THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the
Sri Lanka Medical Association
Volume 52, No.3, September 2007
Quarterly ISSN 0009-0875

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Which β -blocker is best for your patient?

There are subtle but important differences between β -blockers. Cardio-selective agents cause fewer side-effects and are the drugs of choice for cardio-protection.

Propranolol was the first β -blocker to be used in clinical medicine. The credit for this discovery in the late 1950s goes to the Scottish scientist James W Black, for which he was awarded the Nobel Prize in Medicine in 1988. Since the introduction of propranolol for the treatment of hypertension in 1964 by Prichard and Gillam, more than 24 β -blocking drugs have become available. As a class, β -blockers represent one of the five all time major breakthroughs in clinical drug development [1].

There are many indications for β -blockers. These include hypertension, angina, myocardial infarction (MI), cardiac arrhythmia, congestive heart failure, hypertrophic obstructive cardiomyopathy, acute dissecting aortic aneurysm, valvular heart disease, peri-operative mortality reduction, tetralogy of Fallot, neurocardiogenic syncope, Marfan syndrome (chronic treatment with propranolol slows progression of aortic dilation and its complications), prevention of variceal bleeding in portal hypertension, glaucoma, migraine prophylaxis, symptom control (tachycardia, tremor) in anxiety and hyperthyroidism, essential tremor and pheochromocytoma in conjunction with an α -blocker.

To decide which β -blocker should be selected for a particular patient, a few general questions need to be answered. Do β -blockers differ in effectiveness, safety or side-effects in different conditions? Are there subgroups of patients based on demographics (age, racial group, gender), other medications (drug interactions), or co-morbidities (drug-disease interactions) for which one β -blocker is more effective or associated with fewer side-effects?

In patients with hypertension, no β -blocker has been demonstrated to be more efficacious or to result in better quality of life than others, either as initial therapy or when added to a diuretic, angiotensin converting enzyme (ACE) inhibitor, or angiotensin-II receptor blocker (ARB) [2-6]. Evidence from long term trials is mixed; overall, β -blockers are generally less effective than diuretics, calcium channel blockers, ACE inhibitors and ARBs in reducing cardiovascular events.

In patients with chronic stable angina, there were no differences in exercise tolerance or attack frequency in trials of carvedilol vs metoprolol, pindolol vs propranolol, and betaxolol vs propranolol [7]. Atenolol and bisoprolol were equivalent in angina patients with chronic obstructive pulmonary disease (COPD). Atenolol and labetalol (when combined with chlorthalidone) were equivalent in angina patients with hypertension. β -blockers that have intrinsic sympathomimetic activity (ISA) reduce the resting heart rate less than other β -blockers, a potential disadvantage in patients

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6, Wijerama Mawatha
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Fax: +94 11 2698802

Internet home page
<http://www.slma.lk>

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Printed by

Ananda Press
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Mawatha, Colombo 13
Sri Lanka

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Fax: +94 11 2385039

e-mail: anpress@sltnet.lk

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Medical Journal

**This journal is indexed in BIOSIS, CAB
International, EMBASE, and
Index Medicus**

suffering from angina pectoris. For this reason, experts recommend against β -blockers with ISA in patients with angina.

Long term use of a β -blocker after coronary artery bypass grafting (CABG) does not improve mortality or other outcomes [8]. Following recent MI, timolol was the first β -blocker shown to reduce total mortality, sudden death, and reinfarction outcomes [9]. Subsequently, similar total mortality reductions were reported in trials of acebutolol, metoprolol, and propranolol in comparable populations [10]. Similar benefits in sudden death were reported for propranolol and metoprolol and in re-infarction for metoprolol. Carvedilol reduced re-infarction rates in patients with recent myocardial infarction with a left ventricular ejection fraction of 40% or less [11]. Carvedilol is the only β -blocker shown to reduce mortality in post-MI patients who are already taking an ACE inhibitor.

Reductions in mortality, sudden death, cardiovascular death, and death due to chronic heart failure (CHF) were similar for bisoprolol, metoprolol succinate, and carvedilol. Because several carvedilol trials performed in the USA had significant mortality reductions, the evidence for carvedilol may be more relevant to that population. When titrated gradually in stable patients, there is no difference in tolerability among these drugs. In patients with severe heart failure, carvedilol clearly reduced mortality and the combined end-point of mortality and hospitalisations [12, 13]. Carvedilol has the most direct, strongest evidence. In another trial [14], metoprolol succinate showed a mortality reduction similar to that for carvedilol in patients who had a similar mortality risk. This is a weaker level of evidence than that for carvedilol, but the lack of a direct comparator and the difficulty of comparing participants from the different trials makes it uncertain whether any one of these drugs is superior in patients with the differing degrees of heart failure. In a head-to-head trial conducted in patients with mild to moderate failure, carvedilol reduced mortality compared to metoprolol tartrate, the immediate release form of metoprolol [15]. In previous trials, however, metoprolol tartrate had not reduced mortality. The question whether carvedilol is superior to metoprolol succinate or bisoprolol, the preparations that have been shown to reduce mortality, has not been resolved yet.

