

## Chapter (8)

# Beta-Adrenergic Blockers (BABs)

- Classification
- Mechanism of Anti-ischemic Action
- Indications
- Contraindications
- Initiation and Monitoring of Therapy
- Adverse Effects

- The only group of antiischemic drugs with documented efficacy in preventing reoccurrence of coronary events, myocardial infarction (MI) and sudden death following acute MI.
- BABs act as competitive inhibitors of catecholamines at beta-adrenergic receptors (BARs).
- BARs are divided into B<sub>1</sub> (those in the myocardium) and B<sub>2</sub> (present in smooth muscle cells, bronchi and other tissues). Epinephrine and nor-epinephrine are equipotent at B<sub>1</sub> receptors, whereas epinephrine is 10 to 50 fold more potent than nor-epinephrine at B<sub>2</sub> receptors.
- Cyclic adenosine mono phosphate (cAMP) is the major second messenger of BAR stimulation leading to events that increase influx of calcium into the cell and activate glycogen phosphorylases.
- The metabolic effects of cyclic AMP including calcium overloading, high energy phosphate depletion, oxygen wastage by increased free fatty acid metabolism and increased arrhythmogenicity appear to play a role in catecholamine induced ischemic cell injury.

### CLASSIFICATION OF BABS

More than 30 BABs are present worldwide. They are classified according to the following characteristics:

1. Beta-adrenergic specificity- selectivity.
2. Lipid solubility- lipophilicity.
3. Intrinsic sympathomimetic activity (ISA).
4. Vasodilator properties.

#### 1. *Beta-adrenergic specificity- selectivity*

- Some BABs are more specific for B<sub>1</sub> ARs, they are called cardio-selective BABs, examples are atenolol, metoprolol and bisoprolol. Bisoprolol is the most cardioselective BAB (table 8-1). Other BABs are non selective and block both B<sub>1</sub> and B<sub>2</sub> ARs. Examples are propranolol and nadolol.
- In low doses, B<sub>1</sub>- selective blockers may not block the B<sub>2</sub>- receptors that mediate dilatation of arterioles and bronchi and have a number of metabolic effects. Cardioselective BABs are relatively safer in the management of patients with COPD, diabetes and peripheral vascular disease (PVD). However, when given in large doses they block both B<sub>1</sub> and B<sub>2</sub> receptors.

#### *Advantage of B<sub>1</sub>- Selectivity*

- Glucose metabolism: no dose adaptation of oral hypoglycemics.
- Lower risk of masking hypoglycemia.
- Pulmonary function: safe use with COPD.
- Peripheral vascular resistance: lower risk of cold extremities and erectile dysfunction.

## 2. *Lipophilicity*

- Lipid soluble BABs are metabolized by the liver, they have a short duration of action and tend to have central nervous system side effects. Examples are propranolol, metoprolol, carvedilol and timolol.
- Water soluble (lipid insoluble) BABs are excreted through the kidneys, they have a longer duration of action and less central nervous system side effects. Examples are atenolol, bisoprolol, and nadolol.

## 3. *Intrinsic sympathomimetic activity (ISA)*

- BABs with this property slightly activate the BARs in addition to preventing the access of natural or synthetic catecholamines to the receptor. Drugs with partial agonist activity cause less slowing of the heart rate at rest and cause less depression of atrioventricular conduction. Examples are pindolol.

## 4. *Vasodilator properties*

- Some BABs block both alpha and beta ARs and have direct vasodilator activity. Examples are labetalol and carvedilol. Bucindolol is a non-selective BAB with a direct vasodilator activity.

Table 8-1: Adrenergic Receptor Blocking Affinities

Generation/Class	Compound	B <sub>1</sub> / B <sub>2</sub> Selectivity
First/ Nonselective	Propranolol	2.1
Second/ Selective B <sub>1</sub>	Metoprolol	74
	Bisoprolol	119
Third/ B-blocker-vasodilator	Carvedilol	7.3
	Bucindolol	1.4
	Nebivolol	293

## MECHANISM OF ANTI-ISCHEMIC ACTION OF BABS

### A. Decrease in myocardial oxygen requirements

1. Slowing of heart rate.
2. Lowering of blood pressure.
3. Decrease in myocardial contractility.
4. Decrease in fatty acid utilization.

## B. Increase in myocardial oxygen supply

1. Increase in diastolic perfusion and augmentation of coronary blood flow secondary to bradycardia.
2. Augmentation of collateral blood flow and redistribution of blood flow to ischemic areas.

## C. Other actions

1. Stabilization of atherosclerotic plaque and preventing plaque rupture through reduction in vessel wall stress.
2. Decrease in microvascular damage.
3. Stabilization of cell and lysosomal membranes.
4. Inhibition of platelet aggregation.

