

# Beta Blockers

## Reassessing Pharmacological Differences

April, 1998

$\beta$  blockers have grown steadily in number and application since the introduction of propranolol in 1965. This edition will compare the efficacy, safety, and cost of commonly prescribed  $\beta$  blockers. Carvedilol (Coreg®), the latest addition to the newly evolving class of combination  $\alpha$ - $\beta$  blockers is also reviewed.

### Comparative Pharmacology:

Despite a common chemical structure,  $\beta$  blockers possess a number of properties that differentiate one agent from another. Advantages and disadvantages of these properties are often of more theoretical than clinical significance.

**Cardioselective**  $\beta$  blockers include acebutolol (Sectral®/Monitan®), atenolol (Tenormin®), and metoprolol (Lopresor®/Betaloc®). These agents preferentially block  $\beta_1$  receptors found primarily in cardiac muscle, adipose tissue, and the kidney. They have less effect on  $\beta_2$  receptors found in pulmonary and vascular smooth muscle and the pancreas. Cardioselective agents should theoretically cause less coldness of the extremities and less bronchospasm. Unfortunately, selectivity is dose-dependent and varies widely among patients<sup>1</sup> so this property cannot be relied upon to consistently provide improved safety and reduced side effects. Non-cardioselective agents are generally required if used to treat essential tremor or prevent migraine.

Pindolol (Visken®), oxprenolol (Trasicor®), and acebutolol have **intrinsic sympathomimetic activity (ISA)**. These agents act as partial agonists and cause smaller reductions in heart rate and cardiac output. The clinical significance of these effects has yet to be clearly demonstrated.<sup>1</sup> Agents with ISA should be avoided in patients post-MI, or with CHF.

Acebutolol, pindolol, and propranolol (Inderal®) also have a local anaesthetic effect or **membrane stabilizing activity (MSA)**. Supratherapeutic doses are required to produce this effect so it is usually not clinically relevant.<sup>1</sup>

Adverse CNS effects are often thought to be related to  $\beta$  blockers' **lipophilicity**, as fat-soluble agents cross the blood-brain barrier more readily. However, frequency and severity of CNS adverse effects may not be solely related to lipophilicity as fatigue, mood changes, depression, and nightmares have been reported with all  $\beta$  blockers<sup>1</sup> including water-soluble

### **Highlights**

- $\beta$  blockers are considered first line agents along with thiazide diuretics in patients with uncomplicated HTN, due to proven  $\downarrow$  morbidity & mortality and low cost.
- Cardioselectivity may improve safety and tolerability, however, this is not guaranteed.
- **Metoprolol SR** combines cardioselectivity with well-documented efficacy in angina, myocardial infarction and CHF, and provides excellent 24h BP control.
- $\beta$  blockers, unless contraindicated, are often preferred in patients with stable or unstable angina, supraventricular arrhythmia, and previous MI.
- Carvedilol may be beneficial in patients with heart failure who are refractory to other drug therapies.

agents. Cardioprotective efficacy has been associated with a  $\beta$  blocker's degree of lipophilicity (see MI).

### Hypertension:

$\beta$  blockers have a well established role in the treatment of hypertension. They are still considered *first line* agents along with thiazides in the management of uncomplicated hypertension because of clinically proven reductions in morbidity and mortality.<sup>2</sup> At equipotent doses, all  $\beta$  blockers are equally effective in reducing blood pressure.<sup>1</sup>  $\beta$  blockers may be particularly effective antihypertensives in younger patients with high renin activity. The elderly may also benefit from  $\beta$  blockers especially when used in combination with diuretics.  **$\beta$  blockers may be preferred in patients with angina, supraventricular arrhythmia, previous MI, migraine, anxiety,** or other comorbid conditions where  $\beta$  blockers are of benefit.

