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Use of Bivalirudin as an Anticoagulant During Cardiopulmonary Bypass

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Abstract: Bivalirudin is a short-acting direct thrombin inhibitor that has been used in cardiac surgical patients with heparin-induced thrombocytopenia (HIT) or suspected HIT. Although no direct thrombin inhibitor is indicated for anticoagulation during cardiac surgery in patients with heparin-induced thrombocytopenia (HIT) or suspected HIT, use of heparin-alternatives are increasing as the awareness of HIT increases. Reports of anticoagulation with bivalirudin are sporadic, however, with variable dosing and management strategies. In this report, we describe our management techniques for cardiopulmonary bypass with bivalirudin based upon our personal experience. Although the reported clinical experience with bivalirudin in cardiac surgery is reviewed, operative techniques for the perfusionist/surgeon team are discussed in detail. We recognize that the use of bivalirudin during cardiopulmonary bypass is evolving and modifications of technique will undoubtedly occur as further data and experience accumulate. **Keywords:** direct thrombin inhibitors, anticoagulation, cardiopulmonary bypass, heparin induced thrombocytopenia. *JECT. 2005;37:296–302*

Heparin has been an effective anticoagulant during cardiopulmonary bypass for more than 50 years. Its potent anticoagulant effect allows perfusionists to use circulatory support and membrane oxygenation and makes cardiac surgery possible. Although anticoagulation without heparin has been used during extracorporeal membrane oxygenation, these cases are rare. Although off-pump techniques commonly are used for myocardial revascularization, cardiopulmonary bypass with unfractionated heparin remains a cornerstone of cardiac surgery. Heparin is not a perfect anticoagulant. Major limitations include unpredictable pharmacokinetics, the need to monitor for effectiveness, activation of platelets, the need for a circulating co-factor (antithrombin III), and the inability to inhibit clot-bound thrombin. Additionally, reversal of heparin requires administration of protamine sulfate. Although effective as a heparin antidote, protamine is biologically derived and can have powerful vasoactive effects, as well as being strongly immunogenic.

Heparin also can trigger an immunologic reaction in many patients. Acute coronary syndromes result in exposure of thrombogenic substances and thrombin generation, which in turn results in platelet activation and release of platelet factor 4 (PF4) from the alpha granules of the platelet. Heparin binds to PF4, creating a heparin-PF4 complex that is immunogenic. IgG antibodies bind to this complex, which strongly activates platelets, results in the production of large amounts of thrombin, and may result in heparin-induced thrombocytopenia (HIT) or the potentially devastating arterial or venous thrombosis syndrome (HIT/TS). HIT/TS is relatively rare after cardiac surgery, occurring in 1–3% of cases (1). Antibodies to the heparin-PF4 complex are common postoperatively, however, occurring in as many as 50% of patients (2,3). Although the clinical relevance of these circulating antibodies is unclear in the surgical patient, recent data suggest that antibody formation may affect clinical outcomes (4–6).

Alternatives to heparin/protamine for cardiopulmonary bypass are limited. Lepirudin is a recombinant form of hirudin, a direct thrombin inhibitor derived from saliva of the medicinal leech. Lepirudin has been used during cardiopulmonary bypass. Lepirudin is highly specific for thrombin but its long half-life and irreversible binding can result in bleeding complications that are serious and life threatening (7). Argatroban is a synthetic direct thrombin inhibitor that binds to the active site of thrombin. It binds

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irreversibly, with a half-life of 39 to 51 minutes, making its use during cardiopulmonary bypass also problematic. The short-acting direct thrombin inhibitor bivalirudin is a synthetic molecule that has demonstrated superior efficacy compared with heparin in percutaneous interventions and is currently indicated for patients with unstable angina undergoing angioplasty. The use of bivalirudin in patients with acute coronary syndromes and in patients at risk for HIT/TS undergoing both on and off-pump surgical coronary revascularization is under investigation in multicenter, prospective trials. In the recently completed EVOLUTION trials, heparin with protamine reversal was compared with bivalirudin during on- and off-pump cardiac surgery. Data from these investigational efforts await publication. Anecdotal use of bivalirudin during cardiopulmonary bypass also has been reported (8–12). Although the pharmacological profile of bivalirudin makes it potentially attractive as an anticoagulant during cardiopulmonary bypass, the anecdotal experience in this setting is limited to reports using various dosing and monitoring strategies. The purpose of this work is to review the use of bivalirudin during cardiopulmonary bypass based upon our experience, focusing on the needs of the perfusionist/surgeon team. Questions of efficacy and outcomes will require completion of ongoing clinical trials and are beyond the scope of this article.