## INDICATIONS OF BABS

### A. Cardiovascular

1. Chronic stable angina.
2. Acute coronary syndromes.
3. Systemic hypertension.
4. Heart failure with impaired LV systolic function.
5. Congestive cardiomyopathy.
6. Hypertrophic cardiomyopathy.
7. Arrhythmias: sinus tachycardia, PVCs, supraventricular tachycardia, ventricular tachycardia, long QT syndrome.
8. Aortic dissection.
9. Tetralogy of Fallot.
10. Mitral valve prolapse.
11. Digitalis intoxication.

### B. Non-cardiovascular

1. Migraine prophylaxis.
2. Essential tremors.
3. Anxiety (situational).
4. Thyrotoxicosis.
5. Alcohol withdrawal.
6. Glaucoma.

## CONTRAINDICATIONS OF BABS

### A. Absolute

1. Cardiogenic shock.
2. Hypotension (SBP < 85 mmHg).
3. Acute pulmonary oedema.
4. Signs of systemic hypoperfusion: mental deterioration, cold clammy skin, rising BUN.
5. Congestive heart failure with pulmonary crepitations more than one half of the chest or significant volume overload (until adequate diuresis).
6. Symptomatic bradycardia (heart rate < 50/m) or more than grade I AV block in absence of pacemaker.
7. Patients receiving IV inotropes.
8. Status asthmaticus or bronchospasm requiring inhaled beta-agonists.

### B. Relative

1. Bronchial asthma or COPD.
2. Heart failure.
3. Insulin dependent diabetes mellitus.
4. Severe PVD.

## INITIATION AND MONITORING OF BABS THERAPY

- Exclude absolute contraindications.

### In Angina Pectoris (Chronic Stable and Unstable)

- Start with a small dose and build the dose over days, monitor heart rate and blood pressure.
- All types of BABS appear to be equally effective in exertional angina but there is interindividual variability in responsiveness.
- Evaluate anginal symptoms in 1 to 2 weeks.
- Starting dose of atenolol is 25 mg once daily which can be increased as tolerated to a maximum of 200 mg once daily (assuming the renal function is normal) until the resting heart rate is 50 to 60 beats/min and does not exceed 100 beats/min with ordinary activity.
- Starting dose of metoprolol is 25 mg BID, which can be increased to 200 mg BID as tolerated.
- *The efficacy of BABS in relieving angina is dose-dependent. It is important to be certain that adequate beta blockade has been attained. BABS dose is titrated to achieve the following goals:*
  1. *Resting heart rate between 50 and 60 beat/min. Target heart rate for some patients with more severe angina can be less than 50 beats/min, as long as bradycardia is asymptomatic and heart block does not develop.*

2. *Blunting of postural increase in heart rate.*
  3. *Blunting of peak heart rate and blood pressure during exercise, measured during exercise testing.*
  4. *Reduction in the frequency and severity of angina and in use of sublingual nitroglycerin.*
- The following are cardioprotective doses proved effective in preventing sudden death and total cardiac deaths in patients after MI. The beneficial effect of smaller doses is unknown:
    - § Metoprolol 100-300 mg/d.
    - § Propranolol (non smokers) 160-240 mg/d
    - § Timolol 10-20 mg/d
  - *BABs are not effective in Prinzmetal (vasospastic angina) and should not be used in this condition.*
  - *Avoid abrupt cessation of therapy when it is necessary to discontinue BABs. The dose should be reduced gradually over 2 to 3 weeks.*

#### BABs in Acute Myocardial Infarction

- BABs reduce morbidity and mortality when administered following AMI. An up to 40% reduction in mortality in patients with ST elevation (Q wave) or non-ST elevation (non-Q wave) MI.
- After an acute MI, BABs can be given early (within 4 to 6 hours of presentation).
- Early administration: early intravenous atenolol, metoprolol, or propranolol. Intravenous esmolol which has a short half-life of 8 to 10 minutes may be preferable in patients who are at increased risk of hemodynamic deterioration.
- *Intravenous metoprolol* is given in 5 mg increments by slow intravenous administration (5 mg over 1 to 2 min), repeated every 5 minutes for a total initial dose of 15 mg.
- In patients who tolerate the total 15 mg IV dose, oral therapy should be initiated 15 minutes after the last intravenous dose at 25 to 50 mg every 6 hours for 48 hours. Thereafter, patients should receive a maintenance dose of 100 mg twice daily.
- *Intravenous propranolol* is administered as an initial dose of 0.5 to 1.0 mg, followed in 1 to 2 hours by 40 to 80 mg by mouth every 6 to 8 hours.
- *Intravenous atenolol* is initiated with 5 mg IV dose followed 5 minutes later by a second 5 mg IV dose and then 50 to 100 mg per day orally initiated 1 to 2 hours after the intravenous dose.
- *Intravenous esmolol* is administered as a starting dose of 0.1 mcg/kg/min with titration in increments of 0.05mcg/kg/min every 10 to 15 minutes as tolerated by the patient's blood pressure until the derived therapeutic response has been obtained, limiting symptoms develop or a dosage of 0.3 mcg/kg/min is reached. A loading dose of 0.5 mcg/kg may be given by a slow IV administration (2 to 5 min) for a more rapid onset of action.