Optimal antihypertensive therapy requires consistent BP reduction over a 24 hour period. Although several agents may be given once daily (acebutolol, atenolol, nadolol, pindolol, timolol), care should be taken to ensure adequate 24 hour control is maintained. Once daily atenolol may not control blood pressure adequately during the early morning hours.<sup>19,25</sup> Sustained release (SR) metoprolol, given once daily combines excellent 24 hour BP control with cardioselectivity.<sup>25,26</sup>

$\beta$  blockers, particularly in low doses, may be better tolerated than commonly believed. Results of TOMHS (Treatment of Mild Hypertension Study) indicated acebutolol was associated with the greatest overall improvement in quality of life

measures when compared with agents from 4 other classes of antihypertensives (amlodipine, enalapril, chlorthalidone, and doxazosin).<sup>17</sup> Adverse effects are further outlined in **Table 2**.

#### **Angina:**

$\beta$  blockers appear to be the **most efficacious agents for the treatment of stable and unstable angina**. They are the only antianginal agents shown to improve clinical outcomes in patients with myocardial ischemia.<sup>3</sup> Their negative chronotropic and inotropic effects decrease heart rate and contractile force, reducing myocardial oxygen demand and relieving angina. All  $\beta$  blockers improve exercise tolerance and reduce signs and symptoms of angina regardless of differences in ISA and selectivity.<sup>1</sup> Combinations of a  $\beta$  blocker and a long-acting dihydropyridine calcium antagonist are useful in some patients.  **$\beta$  blockers should be avoided in vasospastic angina** as uncompensated alpha receptor stimulation may result in further vasoconstriction.<sup>4</sup>

#### **Myocardial Infarction (MI): Secondary prevention**

Many studies in the last decade have shown the benefit of  $\beta$  blockers in prevention of recurrent MI and other related complications, acutely and in the postinfarction period. Results from major trials show a reduction in overall mortality of more than 20-30%.<sup>6-9</sup>  **$\beta$  blockers with moderate to high lipophilicity (timolol, metoprolol, propranolol) have shown marked reductions in sudden cardiac death.**<sup>7-9</sup> It is postulated that these agents enter the brain rapidly and increase vagal tone. This prevents ventricular fibrillation associated with the increased sympathetic drive and reduced vagal tone during an acute MI.<sup>10</sup>  $\beta$  blockers appear underused in survivors of acute MI.<sup>5</sup> Studies looking at pindolol and oxprenolol showed no effect on mortality.<sup>11,12</sup> As both agents have ISA,  $\beta$  blockers with this property may not be appropriate for use post-MI.<sup>1</sup>

#### **Arrhythmia:**

All  $\beta$  blockers have some inherent (Class II) antiarrhythmic activity. They slow conduction through both the SA node and the AV node. All  $\beta$  blockers appear beneficial in treatment of supraventricular arrhythmias, regardless of MSA, ISA, or selectivity.<sup>1</sup> **Sotalol** (Sotacor®) may be the preferred  $\beta$  blocker for arrhythmias because it has both Class II and Class III antiarrhythmic activity. Caution is required as sotalol also has pro-arrhythmic potential.

#### **Heart Failure (HF):**

The role of  $\beta$  blockers in HF has yet to be clearly established. In the past,  $\beta$  blockers were considered contraindicated due to their negative inotropic effects. Recent application in HF has resulted from the beneficial effects seen in patients with MI. Studies report improvement in hemodynamic parameters and exercise tolerance but this is not always accompanied by significant reductions in mortality.<sup>6</sup> Studies are currently underway to assess the effect of  $\beta$  blockers on survival in HF.<sup>13,14</sup>

$\beta$  blockers appear to have greater clinical benefits in idiopathic dilated cardiomyopathy than in ischemic cardiomyopathy.<sup>15</sup> Effects on exercise tolerance and quality of life favor the cardioselective agents.<sup>14</sup>  $\beta$  blockers with ISA should be

avoided as they do not appear to have any beneficial effect in HF.<sup>15</sup> Initially,  $\beta$  blockers may worsen symptoms of HF but improvement is usually seen with long term therapy (i.e. after 1-2 months). Patients should be stabilized on a regimen of ACE inhibitors, diuretics, and/or digoxin before starting  $\beta$  blockers. Initial doses should be very small, 1/10-1/20th the antihypertensive dose, and titrated up gradually over a period of several weeks (eg. metoprolol 6.25mg BID x 7 days; double dose weekly till 50 mg BID or adverse affects appear).<sup>15,16</sup> Approximately 15% of patients will not tolerate  $\beta$  blocker therapy, developing low output syndrome with bradycardia, hypotension, edema, and progressive heart failure. Patients intolerant to  $\beta$  blockers tend to have right-sided failure with ascites, jugular venous distension, tricuspid regurgitation, increased right filling pressure, and EF of <20%.  $\beta$  blockers are best avoided in this population.<sup>15</sup>

