Perioperative management of Dual Antiplatelet therapy post drug eluting stent-changing time

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Director of Cath Lab
Director of UTHSCSA protonomics center
Overview

• Basic translational pharmacogenomics
• Changing clinical considerations
  • New pathobiology of ACS in dual antiplatelet era
• Guidelines and appropriate use criteria for the practicing physician
• Future considerations with cangrelor and vorapaxar
Translational biology
Translational pharmacodynamics
### 3 main intracellular stimuli - vasodilation of blood vessels

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpolarization (CCB)</td>
<td>Δ intracellular Ca through voltage sensitive calcium channel</td>
<td>Adenosine</td>
</tr>
<tr>
<td>cAMP-mediated</td>
<td>Adrenergic mediated- ↑removal of Ca from cytoplasm</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>cGMP (nitrovasodilator)</td>
<td>Stimulate protein kinase G</td>
<td>Nitric oxide</td>
</tr>
</tbody>
</table>

#### Endogenous vasodilators

- NO receptor (endothelium)-reduces endothelin synthesis
- Epinephrine- B2 receptor
- Histamine receptor
- Bradykinin receptor
- ATP-ADP (↑P2Y receptor)-increases NO
- Platelet activating factor
- Hypoxia

*American journal of physiology. Heart and circulatory physiology 288 (4): H1633–40*
Purines-microcirculation

Ticagrelor inhibits the cellular uptake of adenosine by inhibition of ENT1 (RBC, heart)

Table 1. Tissue distribution of nucleoside transporter proteins

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Permeant selectivity and $K_m$ for adenosine</th>
<th>Co-transported ion</th>
<th>Tissue distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENT1 (SLC29A1)</td>
<td>Purine and pyrimidine nucleosides; $\sim$40 μM</td>
<td>None</td>
<td>Wide distribution, including erythrocytes, heart and CNS – in particular the SG of the spinal cord dorsal horn and dorsal root ganglia. Located primarily in basolateral membranes in polarized epithelial cells</td>
</tr>
<tr>
<td>ENT2 (SLC29A2)</td>
<td>Purine and pyrimidine nucleosides and nucleobases; $\sim$140 μM</td>
<td>None</td>
<td>Wide distribution but particularly abundant in skeletal muscle. Located primarily in basolateral membranes in polarized epithelial cells</td>
</tr>
<tr>
<td>ENT3 (SLC29A3)</td>
<td>Purine and pyrimidine nucleosides and some nucleobases; $\sim$1.9 mM</td>
<td>Unclear, but transport optimal at pH 5.5</td>
<td>Wide distribution but particularly abundant in heart and liver. Intracellular, probably lysosomal</td>
</tr>
<tr>
<td>ENT4 (SLC29A4)</td>
<td>Organic cations, including monoamines</td>
<td>None, but transport of cationic substrates is electrogenic</td>
<td>Wide distribution but particularly abundant in brain and skeletal muscle</td>
</tr>
</tbody>
</table>

Concentration-response of the ‘adenosine component’ of the inhibitory effect of ticagrelor on platelet aggregation in whole blood

Journal of Thrombosis and Haemostasis, 11: 1867–1876
J Cardiovasc Pharmacol Ther 2012; 17: 164 – 72
Platelet micro-particles increase prothrombotic CV risk

Platelet microparticles (MPs) are shed from activated platelets and participate in thrombus

36 y/o Hispanic women
No history of HT
Mom and dad have diabetes

Circ Res. 2011;109:593-606
• Changing clinical considerations
  • New pathobiology of ACS in dual antiplatelet era
Inflammation can promote thrombosis

CD 40 ligand - this protein receptor has been found to be essential in mediating a broad variety of inflammatory responses
CD40 ligand on activated platelets triggers an inflammatory reaction of endothelial cells

CD40 and Tissue Factor in Atheromas

CD40 ligation can induce tissue factor expression in human monocyte-derived macrophages

Acute coronary syndrome: a changing disease
30% plaque erosion

J Am Coll Cardiol 2013;62:1748
Acute coronary syndrome characteristic's by oct

Plaque rupture

Thrombus

Thrombi

Plaque erosion

Cardiology Research and Practice: doi:10.4061/2011/312978
Acute coronary syndrome: plaque erosion / intact fibrous cap

Table 1  Baseline clinical and angiographic characteristics in 57 lesions for 57 patients with ruptured fibrous cap-, intact fibrous cap-acute coronary syndromes, and stable angina

<table>
<thead>
<tr>
<th></th>
<th>RFC-ACS</th>
<th>IFC-ACS</th>
<th>Stable angina</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>25</td>
<td>10</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.7 ± 10.1</td>
<td>61.5 ± 8.2</td>
<td>62.6 ± 8.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>25 (100)</td>
<td>8 (80)</td>
<td>22 (100)</td>
<td></td>
</tr>
<tr>
<td>Clinical presentation (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>15 (60)</td>
<td>4 (40)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>UAP</td>
<td>10 (40)</td>
<td>6 (60)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stable angina pectoris</td>
<td>—</td>
<td>—</td>
<td>22 (100)</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>8 (32)</td>
<td>3 (30)</td>
<td>8 (36)</td>
<td>0.922</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>12 (48)</td>
<td>6 (60)</td>
<td>13 (59)</td>
<td>0.692</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>12 (48)</td>
<td>6 (60)</td>
<td>10 (45)</td>
<td>0.739</td>
</tr>
</tbody>
</table>

European Heart Journal (2011) 32, 2814–2823
Intact fibrous cap-OCT-Erosion

JACC 2013;62:1748–58
Increasing LDL 5 with increasing MS risk factors – increase endothelial cell apoptosis

30 asymptomatic individuals with metabolic syndrome (MetS) and 27 healthy control subjects
Incretins reduce prothrombosis risk: DPP-4 Inhibitor reduces platelet aggregation

- N=50 T2DM patients
- N=10 controls
- Platelet aggregation testing

Sitagliptin significantly inhibited platelet aggregation - (dose dependency - 40% @ 10 ug/ml)

DPP 4 inhibition

Gupta et al Platelets 2012: Sept 5 early
Need case you did yesterday with good stent result of plaque rupture
• Guidelines and appropriate use criteria for the practicing physician
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Thank you

Texas and Murmur
# Clinical guidance

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>BMS</th>
<th>DES</th>
</tr>
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</table>
| Stable CAD      | Class 1A  
>1 month-ideally 12 months (1B)  
Clopidogrel 75 mg/day | Class IIb  
6 Months new generation stents (IB)-EU  
US-1 year | <6 months if high bleeding risk (IIB) |

Aspirin-1A for life-low dose 75-100 mg/day  

Eur Heart J  
2014;35:2541 – 2619
Clinical guidance

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<td>≥12 months (prasugrel, ticagrelor, clopidogrel) (class IB)</td>
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Aspirin-1A for life-low dose 75-100 mg/day

Eur Heart J 2014;35:2541 – 2619
Circulation 2011;124:e574 – e651
### Clinical guidance

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<td>PCI STEMI</td>
<td>≥12 months (prasugrel, ticagrelor, clopidogrel) (class IB)</td>
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<tr>
<td>PCI STEMI</td>
<td>12 months (prasugrel, ticagrelor, [clopidogrel only when prasugrel or ticagrelor are not available or are contraindicated]) (class IA)</td>
<td>12 months (prasugrel, ticagrelor, [clopidogrel only when prasugrel or ticagrelor are not available or are contraindicated]) (class IA)</td>
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