Agents for Peripheral Vascular Disease & Thrombosis

Edward JN Ishac, Ph.D.

Smith Building, Room 742
eishac@vcu.edu
828-2127

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Background and Significance

• Peripheral arterial disease (PAD) is a progressive atherosclerotic disease

• Affects approximately 9 million Americans

• Symptoms of PAD are related to insufficient arterial blood flow, which results in debilitating, activity-induced, ischemic pain (claudication)

• Associated with major limitations in mobility and physical functioning, and decreased quality of life.
**Ankle Brachial Index**

- Ankle BP vs brachial SBP
- Normal 0.95-1.2
- Claudicants 0.5-0.7
- Critical ischemia < 0.4
- May be falsely elevated in calcified vessels (DM)

**Pathology - Peripheral Vascular Disease**

**Causes:**

- Vascular spasm
- Organic vessel damage
- Smoking, diabetes, dyslipidemia, hypertension
- Reduced blood supply to areas served by the vessels is the problem in either case
- Drugs are more effective in vasospastic states
- Poor correlation: lab effects vs clinical efficacy
- “Steal syndrome” is one of many problems

Vasodilators can shift blood to areas not affected by disease
Risk factors for PAD

- Gender (male)
- Age
- Smoking
- Hypertension
- Diabetes
- Hyperlipidaemia
- Fibrinogen
- Homocysteinaemia

PAD

Atherosclerosis

Atherothrombosis

Ischaemic stroke

Myocardial infarction


Pulmonary Embolism
Deep Vein Thrombosis (DVT)

Myocardial Infarction
Classified according to mechanism of action

Older agents: results have been generally unsatisfactory

1. Beta-adrenergic stimulants: not useful, adverse effects

2. Alpha-blocking agents: not useful, adverse effects

3. Calcium entry blockers: some usefulness
   a. Diltiazem, Nifedipine - used for Raynaud’s disease
   b. Nimodipine - used for subarachnoid hemorrhage
      • structurally related to nifedipine
      • highly lipid soluble, crosses BBB well
      • used to inhibit cerebral vasospasm after hemorrhage
        from a ruptured intracranial aneurysm;
        ↓permanent neurological damage from ischemia

Raynaud’s Syndrome

- Excessive sympathetic tone in nerves supplying hands and feet. Minor cold, or even thought of cold, causes pronounced vasoconstriction that can be severe enough to cause necrosis of tissues
- Discoloration of the fingers and/or toes when the patient is exposed to changes in temperature (cold or hot) or emotional events
- Abnormal spasm of blood vessels causes diminished blood supply
- Initially, the digit(s) turn white because of diminished blood supply.
- Then turn blue because of prolonged lack of oxygen
- Finally turn red, the blood vessels reopen, causing a local “flushing”
- Three-phase color sequence (white to blue to red) is typical
- Treatment: Ca++ blockers if severe
Phosphodiesterase inhibitors - cAMP

a. Pentoxifylline (↑cAMP, PDE-4)
• may improve capillary flow by increasing erythrocytic flexibility
• not a vasodilator
• used for intermittent claudication (characterized by difficulty in walking; drug efficacy → increase walking distance)

b. Cilostazol (↑cAMP, PDE-3)
• inhibits platelet aggregation
• vasodilator, increase erythrocytic flexibility
• used for intermittent claudication

Vascular smooth muscle - Calcium / cAMP

Abbreviations: SR, sarcoplasmic reticulum; Gs, Gs-protein; MLC, myosin light chain; MLCK, myosin light chain kinase; Pi, myosin phosphorylation
### Phosphodiesterase-5 inhibitors - cGMP

↑cGMP by inhibition of isoform PDE-5
Potentiate action of nitrates
Cl: Severe hypotension with nitrates or alpha blockers

c. Sildenafil (Viagra): ED, Pulmonary HT
   - selective vasodilation for treating erectile dysfunction
   - visual disturbances, but cause/effect unknown

d. Vardenafil (Levitra): ED
   - ↑QT interval: avoid quinidine, procainamide, amiodarone

e. Tadalafil (Cialis): ED
   - duration much longer (up to 36 hrs)
   - adverse effects include back pain and muscle aches
VIII. Agents Used to Prevent Thrombus Formation or Remove Thrombi

A. Activators of antithrombin (also called antithrombin III)
   - Expose active sites on AT-III, OK in pregnancy
   - Increase rate of thrombin inactivation by antithrombin

1. Unfractionated Heparin (12,000-30,000MW)
   - Main adverse effect is hemorrhage, given iv or sc
   - Variable response, need to monitor aPTT
   - Can also cause thrombocytopenia which is treated with Lepirudin (Refludin)

2. Enoxaparin, Dalteparin, Ardeparin, Tinzaparin, Danaparoid
   - Low molecular weight heparins (6K-15K), given sc
   - More bioavailable, Longer acting (5 hrs vs 1.5 hr)
   - Less hemorrhage, no monitoring required