#### **$\alpha_1$ - $\beta$ Blockers:**

Labetalol (Trandate®) was the first  $\beta$  blocker to combine both non-selective  $\beta$  and vasodilatory  $\alpha_1$  adrenergic blockade in a single drug. Its  $\beta$ : $\alpha$  blockade ratio is  $\approx$  3:1. Labetalol IV is indicated in various hypertensive emergencies.

**Carvedilol (Coreg®)** is a more potent non-selective  $\beta$  blocker and  $\alpha_1$  antagonist. Unlike other  $\beta$  blockers, carvedilol also possesses several unique cardioprotective, anti-ischemic, and antioxidant properties.<sup>22</sup> **Many recent studies lend support to the use of carvedilol in HF.**<sup>23</sup> Most impressive of these, the US Carvedilol Heart Failure Study was terminated early after a 6 month follow-up showed a 65% reduction in overall mortality in carvedilol vs. placebo treated patients. All study patients were stabilized on diuretics, ACE inhibitors, and digoxin. Until further trials are completed, carvedilol serves as a promising alternative in HF patients refractory to other therapy. Although carvedilol is a potent antihypertensive, it is not currently approved in Canada for the treatment of hypertension.

Carvedilol is generally well tolerated. Effective doses are lower than comparable doses of  $\beta$  blockers because of its combined mechanisms of action. Carvedilol's  $\beta$  blocking activity reduces reflex tachycardia and fluid retention usually seen with  $\alpha$  blockers. Complaints of cold extremities, bradycardia, and reduced cardiac output seen with pure  $\beta$  blockers are minimized by carvedilol's vasodilatory effect.<sup>21</sup> Adverse effects are more common early in therapy and are often dose-related. Common complaints include dizziness, headache, and orthostatic hypotension as well as fatigue and asthenia.<sup>20</sup> Unlike other  $\beta$  blockers, carvedilol does not appear to adversely affect lipid profiles or glucose metabolism.<sup>20</sup> Cautious use is still advised in diabetics due to masking of signs of hypoglycemia. Carvedilol does not appear to cause deteriorations in renal function because of its vasodilatory effect, and it actually reduces microalbuminuria.<sup>20</sup>

*References available on request.*

## The Rx Files: Beta Blockers (BBs) Supplementary Tables

Table 1

Contraindications and Precautions
<p><b>Contraindications</b></p> <ul style="list-style-type: none"> <li>• Sick sinus syndrome or 2nd/3rd degree AV block</li> <li>• Cardiogenic shock</li> <li>• Uncompensated CHF</li> <li>• Reactive airway disease (asthma, COPD, emphysema)</li> </ul> <p><b>Precautions</b></p> <ul style="list-style-type: none"> <li>• Severe hypotension (SBP &lt; 100 mm or HR &lt; 60)</li> <li>• Peripheral vascular disease - exacerbated especially by non-selective <math>\beta</math> blockers</li> <li>• Vasospastic angina - uncompensated alpha vasoconstriction</li> <li>• Diabetes - may prolong/exacerbate hypoglycemia in insulin dependent pts. due to inhibition of gluconeogenesis, masking of warning signs (tachycardia/tremor), profound bradycardia and hypertension; In non-insulin dependent pts. may <math>\uparrow</math> hyperglycemia due to inhibition of insulin release and <math>\downarrow</math> tissue uptake</li> <li>• Mental depression - may be exacerbated</li> <li>• Pregnancy - FDA categories B-C; Use cautiously when benefit outweighs risk</li> <li>• Breastfeeding - excreted in breast milk to varying degrees; Monitor infant for hypotension and bradycardia</li> <li>• Pediatrics - use cautiously under guidance of specialist</li> </ul>

