Ximelagatran: Pharmacokinetics and Pharmacodynamics of a New Strategy for Oral Direct Thrombin Inhibition

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Because thrombin is central to the development and propagation of both arterial and venous thrombi, it is a logical therapeutic target. Direct thrombin inhibitors, such as ximelagatran, offer the distinct advantage of inhibiting fibrin-bound as well as free thrombin. The pharmacokinetics and pharmacodynamics of ximelagatran are predictable across a broad spectrum of patients. The half-life of melagatran, ximelagatran's active metabolite, is consistent with twice-daily dosing and fixed-dose administration without the need for monitoring. There have been no known drug interactions with ximelagatran, and the agent is not metabolized by the hepatic cytochrome P-450 system. For these reasons, orally active direct thrombin inhibitors such as ximelagatran will likely become the standard for long-term anticoagulation.
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Key words: Melagatran • Pharmacodynamics • Pharmacokinetics • Thrombin • Ximelagatran

Thrombin is central to the pathogenesis and propagation of thrombi in both the arterial and venous vascular systems. Venous thrombi, which are often precipitated by vascular injury and/or stasis, form under conditions of low sheer stress. In contrast, arterial thrombi are formed under high sheer stress at the sites of spontaneous or provoked (percutaneous coronary intervention) plaque disruption.[1] Endoluminal injury to either arteries or veins

exposes tissue factor and subendothelial matrix proteins, including collagen and von Willebrand factor.[2,3] Platelets adhere to these matrix proteins, become activated, and release vasoactive/procoagulant substances, which prompt platelet aggregation. In addition, tissue factor released by injured tissues binds to factor VIIa, and in the presence of calcium ions, platelet phospholipid membrane and factor Xa subsequently bind to factor Va to form the platelet prothrombinase complex (Figure 1). The prothrombinase complex converts prothrombin to thrombin, which further amplifies its own generation through activation of factors XII and VIII of the intrinsic coagulation pathway (tenase complex) as well as factor Va of the extrinsic coagulation pathway, which then accelerates formation of the prothrombinase complex.[4] Thrombin also directly activates platelets and binds to antithrombin (AT) III, thus depleting the body's major antithrombotic mechanism. Relative depletion of AT III contributes to hypercoagulability.[5] Traditional approaches to anticoagulation have employed indirect thrombin inhibitors (ie, warfarin, unfractionated heparin [UFH], and low-molecular-weight heparins [LMWH]).

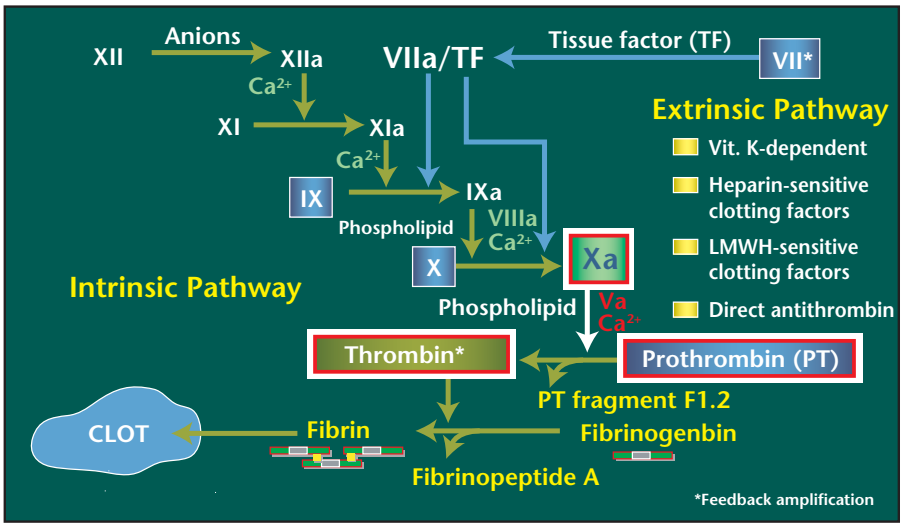

Figure 1. *The coagulation cascade. Tissue factor released by injured tissues activates factor VII, and in the presence of calcium ions, platelet phospholipid membrane and factor Xa subsequently bind to factor Va to form the platelet prothrombinase complex. Thrombin amplifies its own generation through activation of factors XII and V as well as platelet activation. LMWH, low-molecular-weight heparin. Adapted with permission from Walenga et al.* Thromb Res. *1997;86:1-36.*