PHARMACOLOGY OF BIVALIRUDIN

Pharmacodynamics and Monitoring

Bivalirudin is a synthetic 20-amino acid peptide, an analog of the naturally occurring direct thrombin inhibitor hirudin. Bivalirudin is highly specific and binds thrombin at two sites, the active or catalytic site and the fibrinogen recognition site (Figure 1). Slow cleavage of the active-site binding portion of bivalirudin by thrombin itself results in disassociation of the bivalirudin fragments from bivalirudin and exposure of the active site (allowing thrombin to participate in clot formation). This transient binding and self-reversing property of bivalirudin results in a biologic half-life of approximately 25 minutes, distinguishing it from hirudin, which binds thrombin irreversibly. Unlike heparin, bivalirudin effectively inhibits clot-bound thrombin as well as circulating thrombin and does not require a cofactor for effect. Additionally, bivalirudin does not activate circulating platelets, in contrast to heparin. Bivalirudin also has a platelet inhibitory effect via inhibition of thrombin-mediated platelet aggregation.

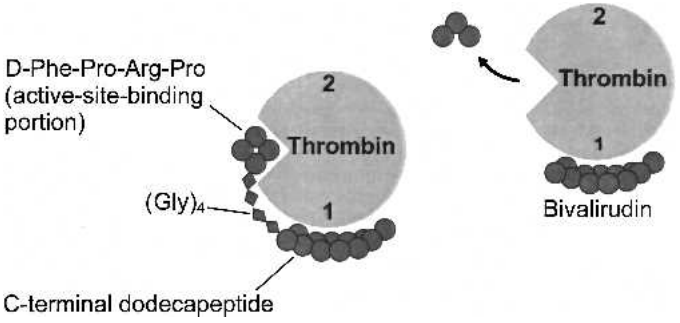

Figure 1. Bivalirudin mechanism of action. Bivalirudin binds thrombin at the active or catalytic site and also at the fibrinogen recognition site. Cleavage of the active-site binding portion by thrombin results in disassociation of bivalirudin from thrombin, re-exposing the active site and allowing thrombin to again participate in clot formation. Unlike heparin, bivalirudin inhibits clot-bound thrombin as well as circulating thrombin and does not require a co-factor for effect.

Bivalirudin immediately inhibits thrombin after intravenous administration, resulting in a systemic anticoagulant effect. Bivalirudin prolongs the prothrombin time (PT), activated partial thromboplastin time (aPTT), and activated clotting time (ACT) in a dose-proportional manner. In a pilot study investigating the use of bivalirudin in cardiac surgery, Koster et al. (13) demonstrated that bivalirudin concentrations significantly correlated with both the ecarin clotting time (Pharmanetics, Raleigh, NC), ACT+ (Hemochron Jr, International Technidyne, Edison NJ), and other clotting tests, although the ACT was less sensitive at higher plasma concentrations than the ecarin clotting time (Figure 2).

Pharmacokinetics

The pharmacokinetics of bivalirudin are linear, allowing for weight-based dosing with a predictable anticoagulant effect. Bivalirudin is predominantly cleared by circulating proteases (approx. 80%), although renal excretion does occur (approx. 20). The elimination of bivalirudin by circulating plasma proteins may be an important consideration for patients undergoing cardiopulmonary bypass, as organ hypoperfusion and splanchnic redistribution of

