Adjunct bivalirudin dosing protocol for neuro-endovascular procedures

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Abstract
Objective: To introduce a protocol for anticoagulation using bivalirudin in neuro-endovascular procedures.

Methods: Three different bivalirudin dosing protocols were used in four consecutive patients undergoing neuro-endovascular procedures. Activated clotting time (ACT) was closely monitored to assess the effect of bivalirudin on ACT. Target ACT was set at 300-350 seconds.

Results: The first dosing protocol led to largely supra-therapeutic ACT values. With the second protocol, ACT remained sub-therapeutic for 25 minutes (33% of monitoring time). The third protocol was applied to two patients and it showed the best results with the ACT being in the therapeutic range for 72% of the combined monitoring time and never exceeding 366 seconds.

Conclusions: The dosing of bivalirudin needs to be adjusted for the use in neuro-endovascular procedures. We are proposing a protocol that seems to provide safe and effective anticoagulation. The safety and efficacy of bivalirudin in neuro-endovascular procedures will need to be further validated in future studies.

Key words: anticoagulation, bivalirudin, carotid angioplasty, intracranial angioplasty.

Introduction
Bivalirudin (Angiomax) is a reversible direct thrombin inhibitor with several distinct advantages over heparin, such as a shorter half-life and a better safety profile. Bivalirudin has been extensively studied by cardiologists in PCI, and is replacing heparin and other indirect thrombin inhibitors as the anticoagulant of choice. In coronary interventions, however, target ACT values are usually higher, and tight ACT control is not as critical as in neuro-endovascular procedures. We studied the effect of bivalirudin on ACT in four consecutive interventions using three different dosing paradigms to lay the foundation for controlled use of bivalirudin in neuro-endovascular procedures.

Methods
Three different dosing protocols were used in four consecutive patients with normal renal function undergoing endovascular procedures (Table 1). At the time of guide-catheter introduction, an initial bolus was administered intravenously and ACT was measured after 5 minutes. The target ACT was set at 300-350 seconds. Further dosing was dependent on the measured ACT value at 5 minutes as outlined in Figure 1. The ACT was monitored further in 10 to 15 minute intervals (Figure 1) until the guide-catheter was removed at which point bivalirudin infusion was discontinued.

For the first patient, we used dosing at the lower end of the range reported in the cardiac literature. Subsequently, the dosing was adjusted empirically (Table 1) to achieve a balance between tighter ACT control and quick onset of therapeutic anticoagulation.

The measured ACT values were connected with spline curves and a line and scatter plot of ACT vs. time was created using SigmaPlot 10.0 software (Figure 2). Using these plots, we extrapolated the time when ACT exceeded and dropped below the values of 300 and 350 seconds. In this way it was possible to estimate for each patient for what period of time they were in the sub-therapeutic, therapeutic and supra-therapeutic range.

Technical Note

Abbreviations, in the order used in this report.
PCI: percutaneous coronary intervention
ACT: activated coagulation time
GP: glycoprotein

Commercial products, in the order referenced in this report.
Angiomax® BenVenue Laboratories, Bedford, Ohio, USA
SigmaPlot® Systat Software Inc., San Jose, California, USA

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Results

Four patients were studied. Patient and procedure characteristics can be found in Table 1. None of the patients had any procedure-related bleeding or other complications.

Case 1

ACT was monitored for a total of 60 minutes. Therapeutic values were achieved at 5 minutes. ACT was therapeutic for 21 minutes (35%), sub-therapeutic for 5 minutes (8%) and supra-therapeutic for 34 minutes (57%). Maximal ACT was 443 seconds.

Case 2

ACT was monitored for 75 minutes. Therapeutic values were achieved at 25 minutes. ACT was sub-therapeutic for 25 minutes (33%), therapeutic for 50 minutes (67%) and it never reached supra-therapeutic values. Maximal ACT was 343 seconds.

Case 3

ACT was monitored for 60 minutes. It became therapeutic after 4 minutes. Sub-therapeutic values were observed for 11 minutes (18%), therapeutic values for 34 minutes (57%) and supra-therapeutic values for 15 minutes (25%). Maximal ACT was 366 seconds.

Case 4

ACT was monitored for 105 minutes. It reached therapeutic levels in 20 minutes. ACT was sub-therapeutic for 20 minutes (19%), therapeutic for 85 minutes (81%) and it never became supra-therapeutic. Maximal ACT was 349 seconds.