Warfarin interferes with Vitamin K–dependent hepatic carboxylation of several coagulation factors, including prothrombin (factor II), VII, IX, and X, as well as the anticoagulant proteins C and S.[6] Depletion of the active coagulation factors by warfarin is gradual, thus full anticoagulant effect may not be achieved for days after initiation of therapy or a change in dose. Furthermore, interpatient response to warfarin varies considerably and is influenced by age, hepatic function (especially cytochrome P-450 isoenzyme activity), underlying disease states, numerous drug–drug interactions, dietary Vitamin K consumption, changes in gut bacterial flora, alcohol ingestion, and other factors. Warfarin therapy is further complicated by a narrow therapeutic window as monitored by the International Normalized Ratio (INR). An INR of ≥ 2.0 is required for efficacy in reducing stroke in patients with atrial fibrillation, whereas an INR > 4.0 increases the risk for intracranial hemorrhage.[7,8] In the context of marked variability in warfarin dose response, it may be difficult to stay within this narrow therapeutic window. The anticoagulant effect of warfarin can be reversed by administering Vitamin K or coagulation factors (eg, fresh frozen plasma, cryoprecipitate).

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Unfractionated heparin (UFH) is a heterogeneous mixture of glycosominaglycan molecules with widely variable molecular weight (mean 15,000 daltons, see Figure 2) of which only one-third exhibit anticoagulant activity.[9] UFH exerts its anticoagulant effect largely through binding to AT III. The heparin–AT III complex induces a conformational change in AT III that enhances (by 1000-fold) AT III affinity for thrombin (factor IIa) and factor Xa. Heparin has both pharmacokinetic and biophysical limitations (Table 1). For example, UFH demonstrates nonspecific binding to plasma and cellular proteins, several of which are acute-phase reactants and thus vary in level both among patients and by clinical scenario in the same patient.[10] This characteristic results in wide variability in UFH dose response as well as biphasic (first order/zero order) saturation kinetics. The pharmacokinetic half-life of UFH is thus dose dependent.

LMWH is derived by the enzymatic or chemical depolymerization of UFH to smaller chain links (average molecular weight 4500 daltons), which have less affinity for plasma proteins (a chain length–dependent property) and thus demonstrate a more reliable, predictable dose response.[9] The shorter chain molecular fragments cannot bind thrombin (IIa) and antithrombin (AT III) simultaneously, thus LMWH compounds demonstrate preferential affinity for factor Xa. LMWH compounds also demonstrate lesser susceptibility to neutralization by platelet factor (PF) 4, a specific heparin antidote stored within the alpha granule, which is released upon platelet activation. Indeed, the heparin-PF4 complex elicits an immune response, and antibodies to this complex are pathogenetically linked to the heparin-induced thrombocytopenia (HIT) syndrome. The manifestations of HIT range from the asymptomatic presence of antiheparin antibodies (33%-50%) to platelet activation (20%), thrombocytopenia (2%), and thrombosis (1%).[11] The prevalence of antiheparin antibodies following cardiac surgery has been reported in 29%-50% of patients. Furthermore, the presence of antiheparin antibodies is associated with adverse clinical outcomes after cardiac surgery and in the late follow-up of patients treated with heparin for acute coronary syndromes.[12,13]

Although LMWH compounds overcome many of the pharmacokinetic limitations of UFH, they nevertheless share similar biophysical limitations. Once bound to AT III, neither UFH nor LMWH can effectively inhibit either thrombin bound to fibrin or factor Xa bound to platelets within the prothrombinase complex.[14,15] Thus, even in the presence of heparin, platelet-associated factor Xa can continue to promote thrombin generation and clot-bound

Table 1
Unfractionated Heparin Limitations

- Inability to bind clot-bound thrombin (steric hindrance)
- Inability to bind factor Xa within platelet prothrombinase complex
- Susceptibility to PF4 (inactivation)
- Direct platelet activation/aggregation
- Heparin (thrombin) "rebound"
- Nonspecific cellular and protein binding

PF4, platelet factor 4.

