatroban · Thrombin inhibitor · Anticoagulant

Abstract

Argatroban is a small molecule direct thrombin inhibitor. The main attributes of this synthetic drug are its rapid onset of anti-thrombin action, rapid reversibility of its anticoagulant effect, potent inhibition of clot-bound thrombin, absence of antibody formation and no need for initial dosage adjustment in patients with renal impairment. It is eliminated by hepatic metabolism. These properties make argatroban a predictable anticoagulant with intravenous use in a routine clinical setting. Argatroban is approved in the US and Canada for both prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT); and it is approved in Japan and Korea for treatment of various thrombotic disorders. Argatroban has been shown in limited trials to provide reliable anticoagulation during percutaneous coronary interventions on HIT and non-HIT patients. Preliminary reports document the feasibility of using argatroban for anticoagulation during peripheral vascular interventions, hemodialysis and as adjunct to thrombolysis for treatment of myocardial infarction. Current recommendations for argatroban monitoring are to use the

activated partial thromboplastin time for low doses and the activated clotting time for high doses. The ease of monitoring argatroban, its 'turn-on/turn-off' characteristic and its consistent safety profile provide the rationale to continue studies of argatroban as an anticoagulant in clinical settings.

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Introduction

Argatroban is a direct thrombin inhibitor that was discovered in the 1970s by Shosuke Okamoto in Japan [1, 2]. Many preclinical as well as pilot clinical studies have been performed and published on argatroban [3, 4].

Argatroban was first clinically used in Japan in patients for treatment of peripheral arterial occlusive disease in the early 1980s. Today it is approved in Japan for treatment of arterial thrombosis (1990), acute cerebral thrombosis (1996) and anticoagulation of AT-deficient patients undergoing hemodialysis (1996). Argatroban is also approved in Korea for use in chronic arterial occlusion and acute cerebral thrombosis. Argatroban was approved in the United States in 2000 for both prophylaxis and treatment of thrombosis associated with heparin-induced thrombocytopenia (HIT) type II. In Canada,

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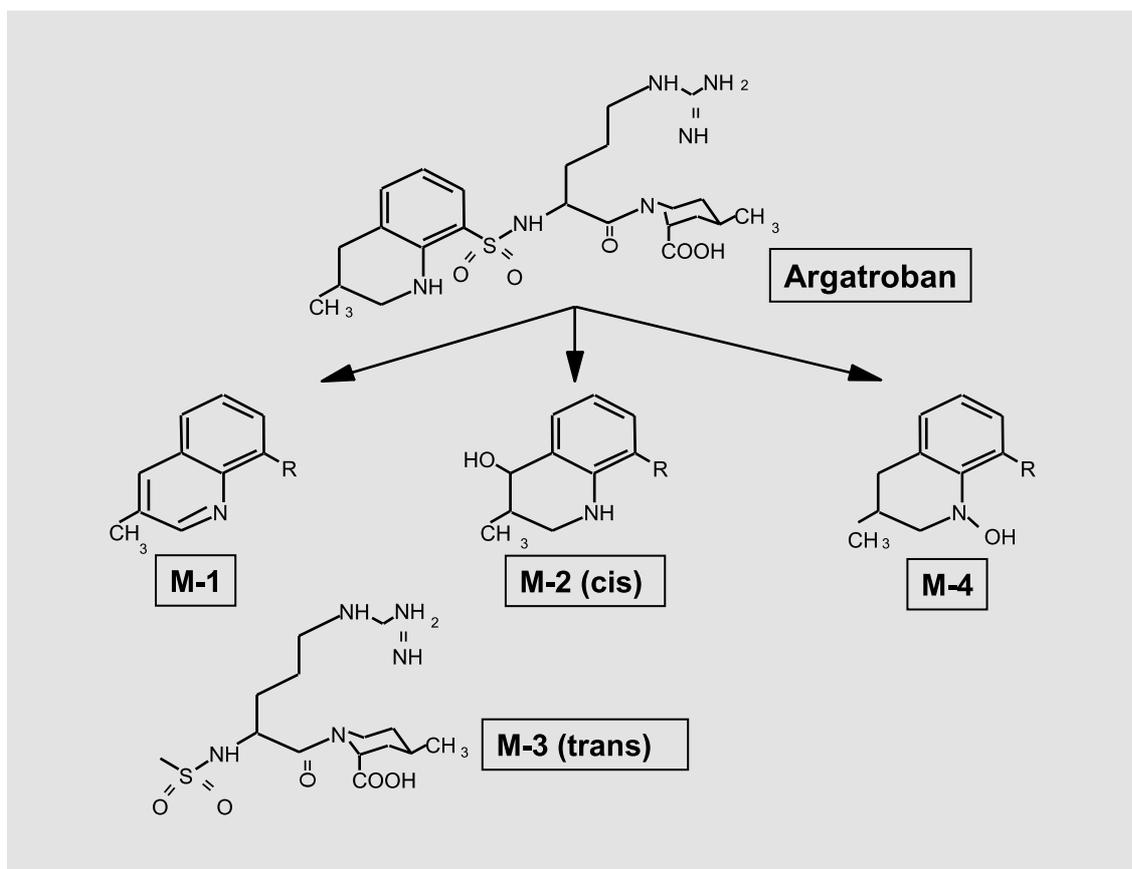


