An Alternative Anticoagulant

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Disclosure

The University of Washington was part of the multi-center trial utilizing Angiomax (bivalirudin) for CPB.
I have received no compensation for participating in this study.
I have received no compensation from the Medicines Company for speaking.
McLean

Discovered heparin to **reduce** blood clotting.
First used Clinically in 1933
Heparin produced in mast cells: Liver, Lungs, Gut, etc.
Available 1950’s
Heparin: a natural product

- Combine 5,000 lbs. intestines, 200 gallons water, 10 gallons chloroform, and 5 gallons toluene. Hold at 90°F for 17 hours.
- Add 30 gallons acetic acid, 35 gallons ammonia, sodium hydroxide to adjust pH, and 235 gallons water. Bring to a boil; then filter.
- Add 200 gallons hot water to filtrate and allow to stand overnight, then skim off the fat.
- Keep pancreatic extract at 100°F for three days, then bring to boil.
- Filter solids and assay for heparin content.
Heparin and Protamine --
Perfect Partners?

“I don’t understand...I thought we were
made for each other.”
Historical Perspective

- 50+ Years of Cardiac Surgery using Heparin
- Enabled Our Specialty to Grow and Prosper
Historical Perspective

- 1960s and 1970s “Golden Age of Cardiac Surgery
- 1980 PTCAs
- 1990s coronary stents
- Late 1990s OPCABS
- 2001 2 million PTCAs worldwide
- Most common medical intervention
- 2003 drug eluding stents
Perfusion Improvements

- CLINICIANS and INDUSTRY
- Early 1990s smaller “blood-friendly” oxygenators
- Late 1990s Reduced Inflammation
  - Coated Circuits
  - Heparin
  - Aprotinin
- Early 2000s Volume Reduction
  - RAP
  - Minimal Prime Circuits
- Pump Sucker Sequestration
New Challenges

PTCA
Stents
Drug Stents

More and more patients having multiple exposures to heparin
thus...

Heparin Antibodies
Heparin Induced Thrombocytopenia
Thrombosis in HIT

High risk for venous and arterial thromboemolism

Propensity for venous limb gangrene
Heparin-induced thrombocytopenia

A syndrome of in vivo thrombin generation

Results from activation of platelets, endothelium, monocytes, coagulation pathways and inflammatory pathways.

Antibody formation to heparin-PF4 complex

Hypercoagulable state with increased risk for venous and arterial thrombosis
Definition of Classic HIT

1. Thrombocytopenia
   < 100,000 – 150,000 mm$^3$ (may not always see very low counts)
   or a 50% drop in platelet count from baseline (more powerful)

2. Exclusion of other causes of thrombocytopenia

3. With or without thrombotic complications
Therapy for HIT

- Interruption of the immune response (e.g., discontinue heparin)
- Reduce thrombin generation (thrombin inhibitors)
- Treatment of thrombosis
Ancrod

Malaysian Pit Viper
Hirudins
Hirudin / Lepirudin / Bivalirudin

Class of anticoagulants derived from leech spit

Hirudin is the naturally occurring molecule

65 amino acid peptide

Lepirudin is a recombinant hirudin

structurally almost identical to natural peptide

Bivalirudin is a synthetic analog

20 amino acid peptide
Mechanism of Action

Blocks clotting activity of thrombin
Binds 1:1 to thrombin (clot-bound and free)
Independent of antithrombin III
Not inhibited by Platelet Factor 4 (PF4)
No cross reaction with HIT antibodies
Bivalirudin

Direct Thrombin Inhibitor
Bivalirudin

Marketed by The Medicines Company

Trade name: Angiomax

Approved for use in patients with unstable angina undergoing PTCA

Reversible inhibition of thrombin

Renal excretion

Reduced dose only for severe renal insufficiency

Monitor with ACT
Bivalirudin in CPB

Off-label use

CHOOSE and EVOLUTION

Patients with / without history or risk of HIT
Heparin

“Shoot and forget”
Long half life
Variable response to AT-III
Allergy
Inflammatory reactions
Protamine

Bivalirudin

Short half life
No reversal
No allergy
No inflammation
ACT ?????

“Not your father’s anticoagulant”

Learn to overcome fear of change
Differences and Concerns

Bolus and drip prior to bypass
Flush solutions
Cell Saver
Cardioplegia
Termination of CPB

Stagnant blood
Perfusionist Issues

Anticoagulation
Bypass Circuit
Cardiotomy Suction
Cardioplegia
Ultrafiltration
“Cell Saver”
Anticoagulation