Figure 2. *Range of molecular weight for unfractionated (UFH) and low molecular-weight (LMWH) heparins. Adpated from Hirsh et al.* Blood *1992;79:1-17.*

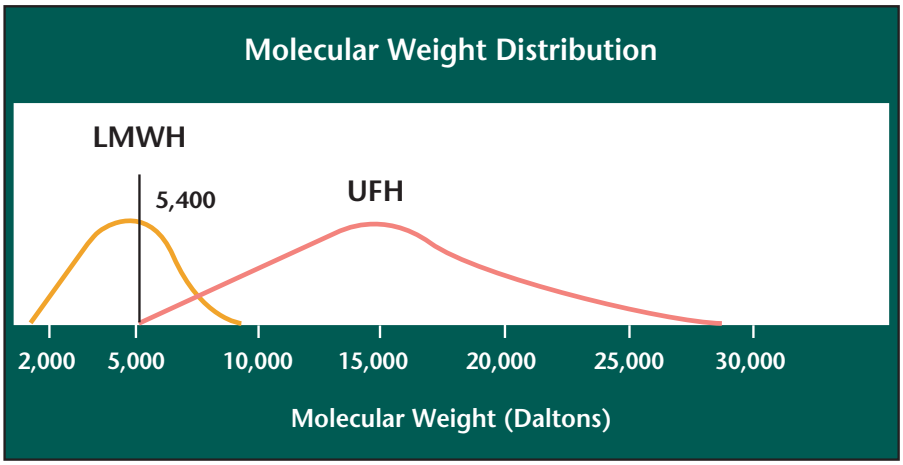
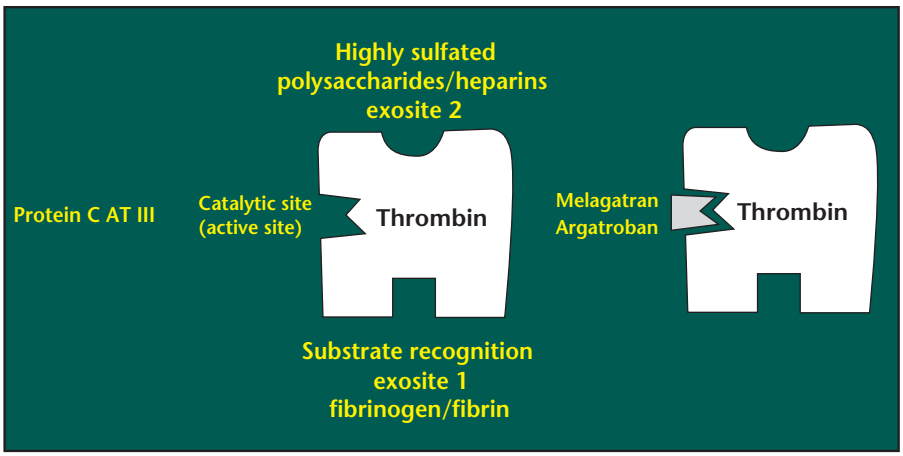


Figure 3. *Geography of thrombin binding sites. Thrombin has a catalytic (active) binding site as well as two exosites. Melagatran binds to the active binding site. AT, antithrombin. Adapted with permission from Nutescu and Wittkowsky.*[4]



thrombin may further promote thrombus growth.[14] The limitations of heparin—AT III complex binding to fibrin-bound thrombin may be explained by the presence of 3 distinct domains on the thrombin molecule (Figure 3).[16-18] In addition to the active catalytic binding site, thrombin also has positively charged domains or "exosites" located on opposite poles of the enzyme. Exosite 1 is the substrate recognition site for binding to fibrinogen or fibrin, whereas exosite 2 is reserved for binding highly sulfated polysaccharides such as heparin. Thus, heparin binds both to exosite 2 on thrombin and to fibrin to form a ternary thrombin/fibrin/heparin complex (Figure 4).[5] The heparin/AT III complex cannot inactivate thrombin within this ternary complex because exosite 2 is already occupied by the ternary complex heparin molecule. In addition to sterically hindering access to thrombin binding, a conformational change in the active site of thrombin induced by formation of the ternary complex may also limit thrombin activity with AT III. In contrast to the heparin/AT III complex, direct thrombin inhibitors (DTIs) target the catalytic (active) site responsible for enzymatic actions of thrombin and/or the substrate recognition site (exosite 1) for binding fibrinogen. Thus, DTIs are capable of inactivating both bound and free thrombin.[19,20]