Table 2

Adverse Effects
<p><b>General:</b> fatigue, cold extremities, depression, sleep disturbance, impotence, etc.</p> <ul style="list-style-type: none"> <li>• May be less frequent/severe with cardioselective agents</li> <li>• May respond to dose reduction</li> </ul> <p><b>Metabolic:</b> loss of glycemic control</p> <ul style="list-style-type: none"> <li>• Usually <math>\uparrow</math> hypoglycemia in IDDM and <math>\uparrow</math> hyperglycemia in NIDDM</li> <li>• May occur less frequently with cardioselective agents</li> </ul> <p><b>Lipids:</b> <math>\uparrow</math> in triglycerides, VLDL, and <math>\downarrow</math> HDL</p> <ul style="list-style-type: none"> <li>• Moderate with non-selective BBs, minor with selective BBs, and neutral with BBs with ISA</li> <li>• unknown if effect detrimental in the long-term; cardioprotective benefits appear to outweigh risk<sup>6</sup></li> </ul> <p><b>Renal:</b> may precipitate/exacerbate renal failure due to <math>\downarrow</math> GFR and renal perfusion</p> <ul style="list-style-type: none"> <li>• exception: nadolol <math>\uparrow</math> GFR by unknown mechanism</li> <li>• may occur less often with cardioselective or ISA BBs</li> </ul> <p><b>Withdrawal phenomena:</b></p> <ul style="list-style-type: none"> <li>• abrupt withdrawal may cause rebound hypertension, exacerbate angina, induce arrhythmia, precipitate MI</li> <li>• patients with coronary artery disease at high risk</li> <li>• gradually reduce dose over a number of days before stopping</li> </ul>

Table 3

### Drug Interactions<sup>18</sup>

- **Amiodarone** -  $\uparrow$  risk of bradycardia, ventricular arrhythmia, cardiac arrest
- **Barbiturates, rifampin** -  $\downarrow$  effect of hepatically cleared BBs due to  $\uparrow$  metabolism
- **Benzodiazepines, phenothiazines** - effect may be  $\uparrow$  with hepatically cleared BBs due to  $\downarrow$  metabolism
- **Calcium Channel Blockers** - potentiate effects and possible toxicity of either group of drugs
- **Cimetidine** -  $\uparrow$  effect of hepatically metabolized BBs due to  $\downarrow$  metabolism
- **Clonidine** - hypertensive reactions when clonidine withdrawn
- **Digoxin** -  $\uparrow$  risk of bradycardia especially with non-ISA BBs
- **Epinephrine, phenylephrine, phenylpropranolamine** - hypertensive reactions especially with non-selective BBs
- **Oral Hypoglycemics** - hyperglycemia due to BB inhibition of insulin release and  $\downarrow$  tissue uptake
- **Magnesium, calcium, aluminum, antacids** -  $\downarrow$  effect of BB due to  $\downarrow$  bioavailability; Space administration times by 2-4hrs
- **NSAIDs** -  $\downarrow$  hypotensive effect of BB
- **Quinolone ("floxacin") antibiotics** -  $\uparrow$  effect of hepatically cleared BBs due to  $\downarrow$  metabolism
- **Theophylline** - all BBs antagonize effects; hepatically cleared BBs  $\downarrow$  metabolism and may  $\uparrow$  theophylline toxicity

Table 4

Comparative Cost For 30 Days Treatment With Commonly Used Antihypertensives <small>(Retail cost to consumer, SK)</small>	
hydrochlorothiazide 12.5-25mg po daily	\$ 8.00
atenolol 50mg po daily	\$ 18.00
metoprolol SR 100 mg po od	\$ 16.00
acebutolol 200mg po bid	\$ 25.00
lisinopril 10mg po daily	\$ 36.00
enalapril 10mg po daily	\$ 42.00
enalapril 5mg po bid	\$ 64.00
felodipine ER 10mg po daily	\$ 43.00
diltiazem CD 180mg po daily	\$ 48.00

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