Fig. 1. The structure of the direct thrombin inhibitor argatroban and its four major metabolites.

argatroban is approved as an anticoagulant for HIT patients who, in the opinion of the attending physician, require anticoagulation. A submission to the European health authorities for use of argatroban in patients with HIT type II is in progress.

Pharmacologic Profile of Argatroban

Mechanism of Action

Argatroban is a synthetic small molecule derived from *L*-arginine with a molecular weight of 527 D (fig. 1) [5, 6]. Its mechanism of action is direct thrombin inhibition through a reversible interaction with the catalytic site of thrombin [7–9]. The thrombin inhibition constant (K_i) of argatroban is $3.9 \times 10^{-8} M$. It is a selective thrombin inhibitor and does not inhibit other serine proteases. Approximately 54% is bound to plasma proteins [10].

The small molecular size of argatroban may offer a therapeutic advantage for treatment of older, more organized thrombi, in that it can penetrate and effectively inhibit thrombin despite the fibrin barrier [11–13]. It has been demonstrated that a 2-fold increase in concentration is needed to penetrate and neutralize fibrin-bound thrombin in vitro or in vivo (vs. inhibition of soluble fibrin) for argatroban. This is compared to a 23-fold (in vitro) or 4,000-fold (in vivo) increase needed for hirudin and a 500-fold (in vitro) or 5,000-fold (in vivo) increase for heparin in the same model systems.

Pharmacokinetics

Argatroban reaches its steady-state plasma levels, measured by its activated partial thromboplastin time (aPTT) anticoagulant effect, 1–3 h after initiation of intravenous administration (faster when a loading bolus is administered) [14, 15]. Low intra- and intersubject variability is observed. Plasma drug concentrations increase propor-

tionally with doses up to 40 µg/kg/min and are well correlated with steady-state anticoagulant effects. The dose-response curve is gentle and predictable, allowing for a wide margin of safety during dose titration. After discontinuation of the drug, aPTT returns to normal within 2–4 h. Its elimination half-life is 39–51 min, and is unaffected by age, gender and renal function [16].

Patients with moderate hepatic impairment, compared with healthy volunteers, have an approximate 4-fold decrease in drug clearance (to 1.5 ml/min/kg) and an approximate 3-fold increase in elimination half-life (to 152 min) [17]. Owing to the decreased clearance, a 4-fold downward adjustment in argatroban dosage is required for individuals with moderate hepatic impairment.

