



PHARMACY CORNER

E . P . C . M . S .

BACKGROUND

Bivalirudin (Angiomax®) is a direct thrombin inhibitor that was approved by the FDA on December 15, 2000. Although it is not a new drug, bivalirudin, as well as the rest of the direct thrombin inhibitors, still manage to cause confusion and insecurity when the decision is made to utilize this treatment in patients. This is probably due to the fact that the conventional anticoagulants, including warfarin and heparin, have been used for many years thereby developing a level of comfort with health care professionals. However, conventional anticoagulants have their drawbacks (e.g. heparin-induced thrombocytopenia or warfarin-induced purple-toe syndrome), which is why new anticoagulants like direct thrombin inhibitors have been developed. Direct thrombin inhibitors are treatment options for heparin-induced thrombocytopenia (HIT) among other indications (see Table 2).¹ Lepirudin and argatroban are two drugs from this class that both have the FDA-approved indication for the management of HIT, while bivalirudin does not. Bivalirudin is a unique direct thrombin inhibitor since it has been FDA approved for use in percutaneous coronary intervention (PCI) and percutaneous transluminal coronary angioplasty (PTCA) (see Table 1).

PHARMACOLOGY, PHARMACODYNAMICS, AND PHARMACOKINETICS

Bivalirudin is a parenteral anticoagulant with concentration-dependent, specific, and reversible actions on thrombin. It is a synthetic, 20-amino acid peptide with a molecular weight of approximately 2100 Dalton (anhydrous free base peptide).² Bivalirudin directly binds to thrombin's catalytic site and anion-binding exosite resulting in inhibition of both the free and bound forms of thrombin in both a competitive and non-competitive manner.² Once bivalirudin binds to thrombin it is cleaved and active-site functions of thrombin are restored; this results in bivalirudin's transient inhibition of thrombin.⁷ Although direct thrombin inhibitors exert an antiplatelet effect by limiting thrombin-mediated platelet activation, bivalirudin is not inhibited by platelet products.^{7,2} Bivalirudin binds minimally to red blood cells (7%), but does not bind to plasma proteins significantly.² It must be acknowledged that bivalirudin does not affect the kinetics and efficacy of tissue-type plasminogen-activator (t-PA), or the human factors VIIa, Xa, XIIa, or plasmin. It has been shown that bivalirudin achieves therapeutic activated clotting time (ACT) levels within 5 minutes of the start of bivalirudin therapy, and that these levels return to subtherapeutic anticoagulant levels within 1 hour of infusion discontinuation.¹ Bivalirudin has linear pharmacokinetics and is extensively distributed into tissues. The mean volume of distribution of bivalirudin is 13 liters, and a mean steady state concentration of approximately 12 mcg/mL is achieved after a 1 mg/kg bolus dose followed by a 4-hour continuous infusion at 2.5 mg/kg/h is administered.¹ It is partially

Bivalirudin (Angiomax®)

Kathryn M. Mier, Pharm.D.
José O. Rivera, Pharm.D.

cleared by both glomerular filtration and proteolytic cleavage.^{2,9} In normal renal function, the half-life of bivalirudin is approximately 25 minutes.¹ Bivalirudin clearance is compromised depending on the degree of renal dysfunction; therefore, worsening renal function prolongs the half-life, which may go up to 3.5 hours in dialysis-dependent patients.⁹ It is dialyzable, and it can be expected that 25% of the drug may be cleared by hemodialysis.

INDICATIONS AND DOSING

Bivalirudin has been FDA approved for the following indications:

- ↑ as an anticoagulant used along with aspirin (ASA) in patients with unstable angina (UA) undergoing percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) with a glycoprotein IIb/IIIa receptor antagonist⁴
- ↑ as an anticoagulant in patients with, or at risk of, heparin-induced thrombocytopenia (HIT) or heparin-induced thrombotic thrombocytopenia syndrome (HITTS) undergoing PCI⁴