As thrombin represents the "final common pathway" for coagulation and is capable of amplifying its own production, it is a logical target for pharmacologic intervention. The attributes of an ideal DTI include a high degree of thrombin selectivity, rapid onset and offset of action, predictable pharmacokinetic and pharmacodynamic properties, lack of drug–drug interactions, a wide therapeutic window, the ability to inhibit both bound and free thrombin, and oral administration.[4,21]

Ximelagatran is a readily absorbed prodrug that is rapidly biotransformed into its active form, melagatran. Melagatran is a low-molecular-weight, potent, competitive inhibitor of thrombin that mimics the NH2-terminal sequence of the thrombin cleavage site on the A α chain of fibrinogen.[4,5,21] With its high affinity for the catalytic (active) binding site of thrombin, melagatran directly binds and inhibits both free and clot-bound thrombin. Once absorbed, ximelagatran is rapidly bioconverted to melagatran via 2 intermediate metabolites, ethyl-melagatran and OH-melagatran.[22] Peak concentrations of melagatran are observed 1.6-2.0 hours following oral ximelagatran administration and, unlike heparin, demonstrate dose-proportional, single-compartment pharmacokinetics.[23] The bioavailability of melagatran is ~20%-23%, with low (< 20%) interpatient variability and no appreciable effect of either alcohol or food consumption on absorption or bioconversion. The pharmacokinetic half-life ($t_{1/2}$) of melagatran is 3-5 hours, protein binding is minimal (< 15%), and 80% of the drug is eliminated via the kidneys.[22,23] The clearance of melagatran has been correlated directly to calculated creatinine clearance, and the volume of distribution is correlated to body weight.[24,25] The pharmacokinetics of ximelagatran have been investigated in a variety of specific patient populations.

The pharmacokinetics of ximelagatran were evaluated in younger (age 20-27 years) and older (age 56-70 years) individuals. Concentrations

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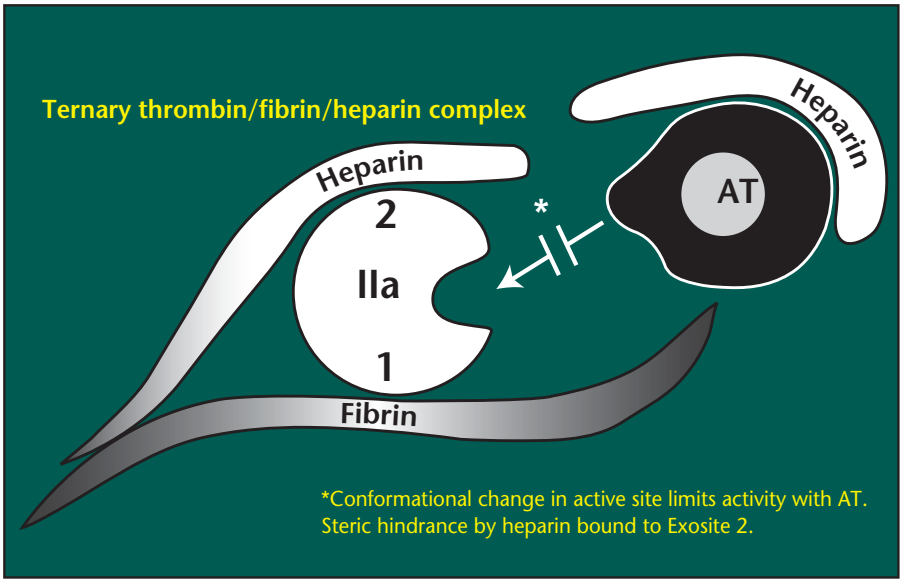
Figure 4. *The limitations of heparin. Heparin bound to exosite 2 on thrombin limits accessibility of antithrombin (AT) III–bound heparin to the thrombin molecule. In addition, a conformational change in the active site limits thrombin reactivity with ATIII. Reproduced with permission from Weitz and Crowther.[5]*



of ximelagatran, melagatran, and melagatran's intermediary metabolites were not different between age groups.[22] Similarly, no pharmacokinetic differences were observed in drug concentration over time (area under the curve, or AUC), by gender or ethnicity (African vs Asian vs Caucasian), or in relationship to food and alcohol consumption.[26] Although melagatran volume of distribution is directly correlated to body weight, no differences in pharmacokinetic profiles were observed between obese (body mass index 32-39 kg/m^2) and nonobese (body mass index 21-26 kg/m^2) individuals.[25]