3. Fondaparinux
   - pentasaccharide, inhibits only Xa
Heparin action

Mechanisms of action of Heparin and related anticoagulants

AT = antithrombin,
Xa = activated factor X.

aPTT = activated partial thromboplastin time test
aPTT measures antithrombin activity
Unfractionated Heparin - Thrombocytopenia

B. Inhibition of Thrombin: Rudins: Hirudin, Bivalirudin, Lepirudin, Desirudin; univalent: Argatroban, 1. - used for anticoagulation during angioplasty

C. Inhibition of Clotting Factor Synthesis
(oral agent)
Warfarin - interfere with vitamin K action to inhibit synthesis of prothrombin (II)
• Best kinetics, intermediate duration
• First order elimination
Warfarin inhibits the ability of Vitamin K to carboxylate the Vit. K dependent clotting factors, reducing their coagulant activity.
### Warfarin vs Heparin

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Heparin (unfrac.)</th>
<th>LMW Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size (mw)</strong></td>
<td>308</td>
<td>12,000-30,000</td>
<td>6,000-15,000</td>
</tr>
<tr>
<td><strong>Routes</strong></td>
<td>oral or i.v.</td>
<td>i.v., s.c.</td>
<td>s.c.</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>2.5 d</td>
<td>1.5 hrs</td>
<td>5 hrs</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Delayed, 12 hr</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>2-5 d</td>
<td>4 hrs</td>
<td>16 hrs</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
<td>Inh. Vit K action ↓ II, VII, IX, X</td>
<td>Activate ATIII → Inhibit Xa, IIa</td>
<td>Activate ATIII → Inhibit Xa &gt; IIa</td>
</tr>
<tr>
<td><strong>Concerns</strong></td>
<td>Many drugs, resins, (s-) 2C9, (r-) 3A4,</td>
<td>Thrombocytopenia Monitor aPTT</td>
<td>No monitoring, bleeding all drugs</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>No (teratogenic)</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td><strong>Toxicity Rx</strong></td>
<td>Vit. K or plasma</td>
<td>Protamine sulfate</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td><strong>Uses</strong></td>
<td>DVT, PE, AF, MI, stroke, (TIA), PCI</td>
<td>DVT, PE, AF, MI, angina</td>
<td>DVT, PE, AF, MI, angina</td>
</tr>
</tbody>
</table>

### D. Anti-platelet Drugs – TXA₂

Drugs inhibiting platelet aggregation and adhesiveness can prevent thrombus formation and are most useful for arterial thrombosis

- **a. Aspirin**: inhibits cyclooxygenase-1 → ↓TXA₂
- **b. Dipyridamole**: inhibits thromboxane synthase → ↓TXA₂, also inhibits PDE → ↑cAMP
- **c. Aggrenox**: fixed dose combo of aspirin & dipyridamole

![Diagram of bloodstream and platelet aggregation](image-url)
### D. Anti-platelet Drugs – ADP Blockers

d. Clopidogrel
- inhibit the ADP pathway for platelet activation by blocking binding of ADP to its receptors (glycoprotein receptors on platelet membrane)
- uses include
  - prevention of TIA or ischemic stroke
  - acute coronary syndrome, acute MI
  - PCI (percutaneous coronary intervention)
- adverse effects - fewer than ticlopidine (no neutropenia)
  - GI effects - nausea, diarrhea (20%), hemorrhage (5%)

e. Ticlopidine
- introduced before clopidogrel, more adverse effects
- associated with neutropenia and thrombocytopenia
- blood tests recommended

f. Prasugrel
- also ADP receptor inhibitor (approved July 2009)

---

### Platelet IIB, IIIA receptor blockers

Abciximab, Eptifibatide, Tirofiban

- IIB and IIIA are platelet membrane proteins
- function as receptors for fibrinogen and von Willebrand factors which link platelets to walls of injured vessels
- Adhesion leads to aggregation and thrombus formation
- used in patients undergoing high-risk angioplasty or atherectomy and for acute coronary syndrome
- administered IV, oral drugs in development
- Adverse effect: increased risk of bleeding
Factors involved in Platelet Activation

Abciximab
- IIb/IIIa antagonists
  - Block fibrinogen, von Willebrand factors

Aspirin
- Irreversible acetylation platelet COX-1 enzyme (low dose < 300mg/dl)
  - Platelet lacks nucleus, cannot generate new enzyme during its ten day lifetime
  - Other NSAIDs have similar but shorter and reversible effect

Dipyridamole

Platelet lacks nucleus, cannot generate new enzyme during its ten day lifetime.