Bivalirudin also has an off-label use for the treatment of HIT in patients not undergoing PCI, and high-risk acute coronary syndrome (ACS) undergoing invasive strategy.⁹ The dose recommendations for bivalirudin begin with an intravenous (IV) bolus of 0.75 mg/kg followed by an IV infusion of 1.75 mg/kg/h for the duration of the PCI procedure. An activated clotting time (ACT) should be taken five minutes after the bolus is given. An additional bolus of 0.3 mg/kg may be given if needed and administration of a glycoprotein IIb/IIIa receptor antagonist may be considered when necessary. For patients with HIT/HITTS undergoing PCI, the recommended dose is an IV bolus of 0.75 mg/kg followed by a continuous IV infusion at 1.75 mg/kg/h for the duration of the procedure. Bivalirudin infusion may be continued for up to 4 hours after PCI based on the physician's discretion. After 4 hours if continuation of bivalirudin is necessary, it may be continued at a rate of 0.2 mg/kg/h for up to 20 hrs. The titration of dosage based on an ACT target is not necessary since bivalirudin has shown in clinical trials a quick and predictable level of anticoagulation.¹ Bivalirudin is intended to be used in conjunction with aspirin (300-325 mg daily). Bivalirudin dosage does require renal adjustment based on degree of renal impairment with the exception of the bolus dose, which does not require reduction. Moderate renal impairment (30-59 ml/min) requires a standard dose of 1.75 mg/kg/h, but in severe renal impairment (CrCl <30 mL/min) the infusion rate should be decreased to 1.0 mg/kg/h. In the case of hemodialysis, the infusion should be reduced to 0.25 mg/kg/h. The dosing regimens for bivalirudin's off-label indications include the following: for ACS undergoing an invasive strategy use an initial dose of 0.1 mg/kg bolus followed by 0.25

Continued on page 11



Bivalirudin (Angiomax®) (Continued)

mg/kg/h, then prior to PCI give an additional bolus of 0.5 mg/kg and increase infusion rate to 1.75 mg/kg/h; for HIT in normal renal function the dose may be initiated at 0.15 mg/kg/hr adjusting based on the goal aPTT of 1.5-2.5 times baseline.⁴

SAFETY

In general bivalirudin is a safer anticoagulant compared to heparin due to its reversible thrombin binding.^{1,4} The most common side effects experienced are fluctuations in blood pressure, pain, headache, nausea, injection site pain, insomnia, and vomiting. More severe, but rare adverse effects that may be experienced secondary to bivalirudin therapy are hemorrhage, biliary hyperplasia, pancreatitis, liver necrosis, and phlebitis at the infusion site.² Bivalirudin is a pregnancy category B since there have been no studies done in human pregnancy; in addition, the safety and efficacy of bivalirudin has not been established in the pediatric patient population.¹

WARNINGS AND PRECAUTIONS

The use of bivalirudin is contraindicated in the presence of active major bleeding or allergy to bivalirudin or any component of its formulation. Bivalirudin is not intended for intramuscular (IM) administration or oral administration. Safety and efficacy have not been established in children or in patients with UA or ACS not undergoing PTCA or PCI. An increased risk of thrombus has been reported with bivalirudin use in gamma brachytherapy, and caution should be used in renal impairment.⁴

CLINICAL TRIALS

Numerous studies have been conducted thus far to assess and investigate both approved indications and off-label uses for bivalirudin. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial was a randomized, double-blind, active-controlled trial that found bivalirudin with provisional Gp IIb/IIIa blockade to be non-inferior to heparin plus planned Gp IIb/IIIa blockade during PCI in regard to the suppression of acute ischemic end points.¹⁰ In this large study (n=6010), bivalirudin was also associated with significantly less bleeding than heparin (2.4% vs 4.1%, p<0.001). The Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia (ATBAT) Study was a smaller study (n=52) that established the safety of bivalirudin in patients with HIT undergoing PCI.¹¹ The primary endpoint was occurrence of a major bleed within 48 hours of drug administration or until hospital discharge, which only occurred in 1 patient (1.9%; 95% CI 0.04-10.65%) of the high dose group who underwent elective bypass surgery. Procedural and clinical success was seen in 98% and 96% of the subjects, respectively, and no patient had significant thrombocytopenia (platelet count <50x10⁹/L). The use of bivalirudin in patients with HIT that are not undergoing PCI, which is an off-label use, has not been investigated with large clinical trials. Most of the current literature consists of case studies, retrospective case series, and several studies of small sample size.¹² A recent retrospective cohort study that involved 37 adults with a diagnosis or history of HIT who were treated with bivalirudin between January 1, 2004 and March 31, 2007 had promising results, but several limitations.¹³ Patients who received bivalirudin for PCI were excluded from this study. Primary outcomes were dose and duration of bivalirudin therapy, while secondary outcomes consisted of occurrence of thromboembolism, mortality, length of hospital stay, and adverse events. The mean initial and maintenance dose of bivalirudin in all patients was ~0.09 mg/kg/hr, which resulted in 51% achievement of therapeutic aPTT goal of 1.5 to 2.5 x baseline after the initial dose. The mean duration of bivalirudin ad-

ministration was ~ 11 days in all patients, and the mean length of hospital stay was 38 days in all patients. Deep-vein thrombosis developed in one patient (3%) during bivalirudin treatment, four patients on bivalirudin formed clots on the continuous renal replacement hemofilter, but there were no deaths as a result of a documented thrombotic event. However, all-cause mortality was 22%. The major adverse effect was clinically significant bleeding attributable to bivalirudin, which occurred in two (5%) patients. This study has limited generalizability since 95% were ICU patients and 59% had concomitant hepatic dysfunction.