Several β -blockers have been used to reduce the heart rate in patients with atrial tachyarrhythmias and to prevent relapse into atrial fibrillation or flutter. A recent good quality systematic review examined 12 studies of rate control in patients with chronic atrial fibrillation [16]. Atenolol, nadolol and pindolol were effective in controlling the ventricular rate, whereas labetalol was no more efficacious than placebo.

β -blockers are effective in the control of ventricular arrhythmias related to sympathetic activation, including stress-induced arrhythmias, acute MI, and heart failure, and in the prevention of sudden cardiac death (SCD) [17, 18]. Most β -blockers have proved effective in reducing the number of ventricular premature beats. In sustained ventricular tachycardia, β -blockers including propranolol, sotalol, metoprolol and oral atenolol have been effective in suppressing the tachycardia, but there is a lack of controlled studies. On the contrary, β -blockers are of proven efficacy in preventing arrhythmias leading to SCD in different conditions, including acute and chronic myocardial ischaemia, heart failure and cardiomyopathies. SCD secondary to ventricular arrhythmias is frequent in patients with hypertrophic cardiomyopathy, especially during exercise and in the presence of left ventricular outflow obstruction. Though propranolol may improve symptoms, the available evidence does not support its routine use in the prevention of SCD in these patients.

In mitral valve prolapse, β -blocking agents are generally considered as first choice therapy in symptomatic patients but the routine or selective use

of β -blockers to prevent sudden cardiac death is not recommended as no prospective studies have been done. Though propranolol is the most frequently used, it is not supported by robust evidence.

β -blockers are indicated to lower blood pressure in patients with suspected or diagnosed aortic dissection, although this therapeutic approach has not been tested in randomised clinical trials. Intravenous β -blockers (propranolol, metoprolol, atenolol, labetalol and esmolol) are preferred to achieve rapid control of blood pressure.

Clinicians should be cautious in the use of β -blockers to prevent adverse cardiac events in surgical patients. Patients should be stratified using a validated risk assessment tool, such as the Revised Cardiac Risk Index [19]. β -blockers may be considered in high risk patients but should be withheld in low risk patients. Patients at intermediate risk might benefit from further risk stratification with non-invasive cardiac stress testing before choosing to use β -blockers.

In migraine, head-to-head trials [20] show no difference in efficacy in reduction of attack frequency, severity, headache days, acute tablet consumption or improvement in any subjective or composite index in any of the comparisons made (atenolol or metoprolol *durules* or metoprolol or timolol vs propranolol). Results from placebo controlled trials on similar outcome measures generally support atenolol, metoprolol *durules* and propranolol. Placebo controlled trial results also show that bisoprolol had a significant effect on attack frequency reduction and that pindolol had no appreciable effects.

In bleeding oesophageal varices, one small trial showed no difference between atenolol and propranolol in rates of non-fatal and fatal re-bleeding and all cause mortality. Results of one trial of nadolol and 8 small placebo controlled trials of immediate release and extended release propranolol do not provide any additional indirect evidence of the comparative efficacy of β -blockers in these clinical outcomes [20]. Long acting propranolol and nadolol are probably superior. The somewhat mixed results across the placebo controlled trials of propranolol suggest that treatment initiation interval may have an effect on re-bleeding rates. Mortality rates were higher than in the placebo group when started early (<72 hours), indicating that it may be preferable to start β -blockers 2 weeks after the acute bleed.

Side-effects are common in patients taking β -blockers. Longer term trials (12–58 months), directly comparing β -blockers in patients with hypertension (atenolol vs bisoprolol vs propranolol), heart failure (carvedilol vs metoprolol), bleeding oesophageal varices (atenolol vs propranolol), and atrial fibrillation (bisoprolol vs carvedilol) showed no differences in any of the safety parameters measured, with one exception. Carvedilol caused more dizziness than metoprolol in a fair quality trial of patients with heart failure [20].

There are no data to suggest that any β -blocker is superior in any subgroup of patients based on demographic or other factors. Mild COPD and peripheral vascular disease (PVD) are not considered as absolute contraindications and high risk patients may obtain a significant benefit from this therapy. Cardio-selective agents (bisoprolol or metoprolol) are preferable in patients with mild chronic bronchitis (but contraindicated in bronchial asthma). If bronchospasm occurs, the patient will respond to a β_2 agonist such as salbutamol. In PVD too, cardio-selective agents are preferred, and vasodilatory β -blockers such as carvedilol and nebivolol have a theoretical advantage. Both selective and non-selective β -blockers modify the symptoms of hypoglycaemia (except sweating). Recovery from hypoglycaemia may be delayed by non-selective β -blockers as glycolysis is mediated mainly by β_2 receptors. A selective β -blocker, therefore, should be preferred. Those most hydrophilic (atenolol, sotalol) are excreted unchanged by the kidneys, whereas the most lipophilic (propranolol, metoprolol, carvedilol) are metabolised by the liver. Hence, the doses of lipid soluble and water soluble ones need to be reduced respectively in liver disease and in kidney disease.

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