Metabolism

Argatroban is rapidly metabolized in the liver and excreted through the bile into the feces [14, 15, 17, 18]. There are three known metabolites of argatroban (M1, M2 and M3) (fig. 1). M1 retains a very modest anti-thrombin effect [19]. The anticoagulant effect of M1 is not clinically apparent with routine intravenous dosing.

Argatroban does not induce the formation of antibodies that neutralize its anticoagulant effect, prolong its half-life or enhance its activity [20].

Antidote

No specific antidote is available for argatroban. If life-threatening bleeding occurs and excessive plasma argatroban levels are suspected, argatroban should be discontinued immediately, and the patient provided symptomatic and supportive therapy. Anticoagulant parameters generally return to baseline within 2–4 h after argatroban discontinuation [14, 15]. This reversal may take at least 6 h and perhaps more than 20 h in hepatically impaired patients [17].

Drug Interactions

There have been no pharmacokinetic or pharmacodynamic drug interactions reported between argatroban and aspirin, erythromycin, acetaminophen, digoxin, or lidocaine [21–23]. In practice, argatroban co-administered with these frequently used medications should require no dosage adjustments.

Warfarin/Argatroban Combined Therapy

Because argatroban is a direct thrombin inhibitor, concurrent use of argatroban and warfarin prolongs the prothrombin time (PT)/International Normalized Ratio (INR) beyond that produced by warfarin alone [24].

Hence, the previously established ('traditional') relationship between the INR and bleeding is altered. In general, with doses of argatroban up to 2 µg/kg/min, argatroban can be discontinued when the INR is >4 on combined therapy [25]. The level of warfarin can be checked 4–6 h after discontinuing argatroban when its effect is negligible. For argatroban doses >2 µg/kg/min the relationship is less predictable. In this case, the argatroban infusion can be temporarily reduced to 2 µg/kg/min, and the INR repeated on argatroban and warfarin 4–6 h after argatroban reduction.

Concurrent use of argatroban and warfarin, compared with warfarin monotherapy, exerts no additional effect on vitamin-K-dependent factor levels [26]. However, because the measurement of coagulation factors by clot-based assays will be affected by argatroban, immunologic or chromogenic-based assays should be used [24].

Monitoring

The anticoagulant effects of argatroban are routinely monitored using the aPTT [24]. Higher levels of anticoagulation such as required during interventional procedures are monitored using the activated clotting time (ACT) [15, 24, 27]. Argatroban also increases the thrombin time and ecarin clotting time (ECT) in a dose-dependent fashion [24].

Clinical Studies of Argatroban

HIT/HITTS (ARG-911)

Patients with HIT have an allergy to heparin and are at high risk of developing life- and limb-threatening thrombosis. Traditionally, warfarin, dextran and aspirin, for lack of better drug options, have been used to anticoagulate these patients. With the availability of direct thrombin inhibitors that have potent anticoagulant activity, the concept of utilizing this drug class to treat patients with HIT was developed. From the ARG-911 multi-center clinical trial, argatroban therapy, at a starting dose of 2 µg/kg/min adjusted to achieve an aPTT of 1.5–3 times the baseline value, has been shown to produce significant benefits in the clinical outcomes of patients with isolated HIT or HIT with thrombosis, compared with historical controls [28]. Argatroban therapy effectively reduced the composite of death, amputation or new thrombosis, lowered mortality from thrombosis, and prevented new thrombotic events. These favorable outcomes were achieved without an increase in bleeding, relative to control, and with no patient experiencing intracranial hemor-

rhage while on argatroban therapy. In addition, patients re-exposed to argatroban at another clinical treatment had equally favorable outcomes [29].

Percutaneous Coronary Intervention

In patients with HIT requiring percutaneous coronary intervention (PCI), aggressive anticoagulation is needed to avoid thrombosis. The hypercoagulable state characterizing HIT together with the endovascular disruption resulting from PCI may place HIT patients at particular risk of thrombosis during PCI. In a pilot study and subsequent clinical trials of argatroban (ARG-216, ARG-310/311), primary efficacy assessments showed satisfactory outcome of the procedure and adequate anticoagulation of patients undergoing their initial PCI with argatroban [27, 30]. No unsatisfactory outcomes occurred during repeat PCIs with argatroban.