SUMMARY

Bivalirudin is an appealing direct thrombin inhibitor since it has a short half-life, predictable renal excretion, and does not require dose adjustments in hepatic insufficiency.¹ Some advantages that bivalirudin may have over heparin include: high specificity and potency for inhibiting free and bound thrombin independently from anti-thrombin, no platelet activation, and no involvement with immune-mediated thrombocytopenia/thrombosis or cross-reactivity with HIT antibodies.¹¹ Bivalirudin has FDA-approved indications for use along with ASA for patients with UA undergoing PTCA or PCI with glycoprotein IIb/IIIa receptor antagonists and for use in patients undergoing PCI with or at risk of HIT/HITTS. Further studies are needed to properly assess its use in HIT patients not undergoing PCI.

REFERENCES

1. Seybert AL, Coons JC, and Zerumsky K. Treatment of heparin-induced thrombocytopenia: is there a role for bivalirudin? *Pharmacotherapy*. 2006; 26 (2): 229-241.
2. Shammas NW. Bivalirudin: Pharmacology and clinical applications. *Cardiovascular drug reviews*. 2005; 23 (4): 345-360.
3. Drugs@FDA: FDA Approved Drug Products. Drug Approvals and Databases. <http://www.fda.gov/Drugs/InformationOnDrugs/default.htm>. Accessed 2/2/2009.
4. Lexi-Comp Online. Argatroban (Novastan®), Bivalirudin (Angiomax®), Desirudin (Iprivask®), Lepirudin (Refludan®) Monographs. <http://online.lexi.com.ezproxy.lib.utexas.edu/crlsql/servlet/crlonline>. Accessed 2/2/2009.
5. Weitz JJ, Hirsh J, and Samama MM. New antithrombotic drugs. *CHEST*. 2008; 133: 234S-256S.
6. Haas S. New oral Xa and IIa inhibitors: updates on clinical trial results. *J Thromb Thrombolysis*. 2008; 25: 52-60.
7. Di Nisio M, Middeldorp S, and Buller HR. Direct thrombin inhibitors. *New Engl J Med*. 2005; 353: 1028-1040.
8. Iprivask® (desirudin) package insert. Manufactured by Canyon pharmaceuticals, distributed by Aventis, 2003.
9. Angiomax® (bivalirudin) package insert. The Medicines Company®, 2005.
10. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 Randomized Trial. *JAMA*. 2003; 289 (7): 853-863.
11. Mahaffey KW, Lewis BE, Wildermann NM, et al. The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: main results. *J Invasive Cardiol*. 2003; 15: 611-616.
12. Dager WE, Dougherty JA, et al. Heparin-induced thrombocytopenia: treatment options and special considerations. *Pharmacotherapy*. 2007; 27 (4): 564-587.
13. Kiser TH, Burch JCB, Klem PM, Hassell KL. Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. *Pharmacotherapy* 2008; 28(9): 1115-1124.

Continued on page 12



Bivalirudin (Angiomax®) (Continued)

Table 1. Summary of bivalirudin (Angiomax®) characteristics

Date of FDA approval³		12/15/2000				
Indication⁴	FDA Approved	Used along with ASA* for UA* undergoing PTCA* or PCI* w/ glycoprotein IIb/IIIa receptor antagonists Anticoagulant used in PCI w/ (or at risk of) HIT* or HITTS*				
	Off-label	HIT, ACS* (moderate-high risk) undergoing invasive strategy				
Dosing⁴						
PK⁴		PB: none, only thrombin	Vd: ~13L 0.2 L/kg	Metabolism: Blood proteases	Elimination: Urine (20%) Proteolytic cleavage	t _{1/2} : 25 min
Precautions⁴		Active bleed, allergy to any components in formulation, not to be given IM or PO, safety & efficacy unknown in children or patients with UA or ACS not undergoing PTCA or PCI				
Adverse Events⁴		fluctuations in blood pressure, pain, headache, nausea, injection site pain, insomnia, and vomiting				
Monitoring⁴		ACT, aPTT				
Drug Interactions¹		↑risk of bleed with: heparin, warfarin, or thrombolytics Physical incompatibility: alteplase, amiodarone, amphotericin B, chlorpromazine, diazepam, prochlorperazine, reteplase, streptokinase, & vancomycin				