- The target resting heart rate is 50 to 60 beat/min while maintaining a SBP above 90 mmHg, unless a limiting side effect is reached.
- Benefits of early BABs therapy versus late administration
  - Lower rate of recurrent chest pain.
  - Lower rate of reinfarction.
  - Lower rate of combined end points of recurrent MI or death within 21 days.
- *Duration of therapy*

Most patients are continued on an oral BAB indefinitely. Patients at high risk have more benefit than low risk patients.

- Patients with relative contraindication to beta blockade e.g. chronic obstructive lung disease (COPD), asthma or heart failure show survival benefit except in patients who had severe COPD or using a beta agonist.
- *Mechanism of benefit in AMI*
  1. Decreased oxygen demand and relief of ischemic chest pain.
  2. Decreased risk of ventricular fibrillation.
  3. Bradycardia reduces afterdepolarization and triggered activity.
  4. Reduction in remodeling.
  5. Improved LV diastolic function with a less restrictive pattern.
  6. Immediate BAB is associated with reduction in the incidence of intracerebral hemorrhage in patients receiving thrombolytic therapy.

Table 8-2: Properties and Dosage of BAB in Clinical Use

Drug	Selectivity (B <sub>1</sub> )	Partial Agonist Activity (Intrinsic sympathomimetic activity)	Usual Dose for Angina
Propranolol (Inderal)	None	No	20-80 mg twice daily
Metoprolol (Betaloc)	Beta-1	No	50-200 mg twice daily
Atenolol (Tenormin)	Beta-1	No	50-200 mg/d
Nadolol (Corgard)	None	No	40-80 mg/d
Acebutolol	Beta-1	Yes	200-600 mg twice daily
Bisoprolol (Concor)	Beta-1	No	10 mg/d
Esmolol (intravenous)	Beta-1	No	50-300 mcg/kg/min
Labetolol (Trandate)	None	Yes	200-600 mg twice daily
Pindolol (Visken)	None	Yes	2.5-7.5 mg 3 times daily
Carvedilol (Dilatrend, Cardilol)	None	None	12.5-25 mg twice daily
Sotalol (Sotacor, Betacor)	None	None	80-100 mg twice daily

## ADVERSE EFFECTS OF BAB

### 1. Cardiac

- Myocardial depression and precipitation of heart failure.
- Profound bradycardia, sinus node dysfunction and AV conduction delay.
- Hypotension.

### 2. Peripheral vascular effects

- Cold extremities.
- Absent pulses, cyanosis.
- Raynaud's phenomenon.
- Worsening of claudication.

### 3. Central nervous system effects

(more common with highly lipid soluble BABs such as propranolol and metoprolol)

- Dreams, hallucinations, insomnia.
- Depression.
- Fatigue.
- Impotence.

### 4. Metabolic effects

- Enhancement of insulin induced hypoglycemia.
- Masking manifestations (tachycardia) of hypoglycemia.
- Hyperlipidemia: increase in plasma triglycerides and decrease in HDL-cholesterol secondary to inhibition of lipoprotein lipase activity.

### 5. Rebound phenomenon

- Sudden discontinuation of BAB specially if it has been administered for a long time (> 3weeks) can lead to profound elevation of blood pressure and tachycardia and may precipitate myocardial ischemia, or infarction.

### 6. Ventilatory function

- Bronchospasm and increase airway resistance in asthmatics.

## Beta-Adrenergic Blockers

- Has a central role in management of coronary patients.
- Beneficial effect through:
  - Anti-ischemic effect: Relieve angina.
  - Anti-arrhythmic effect: Prevent sudden death
  - Anti-remodeling effect: Prevent deterioration in LV function.
  - Atherosclerotic plaque stabilizing effect: Prevent ACS.
- They are indicated in all forms of CAD
  - Stable angina. - Unstable angina / NSTEMI.
  - Acute phase of MI. - Following MI.
  - Ischemic cardiomyopathy.
- Should be administered in adequate dosage to achieve effective beta-adrenergic blockade (attenuation of postural and exercise induced tachycardia).
- They are underutilized by physicians.
- Main contraindications are:
  - SBP < 85 mmHg, more than grade 1 AV block (in absence of pacemaker), acute pulmonary oedema, uncontrolled bronchial asthma requiring inhalation therapy.