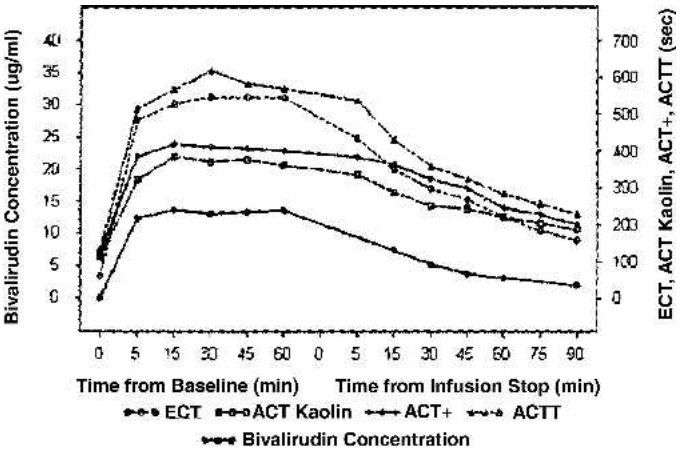

Figure 2. Monitoring anticoagulation during cardiopulmonary bypass Plasma concentration assays indicate that bolus dosing of bivalirudin results in a rapid increase in plasma concentration, which is maintained by the infusion dose. This is reflected by a prologation of clotting time tests. When the infusion is discontinued, the clearance of bivalirudin is reflected by the decrease in the activated clotting time.

blood flow during bypass would not be expected to impede elimination. Because only 20% of bivalirudin is cleared by the kidneys, patients with mild renal impairment do not require dose adjustment. In patients with severe renal dysfunction (below creatinine clearance of 30 mL/minute), the adjustment of dosing is important as excretion is slowed. Temperature has an effect on all enzymatic processes, including the activity of coagulation factors and the proteolysis of bivalirudin. However, no effect of mild hypothermia (from 30° to 36°C) on clearance of bivalirudin was detected in the Koster study (13). Limited data are available for temperatures less than 30°C.

In the pilot study, aprotinin (Trasylol, Bayer, Mannheim, Germany) was used concomitantly with bivalirudin at the discretion of the investigator. When aprotinin was used, a bolus of 2 × 10 (6) kallikrein inhibitor units (KIU) was delivered into the CPB circuit followed by a continuous infusion of 250,000 KIU/ hour during perfusion. Anticoagulation was monitored using the ecarin clotting time. The pharmacokinetics of bivalirudin did not appear to be influenced by the use of aprotinin (Figure 3). Results from ongoing studies (in which aprotinin use was also at the discretion of the surgeon) will clarify the issue of concomitant bivalirudin and aprotinin use. Although aprotinin did not seem to affect the elimination of bivalirudin, ultrafiltration with a 65-kDa filter increased the rate of elimination of bivalirudin in the Koster pilot study (Figure 4).

Dosing

Background: Although currently there is no standard dose for the use of bivalirudin in patients undergoing coronary artery surgery outside of clinical trials, completed and ongoing trials using bivalirudin in the catheterization laboratory provide some guidance. The Bittl Angioplasty Trial (BAT) demonstrated that bivalirudin significantly

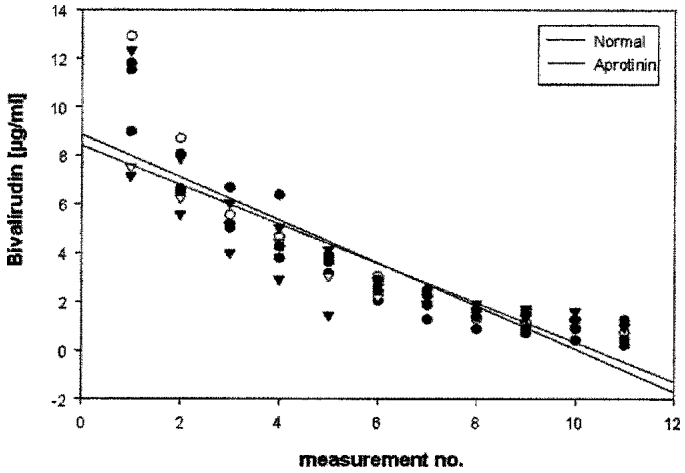

Figure 3. Elimination of bivalirudin in patients with and without aprotinin. In a small substudy, aprotinin did not affect the degradation of bivalirudin during cardiopulmonary bypass, as reflected by the slope of the curves.