ACT

2.5 X Baseline

q30min
## Management

<table>
<thead>
<tr>
<th></th>
<th>Pre CPB</th>
<th>On CPB</th>
<th>Post CPB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td>1.0 mg/kg IV Bolus</td>
<td>2.5 mg/kg/hr IV infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg/kg/hr IV infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flush Solution</strong></td>
<td>0.1 mg/ml</td>
<td>0.1 mg/ml</td>
<td>0.1 mg/ml</td>
</tr>
<tr>
<td><strong>Graft Storage</strong></td>
<td>(Blood based) 1:12 CPD or 0.1 mg/ml in crystalloid sol.</td>
<td>(Blood based) 1:12 CPD or 0.1 mg/ml in crystalloid sol.</td>
<td></td>
</tr>
<tr>
<td><strong>Cell Saver</strong></td>
<td>CPD drip</td>
<td>CPD drip</td>
<td>CPD Drip</td>
</tr>
<tr>
<td><strong>Pump</strong></td>
<td>50 mg in Prime</td>
<td></td>
<td>50 mg bolus in pump then 50 mg/hr</td>
</tr>
<tr>
<td><strong>Plegia</strong></td>
<td></td>
<td>No additional</td>
<td></td>
</tr>
</tbody>
</table>
Circuit

Non coated circuit
Add A-V bridge at table using ¼ tubing
Cardiotomy Suction

If suctions are use, set cardiotomy height so there is no pooling in cardiotomy reservoir
Hemoconcentration

ACT
bolus of 0.3mg/kg
double trip rate
Cardioplegia

4:1 blood
flush line at table prior to each infusion
Cell Saver

Citrate as anticoagulant
Use 1500 ml wash
Check Ionized Calcium if there are significant volumes from CS, treat if clinically meaningful hypocalcemia is diagnosed
Use of Bivalirudin During CPB

Dosing for open heart surgery

1 mg/kg loading dose

2.5 mg/kg/hour infusion dose started when loading dose given

50 mg in the perfusion circuit prime
Anticoagulation Monitoring

A kaolin based act system is used in our hospital

After loading dose is given to the patient expect an increased ACT of 2.5 times baseline

A continuous infusion of 2.5 mg/kg/hr maintains the ACT at this target throughout bypass run

Monitor the ACT every thirty minutes unless the patient is being hemoconcentrated

If hemoconcentrating the patient then monitor the ACT every 15 minutes as the hemoconcentrator does remove bivalirudin

If the ACT should fall below the 2.5 threshold the patient can be rebolused with a dose of 0.2 to 0.5 of the initial loading dose. Adjusting the drip will not raise the drug level in a timely manner
Use of Bivalirudin During CPB

No need to redesign circuit

Normal components are set up in the standard fashion

The overriding concern is the elimination of areas of blood stasis throughout the circuit

Either an open system or a closed system may be used

Retrograde autologous priming may be used as long as initiation of bypass is within minutes

Keep level in venous reservoir around 1000 to 1200 mls. Put any excess volume in CPD bags for later use

Put clamp high on bypass loop around arterial filter to diminish stagnant blood in tubing

Put floppysucker in left chest to remove stagnant blood
Use of Bivalirudin During CPB

Cardioplegia administration

Using bivalirudin on bypass does not affect the choice of cardioplegia, cold or warm, crystalloid or blood based, or the route of administration, antegrade or retrograde.

When using crystalloid cardioplegia it is administered in its usual manner.

When using blood based cardioplegia the time between doses should be minimized to avoid clots in the cardioplegia line. It is our practice to give cardioplegia after every distal or every 15 minutes which is routine in many clinical situations. If the time between doses is longer then it would be prudent to flush the line at the table before each dose.
Use of Bivalirudin During CPB

Weaning from bypass

Make sure the patient is warmed to 37 degrees C

Weaning from bypass is routine. If the patient is stable at 10 to 15 minutes the volume can be moved over to the cell saver and processed and returned to the patient.

If there is a delay in emptying the perfusion circuit, blood should be re-circulated either through an existing bridge or by putting a 3/8” to 1/2” connector on the table and reconnecting the AV loop. An additional 50 mgs of bivalirudin should be added to this circuit.
Special Considerations

Cell saver use is recommended and CPD can be used as an anticoagulant. What amounts of bivalirudin the process of cell saving removes are unclear at this time as there is no data. As mentioned earlier hemoconcentration will remove circulating bivalirudin. Anticoagulation protocols must be monitored more closely and rebolusing used if the act levels fall below the 2.5 baseline threshold.

At the present time it is unclear what impact, if any, the numerous coatings that are available have on a routine patient receiving bivalirudin. It is important to avoid heparin coated circuits and heparin coated catheters on a patient with HIT/TS.

In an emergent conversion to CPB from OPCAB we recommend rebolusing the patient with a 0.5mg/kg dose followed by a 2.5mg/kg/hr infusion. Also 50 mg should be added to the cardiopulmonary bypass circuit. ACT values of 2.5 times baseline should be expected.
Summary

or

In my opinion......

Safe anticoagulant for CPB
Need to look at ACT in a new light
Avoid stasis in circuit

Calls for increased communication among surgeon, anesthesiologist, and perfusionist
Once again….

This is **not** heparin

It has been used with success

The ACT is now a relative number

Avoid stagnation

Don’t be afraid of change
Thank you for your attention
One final question

Does anyone recognize this man?