Action of aspirin and dipyridamole

PLATELET
- Arachidonic acid
  - Aspirin → cyclooxygenase → Thromboxane A2
  - Decreases accumulation → Platelet Aggregation
  - Dipyridamole
    - S-AMP

VESSEL WALL
- Arachidonic acid
  - Cyclooxygenase → Prostacyclin (PGI2)
  - Stimulates accumulation → Inhibition of Platelet Aggregation

Aspirin → irreversible acetylation platelet COX-1 enzyme (low dose < 300mg/dl)
Platelet lacks nucleus, cannot generate new enzyme during its ten day lifetime
Other NSAIDs have similar but shorter and reversible effect
Aspirin to Prevent MI and Death

- Aspirin 75 to 325 mg daily should be used routinely to all patients with acute and chronic ischemic heart disease in the absence of contraindications
  - aspirin exerts an antithrombotic effect by inhibiting cyclooxygenase and synthesis of platelet TXA$_2$
  - in patients with stable angina, aspirin reduces the risk of adverse cardiovascular events by 33%
  - in patients with unstable angina, aspirin decreases the short and long-term risk of fatal and nonfatal MI by 36%
  - aspirin (325 mg), given on alternate days to asymptomatic persons, associated with a decreased incidence of MI

Efficacy of aspirin in preventing MI

- Unstable angina patient      +++
- Post MI patient             ++
- “Healthy” person            +

Optimum dose of aspirin - still unclear

“Low” doses (81 - 325 mg/day) appear more effective than higher doses
Thrombosis

Blood Clot

1. Induces the secretion of TPA

Tissue Plasminogen Activator (TPA)

Plasmin dissolves the blood clot

Plasminogen

Plasmin

Tissue Plasminogen Activator (TPA)

Coagulation Pathways

Extrinsic Pathway

Damage to tissue outside the vessel

Tissue Thromboplastin

Intrinsic Pathway

Damage to the blood vessel

Inactive Factor X

Cascade of clotting factors

Activated Factor X

Prothrombin

Thrombin

Fibrinogen

Fibrin

Factor XII

Blood Clot

Emboliens: clot that travels from site where it was formed

Thrombus: blood clot that forms in a blood vessel
Thrombolytic Agents - “clot busters”

Streptokinase, Alteplase (Tissue plasminogen activator [TPA]), Retaplace, Anistreplase, Tenectplace

Activate plasminogen leading to:
• activation of plasmin, degradation of fibrin and clot
• Accelerate dissolution of thrombi

• Critical factor in use: elapsed time between thrombotic event and administration, greatest if used within 2-3 hrs

Thrombolytics differ with respect to:
• allergenicity, clot specificity
• half-life (or duration required for infusion)
• cost

Properties of Thrombolytics
“Clot busters”

<table>
<thead>
<tr>
<th></th>
<th>Streptokinase</th>
<th>Alteplase</th>
<th>Retaplace</th>
<th>Anistreplase</th>
<th>Tenectplace</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergenic</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clot selectivity</strong></td>
<td>Not selective</td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>Very short</td>
<td>Short</td>
<td>Longer</td>
<td>Long</td>
<td>Long</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Clot selectivity: selective for clot-bound plasminogen
Critical factor: elapsed time between thrombotic event and use
Benefit greatest if used within 2-3 hours
Surface vs Fluid Plasminogen

Fluid Phase

- Plasminogen Activation → Plasmin Degradation → Fibrinogen Factor V Factor VIII
- Nonfibrin-Specific or Less Fibrin-Specific Plasminogen Activators
  - PAI-1
  - α2-Antiplasmin
- Fibrin-Specific Plasminogen Activators

Fibrin Surface

- Fibrin strands network Degradation → Fibrin degradation products

PVD, Antiplatelets, Anticoagulants, Fibrinolytics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAD</td>
<td>Pentoxifylline, cilostazol</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Warfarin, heparin, LMWH, (aspirin)</td>
</tr>
<tr>
<td>DVT: Treatment</td>
<td>Warfarin, heparin, LMWH</td>
</tr>
<tr>
<td>DVT: Surgical</td>
<td>LMWH, (heparin)</td>
</tr>
<tr>
<td>MI: Prevention</td>
<td>Aspirin, clopidogrel, prasugrel, (ticlopidine)</td>
</tr>
<tr>
<td>MI: Treatment</td>
<td>Alteplase, heparin, aspirin, abciximab</td>
</tr>
<tr>
<td>Heart valve</td>
<td>Aspirin, warfarin, (dipyridamole)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Aspirin, clopidogrel, warfarin, (ticlopidine)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Aspirin, LWMH, heparin, abciximab</td>
</tr>
<tr>
<td>Pulmonary E.</td>
<td>Warfarin, heparin, LMWH, (alteplase)</td>
</tr>
<tr>
<td>PCI</td>
<td>Heparin, aspirin, clopidogrel, abciximab, (ticlopidine)</td>
</tr>
<tr>
<td>TIA</td>
<td>Aspirin, (warfarin)</td>
</tr>
<tr>
<td>Raynaud's D.</td>
<td>Calcium blockers</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Sildenafil, Vardenafil, Tadalafil</td>
</tr>
</tbody>
</table>