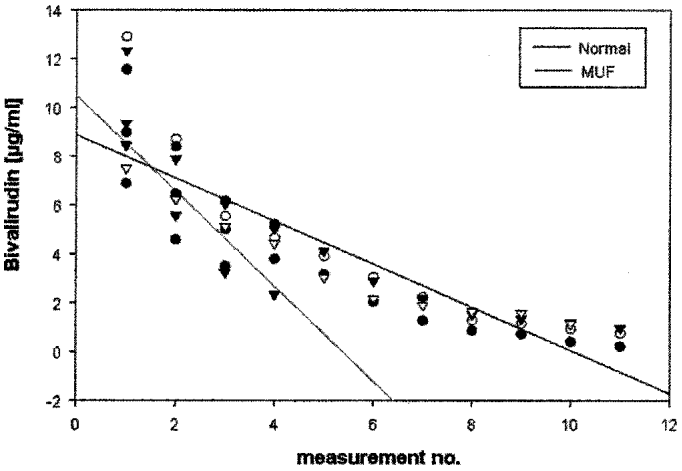

Figure 4. Elimination of bivalirudin in patients with/without modified ultrafiltration (MUF). Modified ultrafiltration, a technique of ultrafiltration performed after termination of cardiopulmonary bypass, increased the clearance of bivalirudin.

reduced the combined end point of death, MI, or repeat revascularization in patients undergoing angioplasty, and that the rate of major bleeding was significantly lower with bivalirudin therapy compared with heparin (14). In the BAT trial, the dose for bivalirudin was 1.0 mg/mL bolus with a 2.5 mg/mL/h infusion. As noted in the current package insert for bivalirudin, this dose achieves a mean steady state bivalirudin concentration of 12.3 ± 1.7 µg/mL (15). This dose is currently under investigation in ongoing clinical trials.

A lower dose was evaluated in the REPLACE-2 trial. This phase III clinical trial randomized 6,010 patients undergoing percutaneous coronary intervention to receive bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h) plus a provisional GPIIb/IIIa antagonist (i.e., abciximab and eptifibatide) or heparin plus routine GPIIb/IIIa inhibitor. The primary end point, a composite of death, myocardial infarction, urgent revascularization, or major bleeding at 30 days, occurred in 9.2% of the patients treated with bivalirudin and in 10% of those treated with heparin ($p = .32$).The rates of major bleeding were significantly lower in patients treated with bivalirudin than in those treated with heparin (2.4% and 4.1%, respectively; $p = 0.001$).

Dosing in Off-Pump Cardiac Surgery: In a prospective, randomized series of patients undergoing off-pump coronary artery surgery with either bivalirudin or heparin, Merry et al. (16) used a 0.75 mg/kg bolus of bivalirudin followed by a 1.75 mg/kg/h infusion with excellent procedural success. Blood loss for the 12 hours after study drug initiation in the bivalirudin group was not significantly greater than in the heparin group Additionally, using a scoring system based upon postoperative catheterization data, graft flow was significantly better in the bivalirudin group than in the heparin group. This dose also was used

successfully in a single surgeon series of over 200 off-pump coronary revascularization procedures with excellent success (17) and is the dose currently used in ongoing clinical trials in off-pump cardiac surgery.

Dosing in On-Pump Cardiac Surgery: In the Koster pilot study, a bolus of 1.0 mg/kg followed by a 2.5 mg/kg/h infusion during cardiopulmonary bypass was used in a cohort of 10 patients. Procedural success was complete and no thrombotic episodes during cardiopulmonary bypass occurred. A mean steady state plasma concentration of bivalirudin of 12.9 μg/mL was achieved with the bolus of 1.0 mg/kg and a 2.5 mg/kg/h IV infusion (Figure 5). Ongoing clinical trials with bivalirudin during cardiopulmonary bypass use the 1.0 mg/kg bolus and 2.5 mg/kg/minute infusion.

