

Plasma-Modified ACT Can Be Used to Monitor Bivalirudin (Angiomax®) Anticoagulation for On-Pump Cardiopulmonary Bypass Surgery in a Patient with Heparin-Induced Thrombocytopenia

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Abstract: Heparin-induced thrombocytopenia (HIT) is a problem of growing significance and concern, affecting an estimated 1-3% of patients among those receiving an estimated 10 million heparin exposures annually in the United States. The prevalence of heparin antibodies has been reported as at least 12.7% in the general cardiac surgery population before surgery and 42% following surgery (1). Various management techniques for anticoagulation in these patients have been proposed. Many of these alternative agents present additional risks for bleeding and efficacy and, furthermore, require the use of nonconventional moni-

toring assays to assess the level of anticoagulation achieved adequately. We report here the successful use of bivalirudin anticoagulation on pump, with no additional morbidity, and the first reported use of the plasma-modified ACT (activated clotting time) test, a simple modification of the standard ACT assay, to monitor the anticoagulant effect of bivalirudin. **Keywords:** plasma-modified ACT, bivalirudin, anticoagulation, on-pump cardiopulmonary bypass surgery, heparin-induced thrombocytopenia. *JECT. 2004;36:174-177*

The challenge of providing an alternative anticoagulation regimen to unfractionated heparin for patients with antiheparin antibodies and heparin-induced thrombocytopenia undergoing cardiac surgery used to be a rare event, one discussed in journal clubs or in specialty discussions at expert subsessions at cardiac anesthesia meetings. However, the problem is becoming increasingly common, as an estimated 3% (34,500) of as many as 1.15 million patients (angioplasty plus cardiac surgery alone) develop signs and symptoms of HIT. Antiheparin antibody formation is much more common than the fulminant variety of HIT with thrombocytopenia and/or with thrombotic events (HITTS). Although previously thought to be nonpathogenic, it would seem that antibody formation represents a "stand-alone" prothrombotic state that adds a risk burden greater than that associated with congestive heart failure

(CHF) or renal failure to the risk of developing a 30-day morbid outcome following cardiac surgery (2).

The physician confronted with a patient with a diagnosis of HIT, according to standard clinical definition criteria (drop in platelet count 50% from baseline, positive ELISA, and/or serotonin release assay), is faced with a variety of alternatives for managing anticoagulation during cardiac surgery. None are approved by the Food and Drug Administration for this purpose, and each requires specific knowledge and expertise. In part, because of concerns about the risk of additional morbidities associated with these agents, most commonly bleeding and possible thrombosis, as well as the relative difficulty in monitoring these agents during cardiopulmonary bypass, many physicians try to postpone surgery until circulating antibody levels are negative, then use a limited exposure to unfractionated heparin for anticoagulation. However, many of these cases are not elective, and additional risks are superimposed by postponing surgery for 3 months.

Heparin-induced thrombocytopenia is now understood as a clinical situation of unchecked and explosive throm-

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bin generation, which is why definitive therapy for the condition mandates use of a direct thrombin inhibitor. Three direct thrombin inhibitors are approved for use in the United States: lepirudin (Refludan®, Berlex Laboratories, Wayne, NJ), argatroban (GlaxoSmithKline, Research Triangle Park, NC), and bivalirudin (Angiomax®, The Medicines Company, Parsippany, NJ). Both lepirudin and argatroban are approved for the treatment of patients with HIT, based on prospective clinical studies of lepirudin in 211 patients, and argatroban in 568 patients (3). Bivalirudin is only approved for angioplasty and has been demonstrated in two double-blind trials of over 10,000 patients to be more effective and safer than unfractionated heparin for this indication (4,5). Bivalirudin has shown favorable results in a prospective clinical study of 52 patients with HIT or HITTS undergoing angioplasty, (6) and is currently being investigated versus heparin for cardiac surgery in patients with HIT. However, neither lepirudin, argatroban, nor bivalirudin are yet approved for use in patients with HIT undergoing cardiac surgery.

Although little is published relative to the use of argatroban in cardiac surgery, (7) and initial trials in cardiac surgery were discontinued because of poor outcomes, a more robust dataset exists for lepirudin in this indication. In the largest series yet reported to date, Koster et al. showed that lepirudin could be used reproducibly to provide anticoagulation for cardiac surgery in combination with forced dialysis and ultrafiltration (8).