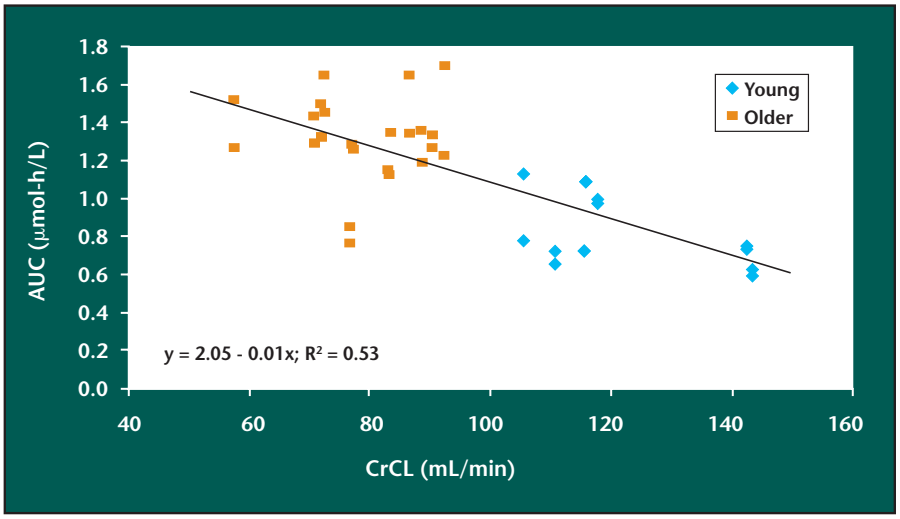


Figure 5. *Influence of renal function as estimated by calculated creatinine clearance (CrCL) (mL/min) on melagatran elimination. Area under the curve (AUC) for melagatran is plotted versus calculated creatinine clearance. Reproduced with permission from Johansson et al.*[24]

Hepatic Dysfunction

The pharmacokinetics and pharmacodynamics of ximelagatran are similar in patients with or without moderate hepatic impairment.[27] Nevertheless, administration of ximelagatran is contraindicated in patients with hepatic impairment because of the associated elevation of hepatic enzymes in 4%-8% of patients on long-term ximelagatran treatment.[28] Hepatic alanine aminotransferase (ALAT) levels have been analyzed in clinical trials evaluating ximelagatran administration for patients undergoing a surgical procedure (knee replacement). Ximelagatran therapy was initiated on the day following surgery at twice-daily doses of either 36 mg (n = 1913) or 24 mg (n = 1097) orally, in randomized comparison with warfarin (n = 2226) for a mean duration of 8 days.[29] Hepatic ALAT levels greater than 3 times the upper limit of normal (x ULN) were observed in 2.1% (36-mg dose cohort) and 1.4% (24-mg dose cohort) of ximelagatran-treated patients compared with 1.3% and 1.5% of warfarin-treated patients, respectively.

Long-term administration of ximelagatran has been evaluated in 5024 patients (≥ 6 months) and 3509 patients (≥ 12 months) in comparison with either warfarin (n = 4967 patients) or placebo (n = 1249 patients). Hepatic ALAT levels greater than 3 x ULN were observed in 7.6% of ximelagatran versus 1.1% of warfarin/placebo-treated patients. Of note, 206 of 531 patients with elevated ALAT levels completed the study without stopping ximelagatran therapy and in most of these patients, ALAT levels spontaneously declined to less than 2 x ULN. Interestingly, of 18 patients who stopped treatment with the study drug due to elevated ALAT and were subsequently rechallenged, only 2 patients developed recurrent ALAT elevation.