Using Bivalirudin During Cardiopulmonary Bypass

Setting Up the Pump: Our surgical team has not needed to redesign the extracorporeal circuit for a cardiac case using bivalirudin. The venous reservoir, oxygenator, cardiotomy suction, and cardioplegia circuit are set up in the standard fashion. The overriding concern for the perfusionist using bivalirudin as an anticoagulant is the elimination of areas of blood stasis throughout the circuit. Areas of stasis, in which bivalirudin levels can be depleted, are potentially at risk for clot formation. Bypass lines that are blood-filled and then clamped off or lines that are intermittently (>20 min) used for perfusion are flushed every fifteen minutes to ensure an adequate concentration of bivalirudin throughout the circuit.

In our experience, either an open system or a closed system may be used for venous drainage. However, a closed system with venous reservoir bags generally has better flow characteristics with more internal mixing than does a hardshell open venous reservoirs and therefore may reduce stasis and the potential for clot formation. In the clinical trials with bivalirudin and cardiopulmonary bypass, 50 mg of bivalirudin was added to the pump prime to avoid clot formation within the bypass circuit prior to going on bypass (18). When a bloodless prime is used, there

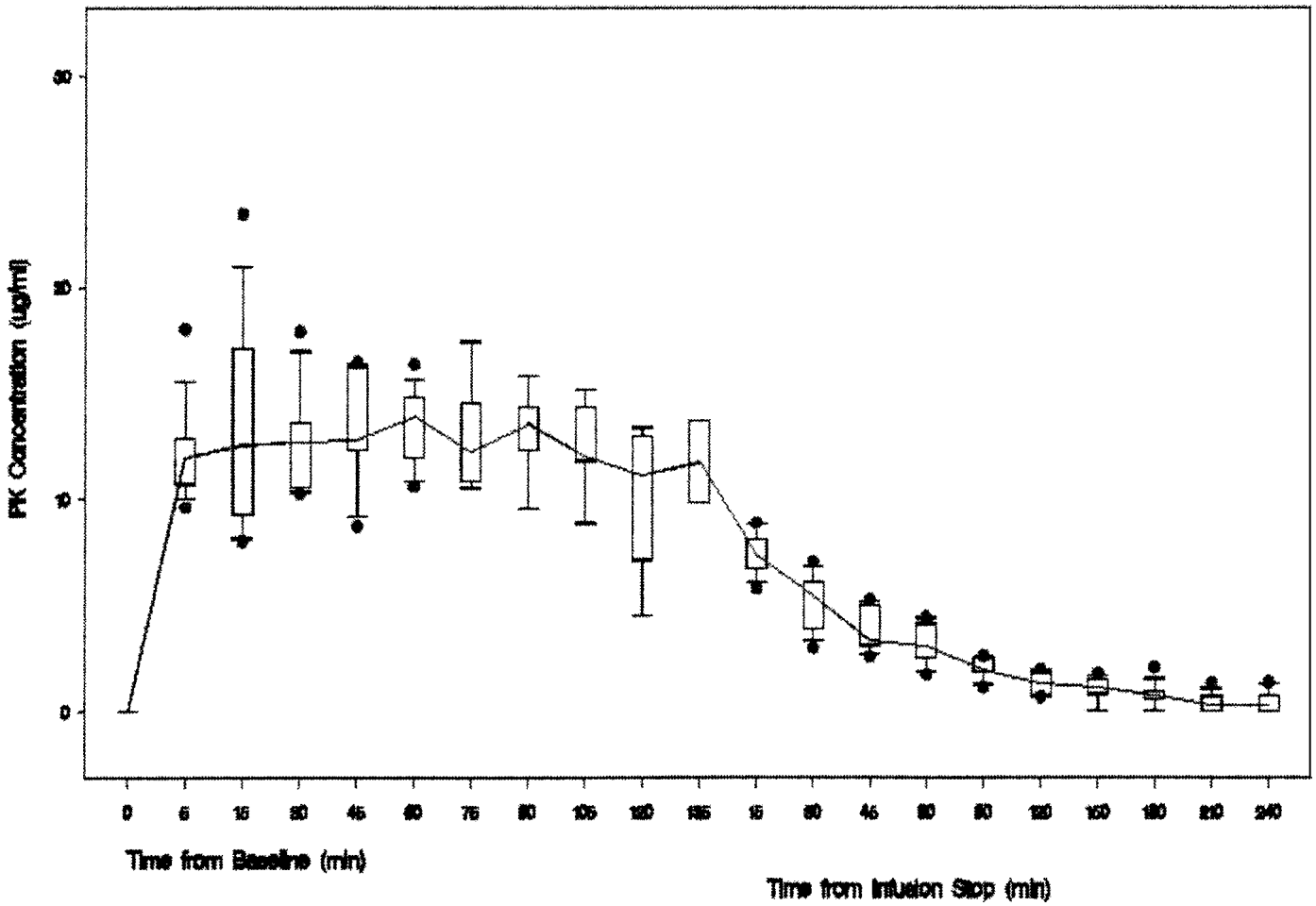

Figure 5. Bivalirudin plasma concentration during cardiopulmonary bypass Weight-based dosing of bivalirudin is possible because of predictable and reliable pharmacokinetics. A 1.0 mg/kg bolus of bivalirudin rapidly results in plasma concentrations above 10 μg/mL. The 1.5 mg/kg/h infusion dose maintains the plasma bivalirudin concentration above this critical level, as demonstrated by the 90th percentile box plots.

is theoretically no critical issue regarding stasis prior to initiation of cardiopulmonary bypass. If blood is added to the pump prime, it should be immediately prior to initiation of bypass to help ensure bivalirudin levels are not depleted with prolonged blood exposure.

Initiation and Maintenance of Cardiopulmonary Bypass: The dosing regimen we have used for bivalirudin in cardiopulmonary bypass is summarized in Table 1. If retrograde autologous prime is used, no additional dosing is needed as long as cardiopulmonary bypass is initiated immediately after adding blood to the prime (within minutes). If a delay exists before initiating bypass, bivalirudin should be administered into the pump circuit, either as a bolus or infusion. The initiation of cardiopulmonary bypass is routine.

