Bivalirudin Monitored with the Ecarin Clotting Time for Anticoagulation During Cardiopulmonary Bypass

Andreas Koster, MD*, Derek Chew, MD†, Marcus Gründel, MD*, Matthias Bauer, MD‡, Herman Kuppe, MD*, and Bruce D. Spiess, MD§

*Department of Anesthesia, Deutsches Herzzentrum Berlin, Berlin, Germany; †Department of Cardiology, Flinders Medical Center, South Australia, Australia; ‡Department for Thoracic and Cardiovascular Surgery, Deutsches Herzzentrum Berlin, Berlin, Germany; and §Department of Cardiothoracic Anesthesia, Virginia Commonwealth University, Richmond, Virginia

The problem of heparin-induced thrombocytopenia (HIT) among patients undergoing cardiac surgery is increasingly being appreciated. However, no safe standard anticoagulation strategy has been established for the management of these patients during cardiopulmonary bypass (CPB). Recombinant hirudin (r-hirudin), a 65-amino acid polypeptide, is a direct thrombin inhibitor that has been used successfully in a larger series of patients with HIT during CPB (1). Because of its protein structure, r-hirudin is not associated with the risk of cross-reactivity to HIT antibodies, the plasma half-life is relatively short (approximately 40 min), and measurement of the ecarin clotting time (ECT) enables reliable on-line monitoring at the point of care (2). However, because of r-hirudin’s exclusive elimination via the kidneys and the lack of an antidote, impairment of renal function may lead to a dramatic increase of the drug’s half-life, a persistent anticoagulant effect, and hemorrhage (1).

Bivalirudin is a new synthetic 20-amino acid polypeptide with a plasma half-life of 24 min. It is also a direct thrombin inhibitor with potent anticoagulant activity and has been successfully used in many patients during coronary angioplasty. A unique feature of bivalirudin is that the part of the molecule that binds to the active site of thrombin is cleaved by the thrombin molecule itself, providing an elimination mechanism independent of specific organ function (3). Therefore, the use of large doses of bivalirudin, as required during CPB, may be safer compared with r-hirudin. However, experience with the use of bivalirudin during CPB is limited, and use of this drug with an ECT-guided strategy has not been reported. We report the use of bivalirudin, monitored at the point of care via ECT, for anticoagulation during CPB in a patient with HIT, a history of severe anaphylactic reaction to unfractionated heparin, and impaired renal function.

Currently there are no clinical data available about the concentrations or doses of bivalirudin needed to provide sufficient anticoagulation during CPB. An r-hirudin concentration of 4–5 μg/mL has been successfully used for anticoagulation during CPB in a larger group of patients (1). We hypothesized that 1) a concentration of bivalirudin that provides a comparable antithrombin effect to r-hirudin concentrations of 4–5 μg/mL should provide an analogous anticoagulant effect during CPB and 2) a bivalirudin concentration that achieves a prolongation of the ECT (the specific assay for direct thrombin inhibitors) (4) equivalent to 4–5 μg/mL of r-hirudin defines the target concentration of bivalirudin for anticoagulation during CPB. Therefore, we performed an in vitro dose-finding study.

After approval by the local ethics committee and informed consent were obtained, blood was collected from 10 healthy volunteers to establish calibration curves with r-hirudin and bivalirudin. Bivalirudin (0, 5, 10, 15, and 20 μg/mL) or r-hirudin (0, 1, 3, and 5 μg/mL) was added to samples of citrated whole blood. Measurement of the ECT (Pharmanetics, Raleigh, NC) was performed as previously described (2): 100 μL of citrated whole blood was diluted with 100 μL of standard human plasma (Behring, Marburg, Germany) to provide sufficient levels of prothrombin that are a prerequisite for reliable measurement of the ECT (2). Of this solution, 30 μL was transferred to the ECT test card, and the test was initiated.
All measurements were performed in duplicate and in parallel. The mean value of both measurements was calculated and used for further calculations. The mean value of the data obtained by the measurements of the 10 individuals was used for the construction of the standard calibration curves.

A concentration of 4–5 µg/mL of r-hirudin prolonged the ECT to 400–450 s. This prolongation of the ECT was achieved with a bivalirudin concentration of 10–15 µg/mL (Fig. 1). This concentration corresponds to the dosage of 1 mg/kg currently recommended for coronary angioplasty. On the basis of this information, the dosage protocol used during coronary intervention was adjusted for the initiation of anticoagulation in the patient described here.

**Case Report**

A 26-yr-old patient (weight, 60 kg) was referred for repeat coronary artery bypass grafting (CABG) six months after an acute myocardial infarction. During the stay at the intensive care unit, while being treated with unfractionated heparin (UFH), the patient showed a rapid decrease of the platelet count and the heparin-induced platelet aggregation assay was positive, resulting in the diagnosis of HIT. Ten days after the myocardial infarction, a two-vessel CABG (left internal mammary artery, free graft of the left radial artery) was performed in another hospital. Anticoagulation management was accomplished with UFH and the platelet glycoprotein Iib/IIIa antagonist tirofiban (5). After the UFH bolus, the patient had a massive anaphylactic reaction, requiring immediate institution of CPB and large dosages of epinephrine (4 mg) and norepinephrine (6 mg) before hemodynamic status stabilized. Five months after surgery, the patient experienced acute angina, and a coronary angiogram revealed significant (70%) stenosis of the anastomoses of the prior massive anaphylactic reaction and a history of severe anaphylactic reaction to aprotinin administration during the first operation, aprotinin was not given.