The risk of hepatic ALAT elevation appears increased in patients who present with an acute coronary syndrome or a venous thromboembolic disorder, as well as in women, patients with low body mass index (< 27 kg/m^2), or those on concomitant statin therapy. Furthermore, the relative risk of severe liver injury (defined as ALAT levels > 3 x ULN and total bilirubin level > 2 x ULN) was 6.6 (95% confidence interval 2.6-16.9) for ximelagatran compared with warfarin/placebo treatment. Thus, it has been estimated that approximately 1 of every 200 patients receiving ximelagatran therapy will develop evidence of severe liver injury. Short term (< 12 days) ximelagatran therapy has not been associated with severe liver injury. The etiology/mechanism of hepatic dysfunction is unclear and functional abnormalities, which develop during 1-6 months of ximelagatran therapy, have been observed to resolve spontaneously (despite continued treatment) as well as after cessation of therapy.[28-31]

Further investigation has demonstrated no interaction of ximelagatran, melagatran, or melagatran's metabolites with the hepatic cytochrome P-450 enzymes, including CYP2C9, 2C19, and 3A4, and no drug–drug interactions with medications that utilize these enzymatic pathways for metabolism.

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Table 2
Antidote for/Reversal of Anticoagulant Effect of Ximelagatran

- General measures/FFP-PRBC or platelet transfusion
- Recombinant factor VII
- Melagatran is dialyzable/ ? charcoal hemofiltration
- Possible future monoclonal antibody directed against melagatran

FFP, fresh frozen plasma; PRBC, packed red blood cells.

Renal Dysfunction

The clearance of melagatran parallels calculated creatinine clearance across a broad range of renal function (Figure 5).[36-38] Because of a reduction in drug clearance and the potential for accumulation, ximelagatran administration is not recommended in patients with creatinine clearance less than 30 mL/min. Dosing recommendations for patients with a more moderate degree of renal dysfunction (creatinine clearance 30-60 mL/min) are similar to those with more normal (> 60 mL/min) function and appear to have similar safety and efficacy across these stratifications of renal function, based on clinical trial experience. Theoretically, an increase in dose interval or a reduced dosage might be useful in patients with significant impairment in renal function;[38] however, further data must become available before such recommendations can be made.

Special Considerations

Although the process of ongoing thrombosis has been demonstrated to significantly influence the pharmacokinetics/pharmacodynamics (PK/PD) of indirect antithrombin agents (UFH or LMWH) and results in variable dose requirements for therapeutic efficacy, no such effect has been demonstrated for ximelagatran. Ximelagatran PK/PD were not influenced by either the presence of pulmonary embolus or change in deep vein thrombus size. In addition, ximelagatran has been demonstrated to inhibit thrombin generation and platelet activation. Indeed, levels of prothrombin fragment 1.2 and thrombin-antithrombin complex are significantly reduced, as is platelet CD62 (P-selectin) expression.[39] These secondary attributes to melagatran likely stem from its ability to inhibit both free and bound thrombin. Despite these salutary effects of ximelagatran on thrombin generation and platelet activation, a slight but definite increase in cardiovascular events has been observed during or following therapy in patients with atherosclerotic cardiovascular disease. Myocardial infarction was reported in 0.75% of ximelagatran- and 0.26% of warfarin-treated patients (P = .0280) enrolled into short-term, and 0.70% versus 0.16% of patients, respectively, (P = .0118) enrolled into longer-term randomized comparative trials of patients with venous thromboembolic disorders.[29]

From preclinical and human studies, the range of pharmacologically active melagatran levels spans ~0.03-0.08 μmol/L, which suggests that some degree of pharmacologic protection extends for 12-24 hours following a dose of ximelagatran should a missed dose occur.

Missed Dose

The currently recommended twice-daily dosing regimen for ximelagatran raises concern regarding lack of patient compliance and the possibility for a "missed dose" to occur. Interestingly, despite the relatively short $t_{1/2}$ of melagatran, data suggest that pharmacologically active levels of drug persist for 20-22 hours following a dose, particularly during steady-state administration.[39,40] In clinical trials, average trough levels of ~0.2 μmol/L were observed and at 2 half-lives following trough (20-22 hours post dose), levels of ~0.05 μmol/L remain. From preclinical and human studies, the range of pharmacologically active melagatran levels spans ~0.03-0.08 μmol/L, which suggests that some degree of pharmacologic protection extends for 12-24 hours following a dose of ximelagatran should a missed dose occur.[39,40] Furthermore, in contradistinction to warfarin, a very rapid

return to peak melagatran effect can be expected following resumption of dosing.