During bypass, stasis of blood should be minimized. For example, placement of a clamp at the top of the bypass loop around the arterial filter can minimize stasis at this site, and the clamp may be intermittently opened to allow for re-mixing of blood. As a second example, a flexible cardiotomy suction catheter may be placed in the open left pleural space to continuously scavenge shed blood that may pool. Without frequent evacuation, blood in the left pleural space will clot.

The venous reservoir deserves particular attention during cardiopulmonary bypass. Regardless of the type of reservoir used, stasis may occur, especially when volumes within the reservoir are greater than one liter. In an open circuit, the fiber sock of the reservoir is the most likely place for clot to form. If an open system is used with a large amount of venous drainage, storage of venous blood in citrate–phosphate–dextrose bags for use later in the case is an effective way of limiting volume and stasis within the reservoir. Cardiotomy suction return to the venous reservoir may also increase the chance for clot formation within the venous reservoir. When cardiotomy suction is used, pro-inflammatory and procoagulant factors are released systemically. Koster et al. (19) have demonstrated that these factors are released regardless of whether heparin or bivalirudin is used as the anticoagulant. Again, mixing of blood within the reservoir and limiting excess volume are key to inhibition of clot formation.

Cardioplegia: The use of bivalirudin does not affect the choice of cardioplegia used (crystalloid or blood-based, cold or warm) or the route of administration (antegrade or retrograde). Crystalloid cardioplegia is given in a routine manner. When blood-based cardioplegia is used, the time between doses should be minimized to avoid clot formation within the blood-filled cardioplegia line. Our practice is to give cardioplegia at least every 15 minutes, which is routine timing in many clinical situations. If continuous cardioplegia is used, no alterations in technique are necessary.