During preparation of the right internal mammary artery, a bolus of 1 mg/kg of bivalirudin was given, and a continuous infusion was started at 2.5 mg·kg⁻¹·h⁻¹. Because the bolus nearly prolonged the ECT to the target level of 400 s, an additional bolus of 0.25 mg/kg of bivalirudin was given, and the continuous infusion rate was increased to 5 mg·kg⁻¹·h⁻¹. This infusion rate was continued during perfusion, and the ECT and kaolin activated clotting time (ACT) (Hepcon HMS ACT; Medtronic, Minneapolis, MN) were monitored at intervals of 15 min (Figs. 2 and 3) and the ECT was maintained at 400–450 s. A residual volume of the citrated whole blood drawn at the time of ACT/ECT was used for the performance of a chromogenic anti-IIa activity assay that was performed as previously described (2). The patient was weaned from the CPB support with moderate dosages of epinephrine, and the volume of the CPB circuit was reinfused. Despite the effort to establish forced diuresis with 40 mg of furosemide, urine production did not exceed 100 mL/h. However, the ECT decreased rapidly from 450 to 200 s (18 to 4 µg/mL of bivalirudin) within 40 min, and by that time, visible clot formation was noted in the operative site. The ACT, however, was still prolonged >400 s. Two red blood cell concentrates (critical hemoglobin, 8 g/dL) and four units of fresh frozen plasma (FFP) were transfused. The total postoperative blood loss was 400 mL, and the patient was weaned from mechanical ventilation approximately 6 h after surgery. The postoperative course was uneventful, and the patient was discharged from the hospital after 10 days.

**Discussion**

In this case report, in a patient with HIT, renal impairment, and a history of severe anaphylactic reaction to UFH, bivalirudin was dosed according to the ECT, and this led to successful completion of CPB for repeat cardiac surgery. In view of the preexisting impairment of renal and cardiac function, the use of r-hirudin or the heparinoid danaparoid sodium was considered to represent an increased risk for severe hemorrhage (1). Because of the patient’s history of a dramatic anaphylactic reaction to UFH, the alternative options of 1) UFH and tirofiban or 2) postponing surgery until HIT antibodies were not detectable were also contraindicated (5,6). Therefore, after risk assessment, we decided to use bivalirudin for anticoagulation during CPB, because bivalirudin provides a rapid elimination
mechanism (plasma half-life of approximately 20 minutes) independent of specific organ function.

In an in vitro investigation based on the measurement of the ECT, we evaluated 10–15 μg/mL of bivalirudin to provide an anticoagulant power comparable to the concentrations of 4–5 μg/mL of r-hirudin that are currently used during CPB (1). Our in vitro calibration curves reveal an almost linear relation between the concentration of bivalirudin and the ECT in the critical range of 300–550 seconds, which translates into bivalirudin concentrations of 5–20 μg/mL (Fig. 1). This enables close control of the drug during CPB to maintain the concentration in the target range of 10–15 μg/mL. However, our data are derived from in vitro analysis. Therefore, future in vivo studies—assessing central markers of the activation of the coagulation system, such as D-dimers and fibrin generation—are necessary to determine whether this concentration of bivalirudin not only prevents thrombus formation during CPB but also represents powerful attenuation of hemostatic activation.

Comparison of the bivalirudin concentrations measured by the anti-IIa assay and the ECT (derived by the standard calibration curve) reveals a close relation between ECT and bivalirudin concentrations (Fig. 2). Further studies in larger patient groups are needed for better validation of the agreement of the two assays. As observed previously with r-hirudin, the ACT seems not to be a reliable assay for monitoring bivalirudin during and after CPB. Visible clot formation in the operation field was observed at concentrations of 4 μg/mL, although the ACT at that moment was still prolonged more than 400 seconds (Fig. 3). Further studies will have to assess whether a modified ACT, as recently used for the monitoring of UFH and r-hirudin during CPB, may provide improved monitoring of bivalirudin (7,8).

The fast decrease of the bivalirudin levels after discontinuation of the infusion from 18 to 4 μg/mL within 40 minutes demonstrates the rapid elimination of the drug. This was achieved during renal failure, where forced diuresis could not be established. Therefore, it is conceivable that the predominant pathway of elimination of the drug was the cleavage of bivalirudin by thrombin. This rapid decrease of the bivalirudin concentration led to a prompt reinstition of coagulation. This translated into a transfusion requirement of two units of red blood cell concentrates and four units of FFP (which is acceptable for a repeat surgical procedure after six months and a patient weight of 60 kg); the postoperative blood loss was limited to 400 mL total.

On the basis of the limited results of a single case managed with our protocol, we conclude that bivalirudin presents an interesting alternative to the use of UFH for anticoagulation during CPB in patients with HIT and/or anaphylaxis to UFH or protamine. Its short half-life offers fast reinstition of coagulation that is independent of the patient’s organ function and therefore may add safety to the procedure. Moreover, our limited data suggest that the ECT may be a useful assay for monitoring bivalirudin during CPB, enabling precise control of the drug. This tight control seems to be mandatory because of the short half-life. Further studies are necessary to evaluate whether the suggested concentrations of bivalirudin or the target prolongation of the ECT provide sufficient attenuation of hemostatic activation during CPB. These studies will also provide additional information with respect to the optimal dosage protocols for anticoagulation during CPB.

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References

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