*ASA=aspirin, UA=unstable angina, PCI=percutaneous coronary intervention, PTCA= percutaneous transluminal coronary angioplasty HIT=heparin-induced thrombocytopenia, HITTS=heparin-induced thrombotic thrombocytopenia syndrome, ACS=acute coronary syndrome

Table 2. Summary of direct thrombin inhibitors

Direct Thrombin Inhibitor		Lepirudin (Refludan®)	Argatroban (Novastan®)	Bivalirudin (Angiomax®)	Desirudin (Iprivask®)
Date approved ³		3/6/1998	6/30/2000	12/15/2000	4/4/2003
Indication ⁴	FDA Approved	Anticoagulation during HIT*	<ul style="list-style-type: none"> • Prophylaxis or treatment of thrombosis in HIT* • Adjunct to PCI* in presence or risk of thrombosis due to HIT* 	<ul style="list-style-type: none"> ♦ Used along with ASA* for UA undergoing PTCA* or PCI* w/ glycoprotein IIb/IIIa receptor antagonists ♦ Anticoagulant used in PCI w/ (or at risk of) HIT or HITTS* 	VTE* prophylaxis in hip replacement ⁷
	Off-label	UA*	maintain extracorporeal circuit patency (prefilter administration) of CRRT* in critically-ill patients with HIT	HIT	
Dosing ⁴		HIT: Bolus dose: 0.4 mg/kg IVP (over 15-20 seconds), followed by continuous infusion at 0.15 mg/kg/hr (maximum initial bolus dose: 44 mg; maximum initial infusion dose: 16.5 mg/hr); bolus & infusion ↓ in renal insufficiency	HIT: Initial dose: 2 mcg/kg/min Maintenance dose: measure aPTT after 2 hrs; adjust dose until the steady-state PTT is within goal; dosage should not exceed 10 mcg/kg/min	PTCA/PCI: Initial: Bolus: 0.75 mg/kg, then continuous infusion: 1.75 mg/kg/hr for entire procedure and up to 4 hours postprocedure if needed; determine ACT 5 min after bolus dose; may administer additional bolus of 0.3 mg/kg if needed. If needed, infusion may be continued beyond initial 4 hours at 0.2 mg/kg/hour for up to 20 hours.	VTE: 15 mg q 12 hr administered by subQ injection w/ initial dose given up to 5-15 minutes prior to surgery, but after induction of regional block anesthesia ⁸
Dose adjustments ⁴		Renal	Hepatic	Renal	Renal ⁸
Monitoring ⁴		aPTT 1.5-2.5 X the control value	aPTT 1.5-3.0 X the initial baseline value, not > 100 sec	ACT* for PCI or PTCA aPTT* for HIT	aPTT 2 X control value ⁸
Adverse effects ⁴		Anemia, bleeding, hematoma, fever, ↑LFTs, lepirudin antibody formation, anaphylaxis	Chest pain, hypotension, GI bleed, increased INR in combination with warfarin	Hypotension, pain, headache, nausea, back pain	Injection site mass, anemia ⁸
Drug interactions ⁴		NSAIDs, salicylates, anticoagulants			

*HIT=heparin-induced thrombocytopenia, HITTS=heparin-induced thrombotic thrombocytopenia syndrome, UA=unstable angina, MI=myocardial infarction, PCI= percutaneous coronary intervention, VTE=venous thromboembolism, CRRT=continuous renal replacement therapy, ASA=aspirin, PTCA= percutaneous transluminal coronary angioplasty, ACT=activated clotting time, aPTT=activated partial thromboplastin time

Continued on page 13



Bivalirudin (Angiomax®) (Continued)

Table 3. Direct thrombin inhibitors in the developmental pipeline⁵

	Flovagatran	Pegmusirudin	Dabigatran etexilate	Ximelagatran
Indication	alternative to heparin during HD* in patients w/ ESRD* w/ antibodies to the heparin/PF4 complex ⁵	HD* patients to provide prolonged anticoagulation ↓ risk of vascular access graft occlusion ⁵	VTE prophylaxis after orthopedic surgery ⁶	VTE treatment ⁷ currently removed from the market due to hepatotoxicity)
Route	IV*	IV*PO*	PO*	

*HD=hemodialysis; ESRD=end-stage renal disease; IV=intravenous; PO=oral

Kathryn M. Mier, Pharm.D., University of Texas at El Paso College of Health Sciences, University of Texas at Austin College of Pharmacy.

José O. Rivera, Pharm.D., University of Texas at El Paso College of Health Sciences, University of Texas at Austin College of Pharmacy, Texas Tech University Health Sciences Center Paul L. Foster School of Medicine.