The use of argatroban in patients without HIT has been studied in the setting of PCI. In three pilot studies, procedural success was reported [31–33]. A multi-center clinical trial in North America on the use of argatroban anticoagulation for non-HIT patients undergoing PCI is nearly completed, and results will be available in early 2003.

Case reports have also described the successful use of argatroban anticoagulation in patients with HIT during carotid and renal stent implants [34, 35]. Argatroban dosing was similar to that for coronary interventional procedures. Argatroban has shown an acceptable safety and tolerability profile in these patients.

Stroke

In Japan, argatroban is used for the treatment of acute cerebral thrombosis [36]. A preliminary multi-center clinical trial in North America to establish the safety and explore the efficacy of argatroban as a treatment for acute ischemic stroke is nearly complete. Results will be available in early 2003.

Other Thrombotic States

Anticoagulation with argatroban has been evaluated in acute myocardial infarction, unstable angina, peripheral arterial obstructive disease and as an adjunct to thrombolytic therapy [37–40]. In each of these settings, argatroban produced predictable anticoagulant effects and was generally safe and well tolerated.

A few cases describing the successful use of argatroban anticoagulation during hemodialysis in HIT patients have been reported [41, 42]. No relevant differences were shown, compared with patients who did not require

hemodialysis, in major bleeding or the composite endpoint of death, amputation or new thrombosis over 37 days.

Argatroban versus Other Antithrombotic Drugs

Heparins and Coumadin Derivatives

Argatroban offers several advantages over the traditional anticoagulants heparin and warfarin. In comparison to heparin, argatroban is a selective, direct inhibitor of thrombin that is not dependent on AT or other cofactors. It is a more potent inhibitor of bound thrombin than heparin or low molecular weight heparins, and the mechanism of action of argatroban is less complex than that of warfarin. Warfarin can be associated with limb gangrene when used in patients with HIT. Argatroban does not cross-react with the heparin antibody in patients with HIT as do low molecular weight heparins and to a lesser extent danaparoid.

Other Direct Thrombin Inhibitors

Two other thrombin inhibitors, lepirudin (Refludan®) and hirulog (Angiomax®), have received approval in the US. These drugs are pharmacologically distinct from argatroban and exhibit different safety/efficacy profiles. Argatroban has a rapid onset of action and is rapidly reversed following discontinuation. This characteristic provides a wider safety net than that of the less quickly reversed hirudin (or danaparoid).

Hirudin is a protein and thus generates antibodies that increase its anticoagulant activity by prolonging the half-life or antibodies that decrease its anticoagulant effect by neutralizing the drug [43]. Because it is of similar structure as hirudin, hirulog may also generate antibodies. Immunogenicity to argatroban has not been reported [20].

Argatroban is cleared through the liver not the kidney, and thus it can be used in patients with kidney disease with no adjustment of starting dose. In contrast, hirudin is cleared through the kidneys and patients with renal impairment require dose reduction to avoid excess plasma concentrations.

The thrombin inhibitors have varying effects on the traditional clotting assays. The aPTT and ACT can typically be used for monitoring depending on the dose of the drug. Because argatroban has a linear dose-dependent effect on these assays, they can be used with confidence for dose adjustment minimizing the bleeding risk.

Summary

The introduction of thrombin inhibitor drugs, such as argatroban, has added a new dimension to the management of thrombosis. These drugs offer a unique substitute for anticoagulation in patients who are heparin compro-

mised, an option we have not had prior to now. Argatroban appears to be a safe, easy to dose drug, with consistent response between individuals. Current clinical trials of argatroban are focusing on its expanded use in stroke and other thrombotic disorders.

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