Monitoring Anticoagulation During Cardiopulmonary Bypass: A major weakness of unfractionated heparin as an anticoagulant is its biologic variability, mandating close monitoring for effect. In contrast, a significant advantage of bivalirudin as an anticoagulant is its predictable and reliable pharmacology. When bivalirudin is used during cardiopulmonary bypass, circulating plasma levels at doses outlined above are consistent and reproducible, producing predictable thrombin inhibition (Figure 5). The consistency in dosing and the reproducibility of thrombin generation theoretically makes monitoring unnecessary. However, we consider the ACT a useful, if imperfect, tool for monitoring anticoagulation during cardiopulmonary bypass with bivalirudin. Using the ACT, documentation of anticoagulation is possible after dosing with bivalirudin. In our practice, we draw a baseline ACT and expect an increase of 2.5 times baseline after the 1.0 mg/kg bolus dose. This initial increase in ACT is useful to confirm the patient successfully received the bolus dose and to avoid the inadvertent misadministration of drug. In our experience, a continuous infusion of 2.5 mg/kg/min maintains the ACT at this target throughout the bypass run.

Weaning From Cardiopulmonary Bypass: Weaning from cardiopulmonary bypass is routine. It is our practice to fully warm the patient to 37°C prior to weaning from bypass. . If the perfusionist/surgeon team decides to empty the circuit soon after coming off bypass (within 10–15 minutes), blood within the circuit may be moved to the cell saver, processed, and returned to the patient at the team's discretion. No data are currently available on the effects of cell saving on the pharmacokinetics of bivalirudin. If there

Table 1. Dosing recommendation for cardiopulmonary bypass (CPB).

	Before CPB	During CPB	After CPB
Patient	1.0 mg/kg IV bolus 2.5 mg/kg/h IV infusion	2.5 mg/kg/h IV infusion until discontinuation	
Flush solutions	0.1 mg/mL Angiomax	0.1 mg/mL Angiomax	0.1 mg/mL Angiomax
Graft storage	(blood based) 1:12 CPD1 OR 0.1 mg/mL Angiomax in crystalloid solution	(blood based) 1:12 CPD1 OR 0.1 mg/mL Angiomax in crystalloid solution	
Cell saver	1:12 sodium citrate/CPD	1:12 sodium citrate/CPD	
CPB pump	50-mg priming dose		50 mg priming dose followed by 50 mg/h while recirculating

Dosing recommendations for the patient and cardiopulmonary pump are outlined above. These doses reflect the anticoagulation strategy used in our patients and are identical to doses currently under investigation in the EVOLUTION and CHOOSE clinical trials.

is a delay in emptying and dismantling the pump, blood may be recirculated by joining the arterial and venous lines at the table through an existing bridge or with the addition of a 3/8" to 1/2" connector. Bivalirudin (50 mg) should be added to this circuit and an additional infusion may be used if the circuit is needed indefinitely. In our experience, resumption of cardiopulmonary bypass after a prolonged period of time (approximately 20–30 minutes), requires additional rebolusing (we recommend a full 1.0 mg/kg dose). We do not give an additional bolus in the pump circuit if recirculation has been performed as described.

Chest Closure: Because there is no reversal agent or antidote for bivalirudin, adequate hemostasis will occur when bivalirudin has been metabolized sufficiently to allow for thrombin generation and clot formation. At normothermia, the biologic half-life of bivalirudin is 25–30 minutes, and in our experience the surgical field is usually dry enough to close two half-lives (or approximately 1 hour) after cessation of the bivalirudin infusion. In our early experience, when the bivalirudin infusion was discontinued at the end of cardiopulmonary bypass, the time to chest closure was prolonged accordingly. Currently, we discontinue the bivalirudin infusion approximately 15 minutes before the termination of bypass and have found that this significantly reduces the time between the end of cardiopulmonary bypass and chest closure. When performing coronary artery bypass grafting, the timing of bivalirudin discontinuation typically corresponds to the time of the last proximal anastomosis. Obviously, this is a clinical judgment that must be individualized. For patients with impaired left ventricular function or in patients in whom weaning from cardiopulmonary bypass may be difficult, prudence would dictate stopping the infusion after successful termination of bypass.

