Beta blockers in primary hypertension

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Development of antihypertensive drugs

- **Veratrum alkaloids**
- **Rauwolfia alkaloids**
- **Thiocyanates**
- **Ganglion blockers**
  - hexamethonium
  - pentolinium
  - meclylamine
- **Alpha-blockers**
- **Beta-blockers**
  - dichloroisoproterenol
  - propranolol
  - metoprolol
- **Calcium antagonists**
  - verapamil
  - nifedipine
  - felodipine
- **Loop diuretics**
  - chlorothiazide
- **K⁺-sparing diuretics**
  - captopril
- **ACE inhibitors**
  - saralasin
  - losartan

Timeline:
- 1930
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990

All As

- 1950
Beta blockers

- 1958 - The first beta-blocker, dichloroisoproterenol, was originated by Powell and Slater
- During the 1960s, James Black and colleagues produced a range of beta-blocking agents, eventually synthesising propranolol
- The first beta-blocker to have a selective action on the beta-1 receptors as metoprolol, which was introduced in 1975
- Several major trials of beta-blockers were reported in the late 1980s
β-receptors

- β1 (heart)
- β2 (lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle)
- β3 (fat cells)
## Adrenergic Receptors

<table>
<thead>
<tr>
<th>Effector Organs</th>
<th>Receptor Type</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA node</td>
<td>$\beta_1, \beta_2$</td>
<td>$\uparrow$ HR</td>
</tr>
<tr>
<td>Atria</td>
<td>$\beta_1, \beta_2$</td>
<td>$\uparrow$ contractility &amp; conduction velocity</td>
</tr>
<tr>
<td>A-V node</td>
<td>$\beta_1, \beta_2$</td>
<td>$\uparrow$ conduction velocity</td>
</tr>
<tr>
<td>His-Purkinje System</td>
<td>$\beta_1, \beta_2$</td>
<td>$\uparrow$ conduction velocity</td>
</tr>
<tr>
<td>Ventricles</td>
<td>$\beta_1, \beta_2$</td>
<td>$\uparrow$ contractility</td>
</tr>
<tr>
<td><strong>Arterioles</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>$\beta_2$</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Skin &amp; Mucosa</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Constriction</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>$\alpha_1$</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>$\beta_2$</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Cerebral</td>
<td>$\alpha_1$</td>
<td>Constriction</td>
</tr>
<tr>
<td>Effector Organs</td>
<td>Receptor Type</td>
<td>Response</td>
</tr>
<tr>
<td>------------------</td>
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<td>------------</td>
</tr>
<tr>
<td>Renal</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>$\beta_1, \beta_2$</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Systemic veins</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>$\beta_1$</td>
<td>Dilatation</td>
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<tr>
<td>Pulmonary</td>
<td>$\alpha_1$</td>
<td>Constriction</td>
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<tr>
<td></td>
<td>$\beta_2$</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Abd. Viscera</td>
<td>$\alpha_1$</td>
<td>Constriction</td>
</tr>
<tr>
<td></td>
<td>$\beta_2$</td>
<td>Dilatation</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>$\alpha_1, \alpha_2$</td>
<td>Constriction</td>
</tr>
</tbody>
</table>
β-Receptor antagonism

β<sub>1</sub> + → +ve chronotropic & ionotropic action

-ve chronotropic & ionotropic action

β<sub>2</sub> + → smooth muscle relaxation

Vasodilatation

Bronchodilation

Tremor

↑ glycogenolysis

β<sub>3</sub> + → lipolysis

↓ lipolysis

antagonist

Vasoconstriction

Bronchoconstriction

↓ tremor

↓ glycogen
Intrinsic sympathomimetic activity

- Some beta blockers (e.g. oxprenolol and pindolol) exhibit ISA
- exert low level agonist activity at the β-adrenergic receptor while simultaneously acting as a receptor site antagonist
Examples of beta blockers

- Historical
  - Dichloroisopropranaline
  - Practolol
  - Pronethaolol
Examples of beta blockers

- Non-selective agents
  - Propranolol
  - Nadolol
  - Oxprenolol
  - Penbutolol
  - Pindolol
  - Sotalol
  - Timolol
Examples of beta blockers

- β1-Selective agents
  - Atenolol
  - Acebutolol
  - Bisoprolol
  - Esmolol
  - Metoprolol
  - Nebivolol
Examples of beta blockers

- β2-Selective agents
  - Butoxamine
Examples of beta blockers

Mixed $\alpha_1/\beta$-adrenergic antagonists
  – Carvedilol
  – Celiprolol
  – Labetalol
α1-Receptor antagonism

Some beta blockers (e.g. labetalol and carvedilol) exhibit mixed antagonism of both β- and α1-adrenergic receptors

provides additional arteriolar vasodilating action.
Clinical use

- Hypertension
- Angina
- Cardiac arrhythmia
- CCF
- Mitral Valve Prolapse
- MI
- Glaucoma
- Migraine prophylaxis
- Essential tremor
- Phaeochromocytoma in conjunction with alpha blocker
- Thyrotoxicosis
Clinical use

- Hypertrophic obstructive cardiomyopathy
- Acute dissecting aortic aneurysm
- Marfan syndrome
- Prevention of variceal bleeding in portal hypertension
- Possible mitigation of hyperhidrosis
Evidence based clinical recommendation in the management of HTN

HTN is one of the main preventable causes of premature death in industrialized countries.

Lancet 2002;360:1347-60

Treatment of HTN remain the subject of controversy and regional differences in clinical opinion persist.

contd......
Hyper homocystinemia might play a role in the pathogenesis of primary hypertension. Metopropol reduces significantly the level of homocystine.

Atherosclerosis, 2005; 181 (2): 399-402
CCF is a significant public health problem that affects an 5.7 million Americans and 20 million people worldwide.

Data from Framingham heart study says 4,65,000 new cases of CHF identified each year in USA
Hypothetical Conception

CCB and ACE I are more effective than BB and Diuretics. Until recently there have been limited data on the efficacy of newer regimen particularly combination therapy.
ALLHAT
CAPPP
STOP HTN

With ACE I as mono therapy or in combination with diuretics do not differ significantly from BB or Diuretics in terms of cardiac mortality.
Clinical trial design and the study results played significant role in shaping differing clinical opinion led to differences in official recommendations in different countries.

It is recognize that majority of patients will require more than one agent to achieve target BP.

Lancet 2005; 366:895-906
LIFE study-Losartan significantly reduce the incidence of stroke but had no effect on cardiovascular death or MI in comparison to BB & Diuretic therapy.

Lancet 2002; 359: 2002-31
In VALUE study-Valsartan produced 19% increase in MI in comparison with Amlodipine therapy.

Lancet 2004; 363: 2022-31

NICE and BHS guide line recommended the use of ARB only in patients who are intolerant to ACE I.

Press release, September 8, 2006
Thankyou