Reversal of Anticoagulation

At present, no specific antidote exists for melagatran's anticoagulant effect. Considering the direct mechanism for melagatran action, concentrated factor replacement (fresh frozen plasma, cryoprecipitate) may be expected to provide minimal (if any) benefit. Current recommendations for dealing with hemorrhage related to ximelagatran therapy (Table 2) include general measures for maintaining hemostasis (compression, surgical repair, cautery) in addition to transfusion of fresh frozen plasma, packed red blood cells, or platelets, as required.[21,41] Recent data suggest benefit (enhanced hemostasis) associated with treatment using recombinant factor VII (NovoSeven; Novo Nordisk Pharmaceuticals, Princeton, NJ).[42] Primate capillary bleeding times were nearly normalized following NovoSeven, despite melagatran therapy. Furthermore, ximelagatran/melagatran is readily dialyzable and may be rapidly cleared from circulation by hemodialysis.[43] Additional benefit from charcoal hemoperfusion has theoretic appeal but has yet to be proven. Finally, the development of a specific monoclonal antibody to melagatran similar to that available for digoxin (Digibind; GlaxoSmithKline, Philadelphia, PA), although intuitively attractive, has been hindered by regulatory issues.

Monitoring

Currently, no specific recommendations for monitoring therapy with ximelagatran exist.[4,21,41] Melagatran has demonstrated a concentration-dependent and nonlinear prolongation of the activated partial thromboplastin time as well as widely variable prolongation of the INR, depending on the reagent used.[23,44] In addition, the relationship between plasma concentrations of melagatran and prolongation of the activated clotting time is not adequately sensitive to provide a useful measurement of melagatran effect for monitoring. A better direct correlation between plasma melagatran levels and either the thrombin time or ecarin clotting time has been demonstrated.[12,45] Although either of these tests may provide a more accurate assessment of melagatran's anticoagulant effect, optimal therapeutic targets (ranges) have not been determined and correlation to clinical outcomes has not been established. Furthermore, the optimal objective for monitoring (ie, peak or trough level vs AUC) remains to be defined.

Conclusions

Thrombin is central to the pathogenesis of both arterial and venous thrombosis and represents a logical therapeutic target. Direct thrombin inhibitors offer the distinct advantage of inhibiting both fibrin-bound and free thrombin. Ximelagatran, the first orally active direct thrombin inhibitor, is a readily absorbed prodrug that is rapidly converted to melagatran, its active metabolite. Melagatran is largely (≥ 80%) cleared by the kidney. Ximelagatran/melagatran has a predictable PK/PD profile across a very broad spectrum of patients. The pharmacologic half-life of melagatran (3-5 hours) is consistent with twice-daily dosing and fixed-dose administration, without the requirement for monitoring that is currently recommended. Ximelagatran therapy is not indicated for patients with severe renal (creatinine clearance < 30 mL/min) or hepatic dysfunction. Remarkably,

Main Points

- Because thrombin represents the final common pathway for coagulation and is capable of amplifying its own production, it is a logical target for pharmacologic intervention. The attributes of a direct thrombin inhibitor include a high degree of thrombin selectivity, rapid onset and offset of action, predictable pharmacokinetics and pharmacodynamics, lack of drug–drug interactions, a wide therapeutic window, the ability to inhibit both bound and free thrombin, and oral administration.
- Although the dosing recommendations for ximelagatran are similar in patients with moderate renal dysfunction and those with normal renal function, this agent is not recommended for patients with creatinine clearance < 30 mL/min.
- Although the process of ongoing thrombosis has been demonstrated to significantly influence the pharmacokinetics/pharmacodynamics of indirect antithrombin agents and results in variable dose requirements for therapeutic efficacy, no such effect has been demonstrated for ximelagatran.
- Despite the relatively short $t_{1/2}$ of melagatran, data suggest that pharmacologically active levels of drug persist for 20-22 hours following a dose, particularly during steady-state administration.
- Ximelagatran has no known drug interactions and is not metabolized by the hepatic cytochrome P-450 system.

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