Discussion

Although bivalirudin has been studied extensively in the cardiac literature, and has been replacing heparin as the most widely used anticoagulant for PCI, it is not being widely used for neuro-endovascular procedures. We observed that the dos-

Table 1. Case information and bivalirudin dosing.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Procedure</th>
<th>Initial Bolus (mg/kg)</th>
<th>Drip Rate (mg/kg/h)</th>
<th>Additional Bolus If Sub-therapeutic (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/M</td>
<td>Symptomatic cervical ICA stenosis</td>
<td>Angioplasty and stent placement</td>
<td>0.75</td>
<td>1.75</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>54/M</td>
<td>Symptomatic basilar artery stenosis</td>
<td>Primary angioplasty</td>
<td>0.5</td>
<td>1.0</td>
<td>0.15 (and increase drip rate to 1.25)</td>
</tr>
<tr>
<td>3</td>
<td>66/M</td>
<td>Symptomatic intracranial ICA stenosis</td>
<td>Primary angioplasty</td>
<td>0.6</td>
<td>1.25</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>68/F</td>
<td>Asymptomatic cervical ICA stenosis</td>
<td>Angioplasty and stent placement</td>
<td>0.6</td>
<td>1.25</td>
<td>0.15</td>
</tr>
</tbody>
</table>
ing protocol used in PCI leads to high ACT levels which are not acceptable for neuro-endovascular procedures. Therefore, the dosing of bivalirudin needs to be adjusted but to our knowledge, no dosing protocols for neuro-endovascular procedures have been published.

There are important similarities and differences between Bivalirudin and heparin.

Both drugs have essentially immediate onset of action. Therapeutic ACT values are typically reached in less than 5 minutes. However, Bivalirudin has a shorter half-life (25 vs. 90 minutes) which is not dose-dependent. Therefore, sheath removal is possible earlier, and ACT values are more predictable when Bivalirudin is used. Bivalirudin has been shown to be superior to heparin in reducing peri-procedural ischemic complications. Also, Bivalirudin with or without concomitant use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors is non-inferior or superior to heparin combined with GPIIB/IIIa inhibitors. Bivalirudin has significantly less hemorrhagic complications than heparin combined with GPIIB/IIIa inhibitors. Bivalirudin and therefore rates of cerebral hemorrhagic complications might prove to be lower with further study of the drug. Finally, Bivalirudin can be used in patients who have a history of heparin-induced thrombocytopenia.

A clear drawback to the use of Bivalirudin is that its cost is significantly higher than that of heparin. In cardiac interventions, this is offset by the fact that it is still more economical than the combination of GPIIB/IIIa inhibitors and heparin which it can replace in some occasions. In neuro-endovascular procedures, the use of GPIIB/IIIa inhibitors is relatively limited.

A further drawback is that it is not possible to reverse the action of bivalirudin as is the case with heparin. Bivalirudin does have a much shorter half-life of only 25 minutes, but there are still cases where very rapid reversal of anticoagulation is paramount.

The optimal ACT value for neuro-endovascular procedures is still a subject of debate. In high-risk procedures such as angioplasty and stenting we use the 300-350 second range. A lower ACT range (i.e. 250-300) is advocated by some authorities in the field. In any case, it is clear that avoiding ACT values in excess of 350 is paramount if hemorrhagic complications are to be avoided.

In Patient 1, the dosing used by interventional cardiologists led to largely supra-therapeutic ACT values. In the second patient, more cautious dosing caused a significant delay in achieving a therapeutic ACT (25 minutes) and stable therapeutic values were achieved only after the drip rate was increased to 1.25 mg/kg/hr. The regimen used in patients 3 and 4 appears to offer the best combination of safety and effectiveness. It is important to note that dosing needs to be adjusted in patients with impaired renal function.

Our goal was to present a protocol which can provide a safe starting point for adjunctive use of bivalirudin in neuro-endovascular procedures. Other operators will need to validate and possibly modify the protocol based on institutional practice. The efficacy and safety of bivalirudin for neuroendovascular procedures will have to be established in larger numbers of patients, preferably in the setting of a prospective randomized study.
Conclusion

Bivalirudin dosing for neuro-endovascular cases cannot be extrapolated from the standards for coronary interventions. In our hands, an empirical trial involving four cases suggests that bivalirudin can be initiated with a bolus of 0.6 mg/kg and maintained with a drip of 1.25 mg/kg/h, although additional boluses or adjustments of drip rate may be necessary to titrate the ACT to a target range of 300-350 seconds.

References