Special Considerations

The Cell Saver: When using bivalirudin as an anticoagulant for cardiac surgery, we use citrate-based anticoagulant (citrate–phosphate–dextrose, acid–citrate–dextrose, sodium citrate) to anticoagulate the cell saver. Typical protocols call for 100 mL of anticoagulant solution to be run into the reservoir initially to coat the sock and then subsequently running the anticoagulant solution at a rate of one drop a minute or a 1:7 to 1:10 ratio of citrate to blood in the reservoir. However, large amounts of citrate used in the cell saver may result in transient hypocalcemia. The ionized calcium should be checked after the use of significant volumes of cell saver product and treated if clinically meaningful hypocalcemia is diagnosed. We have also used a 0.1 mg/ml bivalirudin solution as the anticoagulant for the cell saver. Using 100 mL of this solution should coat the filter sock initially and the infusion continued at 100 mL/hour. Whether the process of cell saving removes bivalirudin is unclear, as no data are available on the effect of cell saving on the pharmacokinetics of bivalirudin.

Hemoconcentration: There is no data available concerning the intraoperative use of hemofiltration for bivalirudin-treated patients. As previously described, Koster et al. have demonstrated that hemoconcentration after cardiopulmonary bypass (modified ultrafiltration) increases the elimination of bivalirudin (13). We have used hemoconcentration during cardiopulmonary bypass with bivalirudin to reduce circulating plasma volume. Our practice is to ensure that the ACT remains 2.5 times baseline during bypass. If the ACT should fall below this level, we have used additional bolus dosing to keep the ACT appropriate. We recommend re-bolusing rather than adjusting the infusion rate to ensure adequate plasma concentrations.

Postoperative bleeding: Postoperative bleeding may occur in any patient after cardiac surgery using cardiopulmonary bypass. The differential diagnosis of excessive postoperative hemorrhage in a bivalirudin patient are the same as in a heparin patient and include (1) surgical bleeding, (2) platelet dysfunction, (3) factor deficiency and dilutional coagulopathy, (4) excessive fibrinolysis. Management of excessive postoperative bleeding for a patient anticoagulated with bivalirudin is similar to a patient anticoagulated with heparin. Early re-exploration to rule out surgical bleeding and avoid cardiac tamponade is appropriate. Suspected platelet dysfunction should be managed by transfusion therapy. Coagulation factor deficiency can be more difficult to diagnose in patients in whom bivalirudin was used during cardiopulmonary bypass as the prothrombin time is routinely prolonged in these patients postoperatively (unlike when protamine is used to reverse the anticoagulant action of heparin). With significant early bleeding, dilutional coagulopathy and fresh-frozen plasma transfusion may be considered.

Emergency Conversion to CPB From OPCAB: Should conversion to cardiopulmonary bypass be necessary during off-pump coronary revascularization, we recommend rebolusing the patient with a 1.0 mg/kg dose followed by a 2.5 mg/kg/minute infusion. In addition, 50 mg of bivalirudin should be added to the pump circuit prior to the initiation of cardiopulmonary bypass pump. ACT values 2.5 times baseline should be expected.

Special Coatings on CPB Circuit: Numerous coating options are currently available for extracorporeal circuit surfaces. The impact of these coated surfaces in a routine patient receiving bivalirudin as an anticoagulant is unclear. Of more concern is the effect of heparin-based coatings in a patient with HIT/TS. In these patients, avoidance of heparin exposure in any form is recommended and heparin coatings should be avoided.

CONCLUSION

The need for alternatives to heparin for patients undergoing cardiac surgery is growing. Although a review of heparin-induced thrombocytopenia in cardiac surgery is outside the scope of this article, excellent current reviews are available, including experience with other direct thrombin inhibitors such as argatroban and lepirudin. However, off-label use of bivalirudin as an anticoagulant during cardiac surgery is growing as its favorable pharmacologic profile is becoming recognized. Current reports of bivalirudin use during cardiac surgery are mostly anecdotal, and not unexpectedly, variation in dosing strategies, indications for use, and outcomes have been reported. With this paper, we describe our practical recommendations for the use of bivalirudin during cardiopulmonary bypass and in doing so, hope to assist other perfusion/surgeon teams in caring for these patients. We acknowledge that the use of bivalirudin during cardiac surgery is an emerging technology and future developments and modifications of technique are to be expected. Ongoing prospective, randomized clinical trials will provide important information regarding safety and efficacy of the use of bivalirudin during cardiac surgery.

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