Bivalirudin Provides Rapid, Effective, and Reliable Anticoagulation During Off-Pump Coronary Revascularization: Results of the “EVOLUTION OFF” Trial

In the EVOLUTION OFF trial, we evaluated the safety and efficacy of bivalirudin during off-pump coronary artery bypass grafting as compared with heparin-protamine. In this subanalysis of EVOLUTION OFF data of bivalirudin-treated patients, we assessed the pharmacokinetics (PK) and effectiveness of bivalirudin anticoagulation to achieve target activated clotting time (ACT+) values. Data from 101 patients were assessed. A bolus of 0.75 mg/kg of bivalirudin was followed by a continuous infusion of 1.75 mg $\cdot$ kg$^{-1} \cdot$ h$^{-1}$ during the grafting procedure. An ACT+ value of $>300$ s was the target. In four patients, PK data for bivalirudin were obtained. Only in exceptional cases were repeat fractional boluses or an increase of the infusion rate required. Assessment of the PK data showed a mean concentration of bivalirudin after the initial bolus of $11.0 \pm 0.53$ g/mL and a mean concentration during infusion of $11.2 \pm 2.32$ g/mL. Pearson’s correlation between bivalirudin concentrations and ACT+ values was 0.92. Bivalirudin PK data consistently exceeded concentrations of $6.5$ g/mL, which have been evaluated as effective during percutaneous coronary intervention. The correlation between bivalirudin levels and ACT+ values was good, and the target ACT+ values were almost always achieved. These results suggest that bivalirudin, given according to the current protocol, provides reliable and effective anticoagulation during off-pump coronary artery bypass graft surgery.

The use of unfractionated heparin (UFH) is associated with significant limitations, including indirect anticoagulant action via activation of antithrombin, large interindividual variation of the anticoagulant effect, and the development of heparin resistance or heparin antibodies (1). In percutaneous coronary intervention (PCI), UFH is often combined with platelet inhibitors, such as aspirin, clopidogrel, and platelet glycoprotein IIb/IIIa (GP IIb/IIIa) antagonists, to improve systemic anticoagulation. Additionally, UFH is also increasingly being replaced by other anticoagulants, such as the direct thrombin inhibitor bivalirudin (Angiomax®, The Medicines Company, Parsippany, NJ) and low molecular-weight heparins in patients undergoing PCI. However, in cardiovascular surgery, UFH remains the “gold standard” anticoagulant. Important reasons for its use in the cardiac surgical patient include the ability to reverse the anticoagulant effect with protamine and the availability of the activated clotting time (ACT) as an effective point-of-care monitoring test.

Bivalirudin is a bivalent reversible direct thrombin inhibitor. The pharmacokinetics (PK) of bivalirudin are characterized by a short half-life of approximately 25 min and an elimination that is mainly (80%) achieved by proteolytic cleavage with a minor contribution by renal excretion (2). This fast elimination mechanism, largely independent of particular organ functions, renders bivalirudin an attractive alternative to UFH for large-dose anticoagulation. Bivalirudin has shown favorable outcomes as compared with UFH in large PCI trials (3). In a pilot investigation involving 20 patients undergoing coronary artery bypass grafting, bivalirudin was successfully used for anticoagulation during cardiopulmonary bypass (4). Also, in a larger single-center trial comparing bivalirudin and heparin-protamine in patients undergoing off-pump coronary artery bypass grafting (OPCAB), the use of bivalirudin...
was associated with bleeding and transfusion rates comparable to those of heparin and protamine while demonstrating improved graft patency (5,6).

The multicenter EVOLUTION OFF trial was designed to evaluate the safety and efficacy of bivalirudin during OPCAB surgery compared with heparin-protamine. This subanalysis of EVOLUTION OFF data assesses the PK of bivalirudin and the effectiveness of bivalirudin anticoagulation during OPCAB surgery.

METHODS

After receiving local ethics committee approval and informed consent from the patients, we enrolled patients in the multicenter EVOLUTION OFF trial. A total of 157 patients scheduled for primary elective OPCAB surgery were treated with bivalirudin (101 patients) or with heparin anticoagulation with protamine reversal (56 patients) (safety population). Inclusion criteria included age of at least 18 yr, acceptance for elective OPCAB surgery, four or fewer planned coronary artery bypass grafts, and a left ventricular ejection fraction of >30%. Exclusion criteria included known disturbances of the hemostatic system, stroke within 6 mo before randomization, and recent exposure to clopidogrel or GP IIb/IIIa inhibitors.

Monitoring of bivalirudin anticoagulation was performed with the ACT cartridge for the Hemochron Jr. microcoagulation system (International Technidyne Corp. [ITC], Edison, NJ). This whole blood microcoagulation system (15-μL sample volume), which is used during PCI and cardiac surgery, is stimulated by silica, kaolin, and phospholipids. The device extrapolates the measurements to an ACT value of >300 s was defined as target.

Administration of bivalirudin followed the PCI dose, which was also used in a pilot study of OPCAB (5). A bolus of 0.75 mg/kg of bivalirudin was followed by a continuous infusion of 1.75 mg · kg⁻¹ · h⁻¹ maintained during the grafting procedure (3). ACT+ measurements were performed 5 min after the initial bolus and thereafter at intervals of 30 min. Additional boluses of 0.1–0.5 mg/kg were given or the infusion rate was increased when the ACT+ value was less than the target value.