However, the patient population evaluated by Koster was characterized by a lower incidence of renal dysfunction than is commonly seen in the United States. Only 7% of patients had a preoperative serum creatinine of >1.5 mg/dL, versus 11% in the U.S. population as demonstrated in a prospective series of more than 4000 cardiac surgery patients by Stafford-Smith et al. (9). Nevertheless, Koster et al. found that their patients had an average transfusion requirement of 2.5 units of packed cells and 2.7 units of FFP. Seven percent of patients had massive bleeding (>9 units transfused) and 28% of patients had 24-hour postoperative bleeding of more than 500 mL, with particularly extensive bleeding in those patients who manifested renal dysfunction postoperatively.

Koster et al. separately reported a second technique of combining unfractionated heparin with a bolus dose of tirofiban, a glycoprotein (GP) IIb/IIIa antagonist, to inhibit platelet reactivity with the heparin-platelet factor four (PF4) antibody (10). Because the kinetics of the platelet inhibitor in this technique are much shorter than that of unfractionated heparin, it was necessary to continue an infusion postoperatively of a direct thrombin inhibitor, (lepirudin, in this instance). However, a potential pitfall of this technique is the inability to predict reliably that adequate platelet inhibition has occurred, as pointed out by Kabbani et al. These authors showed that fre-

quently inadequate platelet inhibition was measured 15 minutes to 60 minutes following bolus administration of tirofiban (11). Moreover, the use of GP IIb/IIIa receptor inhibitors have consistently been associated with increased bleeding when used with unfractionated heparin at high activated clotting time (ACT) values in the cardiology literature, in several very large trials, and have also been associated with increased bleeding when used in this particular application in cardiac surgery in conjunction with heparin, which has produced a manufacturer's warning letter overseas (12–14).

Thus, we believed that bivalirudin (Angiomax®), a thrombin-specific anticoagulant approved for use in angioplasty, with a 25-minute half-life and a more favorable metabolic profile than other direct thrombin inhibitors, might be the optimal choice for anticoagulation of our patient. Bivalirudin is 80% metabolized in the plasma, primarily through proteolytic cleavage, and approximately 20% dependent upon renal elimination pathways. Bivalirudin demonstrates effective thrombin inhibition with a rapid return to hemostatic capacity following discontinuation of the drug, and has and a lower propensity for bleeding by virtue of its mechanism of action. The bivalirudin molecule first binds specifically to the thrombin catalytic site and exosite 1, then is enzymatically cleaved by thrombin, allowing thrombin to resume its hemostatic function. The temporary binding of bivalirudin to thrombin contrasts with the irreversible, tight binding affinity of lepirudin at the thrombin exosite 1 and catalytic site (15).

With any anticoagulant, an issue of concern lies in the ability of commonly used monitoring tests to reflect the level of anticoagulation properly and the concentration of the anticoagulant. This is of greater concern during cardiopulmonary bypass, caused by the effects of dilution and mechanical disruption of coagulation factors, which, in fact, affect monitoring with unfractionated heparin as well.

Koster et al. demonstrated that the accuracy of monitoring unfractionated heparin levels post bypass could be improved by 60% through a modification of the standard ACT assay, termed the plasma-modified ACT assay (16). In this assay, a sample of platelet-poor plasma, either of commercial or blood bank origin, is added in a one-to-one dilution to whole blood measured with the ACT tube and assay. The theory is that platelet-poor plasma will contain the necessary concentration of factors to correct for any dilutional effect caused by bypass or mechanical pump disruption. Thus, one mL of plasma is added to one mL of whole blood, and the ACT is then measured in normal fashion, assuming a 2-mL sample volume as is the case with the Hemochron® (International Technidyne Corp., Edison, NJ) or the HemoTec® (Medtronic Inc., Minneapolis, MN) apparatus. This assay technique has improved the accuracy of monitoring lepirudin concentrations and its anticoagulation effect on bypass (17). We reasoned that

the assay might provide useful information in monitoring bivalirudin concentration and effect during and following cardiopulmonary bypass. We herein present the results of our findings.

DESCRIPTION

Bivalirudin provided effective anticoagulation for our patient undergoing on-pump cardiopulmonary bypass and seemed to be safe. The patient's total intraoperative blood loss was 300 cc, and post-operative blood loss was 500 cc over the first 2 hours. No transfusion of any blood products was required either intraoperatively or postoperatively. The plasma-modified ACT test seemed to track in good correlation with the standard ACT assay (Hepcon® HMS, Medtronic Inc., Minneapolis, MN). ACT was maintained at greater than 480 seconds throughout the time period of therapeutic anticoagulation. Plasma-modified ACT values were maintained at >240 seconds throughout the same time period, see Table 1. Post-bypass elimination of bivalirudin is likely augmented through forced diuresis with furosemide and mannitol to augment the 20% of bivalirudin elimination that is renal in nature. However, most bivalirudin is metabolized through direct action of thrombin and plasma esterases, and our experience was that this elimination pathway was sufficient. Hemoconcentration remains a further available option to remove bivalirudin from the circulation rapidly, and up to 70% of bivalirudin may be removed in this fashion (16). Pump thrombosis and clotting can occur if bivalirudin concentrations fall to subtherapeutic levels during or after stopping the bivalirudin infusion at the end of cardiopulmonary bypass, thus maintaining adequate levels of antico-

agulation are of paramount importance during the CPB period (18).