In four patients from a single center, PK data for bivalirudin were obtained from blood samples drawn at 15-min intervals until 4 h after the drug infusion had been stopped. Bivalirudin concentrations were measured using liquid chromatography mass spectrometry (2).

Data are presented as mean ± sd. The correlation between ACT+ values and PK data and ACT+ values and blood loss data was calculated using Pearson correlation coefficient. The Statistical Package for Social Science (SPSS) 10.0. for Windows (SPSS Inc., Chicago, IL) was used.

RESULTS

Results from the bivalirudin-treated patients (n = 101) in the EVOLUTION OFF safety population (defined as all patients receiving at least one dose of the study drug) are presented. There were 24 women and 77 men, with a mean age of 64.5 ± 10.3 yr and mean weight of 89.6 ± 19.1 kg. The mean duration of the procedure was 205 ± 84 min. Median intraoperative
bivalirudin plasma concentrations and the ACT (initial half-life) (Fig. 1). Pearson correlation between the bivalirudin concentration was less than 6.5 mg/mL. Based on the mean concentration of bivalirudin after termination of the continuous infusion, the initial plasma half-life of bivalirudin measured in this study was approximately 25 minutes (Fig. 1) (2).

The close correlation of bivalirudin PK data (Fig. 2) to the ACT+ values is consistent with data from larger PCI trials in which correlation coefficients in the range of 0.9 have been reported, but no correlation was found between ACT values and clinical outcomes (10,11). In PCI, these data have led to the suggestion that bivalirudin use during PCI does not require monitoring (12). In the present study, only a small number of ACT+ values were less than target value, and ACT+ values did not correlate with perioperative measurements of hemorrhage (Fig. 3A) or chest closure time (Fig. 3B). However, given the limited number of low ACT+ values, we still believe that monitoring of anticoagulation is required during cardiac surgery. Our data suggest that the ACT+ is a reliable tool for this.

In the present study, only a small number of patients were assessed for PK values. This must be clearly outlined as a limitation. Furthermore, adequacy of bivalirudin anticoagulation was not evaluated by determination of markers of hemostatic activation or the correlation of ACT+ values to clinical outcomes, such as differences in myocardial infarction rates, graft patency, and need for revascularization. Adequacy of anticoagulation was measured using a new ACT assay. The nonclinical, surrogate end point was defined at an ACT+ value >300 seconds. However, the current protocol was almost identical to that of the above-mentioned clinical investigation, which showed improved graft patency with bivalirudin compared with heparin-protamine during OPCAB surgery (5,6). In addition, even considering substantial differences between PCI and OPCAB surgery in hemostatic activation, such as the influence of operative trauma or the effect of co-medications used during PCI (e.g., clopidogrel or platelet GP IIb/IIIa antagonists), early PCI studies with Hirulog, the precursor of bivalirudin, showed a marked reduction in the incidence of abrupt vessel closure when ACT values of >300 seconds were achieved (9). Therefore, we consider a target ACT+ value of >300 seconds to be a rational, not arbitrary, secondary end point that is supported by substantial evidence from clinical studies.

**DISCUSSION**

The current data demonstrate that bivalirudin, administered according to the current protocol, provides rapid, reliable, and effective anticoagulation to desired ACT+ values during OPCAB surgery. Using a 0.75-mg/kg bolus and a 1.75-mg·kg⁻¹·h⁻¹ infusion, the need for additional boluses or changes in the infusion rate was infrequent, and the target ACT+ value of >300 seconds was consistently achieved. The PK data obtained in 4 patients revealed essentially constant plasma concentrations of 10–12 µg/mL, which thereby markedly exceeded the concentration of 6.5 µg/mL that was associated with a significant reduction of ischemic events in PCI (9). In line with the reported short half-life in patients with normal renal function undergoing PCI, the initial plasma half-life of bivalirudin measured in this study was approximately 25 minutes (Fig. 1) (2).

In 4 patients, 72 samples were assessed for PK data (Fig. 1). The mean concentration of bivalirudin after the initial bolus was 11.0 ± 0.53 µg/mL (n = 4), and the mean drug concentration during continuous infusion was 11.2 ± 2.32 µg/mL (n = 29). In one sample, the bivalirudin concentration was less than 6.5 µg/mL. Based on the mean concentration of bivalirudin after termination of the continuous infusion, the time required for bivalirudin concentration to decrease to half this value was approximately 25 min (initial half-life) (Fig. 1). Pearson correlation between bivalirudin plasma concentrations and the ACT+ values was r² = 0.92 (Fig. 2; P < 0.001). There was no correlation or only a marginal correlation between ACT+ values, intraoperative or postoperative hemorrhage, and chest closure time (Fig. 3, A and B).

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Based on the results of previous studies and those of our investigation, showing that ACT+ measurements closely correlate with bivalirudin PK data and that target ACT+ values were almost consistently achieved, we conclude that bivalirudin, administered according to the EVOLUTION OFF protocol, provides reliable and effective anticoagulation during OPCAB surgery.

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REFERENCES


Figure 3. Correlation of activated clotting time (ACT)+ values and (A) perioperative blood loss values and (B) chest closure time. One outlier patient with excessive blood loss has been removed.