Bivalirudin was administered as a bolus dose of 1.5 mg/kg, and a continuous infusion of 2.5 mg/kg/h was run from the time of bolus until the last proximal anastomosis was completed. In addition, the cardiopulmonary bypass pump was primed with a separate bolus of 50 mg of bivalirudin. The pump was continuously recirculated post separation from the patient, with an additional post-separation bolus of 20 mg of bivalirudin to prevent the pump from rapidly clotting, which has been previously reported with lepirudin use (18,19).

DISCUSSION

In this case, ACT testing did seem to track bivalirudin effect with reasonable correlation, comparable to the ability of this assay to monitor heparin anticoagulation. However, the frequency with which the ACT assay and the plasma-modified ACT assay were performed in this report may have been somewhat misleading in this regard. More frequent assays may have revealed a trend not seen in this analysis.

The ACT assay has been used successfully in a Phase II study, which compared bivalirudin to heparin in 100 patients (50 bivalirudin patients) and showed good correlation of the ACT with anticoagulant effect (20). Other authors have reported that ACT levels following bypass seem to decrease somewhat less rapidly than one might expect with a drug with a 25-minute half-life, and that ecarin clotting time (ECT) can be used to monitor anticoagulation with bivalirudin during cardiopulmonary bypass (21). Koster further speculated (21) that ACT may not, in fact, be a reliable indicator of bivalirudin effect during cardiopulmonary bypass because fibrin formation was seen in the pericardial cavity when ACT values were above 400 seconds.

The difficulty with Koster et al.'s assertion is that these ACT values were measured from the arterial line, rather than from the actual blood volume within the pericardial cavity where the fibrin formation was seen. Because bivalirudin is cleaved by thrombin, and because thrombin is produced in enormous quantities in pooled, stagnated blood within the pericardial cavity as its exposed wound edges generate tissue factor, it is almost certain that the ACT measured in the chest cavity blood would have been substantially lower than the 400 seconds obtained from the arterial line. Baker recently reported better correlation between anticoagulation levels and high-dose thrombin times, although the delta between the ACT and this test occurred while on bypass, rather than following the bypass period (22). Yet another anecdotal report found the thromboelastograph to provide useful information as well [The Medicines Company, (23)]. A recently completed

Table 1. Dosing, plasma modified ACT and ACT measurements with bivalirudin.

Time'	Bolus Dose (mg/kg)	Infusion Dose (mg/kg/h)	ACT Test (s)	mACT Test (s)
Baseline			150	130
5'	1.5 bolus	2.5 infusion	445	306
15'	0.5 bolus	2.5 infusion	484	345
30'	0.5 bolus (on pump)	2.5 infusion	544	374
60'		2.5 infusion	615	409
95'		2.5 infusion	524	385
110'	0.25 bolus	2.5 infusion	559	385
120'		Infusion	434	300
(off pump)		stopped		(clot viewed)
170' (ICU)			401	272

ACT = activated clotting time.

mACT = plasma-modified ACT.

mg/kg = milligrams per kilogram.

mg/kg/h = milligrams per kilogram per hour.

s = seconds.

ICU = intensive care unit.

pilot study (The Medicines Company, unpublished data) of bivalirudin in on-pump, non-HIT patients has evaluated correlation of the ACT assay with plasma bivalirudin concentrations, as well as ECT values, but the results of this study are not yet published.

Our experience with bivalirudin for anticoagulation in this patient with HIT was highly favorable. We experienced none of the complications reported with the use of other direct thrombin inhibitors for cardiopulmonary bypass, such as bleeding, thrombosis, or difficulty achieving and maintaining therapeutic levels of anticoagulation. ACT monitoring seemed to provide adequate assessment of anticoagulation status, as did plasma-modified ACT. Given the simplicity of the plasma-modified assay, we recommend that this test be performed in conjunction with ACT monitoring until a definitive answer is known as to the superiority or superfluity of one or the other, or until an alternate monitoring assay is known. Furthermore, our recommendation is that bivalirudin be considered for use as a possible alternative for anticoagulation in cardiac surgery in patients with known or suspected HIT.

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