REVIEW ARTICLE

BETA BLOCKERS: AN IMPORTANT THERAPEUTIC MODALITY FOR HYPERTENSIVE DIABETICS

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THE ISSUE

Diabetes mellitus and hypertension are amongst the most common non-communicable diseases in Pakistan effecting nearly 2.7 and 10.8 million individuals respectively[1]. Both diseases are risk factors for cardiovascular disease and death[2]. The prevalence of hypertension is double among diabetics as compared to non-diabetics in the western world[3]. Similar findings have also been reported from Pakistan[4]. The risk of Cardio-vascular death in a hypertensive diabetic is twice that of a non-diabetic hypertensive and four times that of a non-diabetic without hypertension[5]. However it is distressing to know that a very low percentage of the Pakistani population is aware as well as treated for these conditions[1].

Beta-blockers (β-blockers) are well established in the treatment of coronary heart disease and hypertension[6]. However until recently they were considered relatively contraindicated among diabetic patient[7-10]. A recent meta-analysis by Psaty et al[11], which was based on the results of 18 Randomized Controlled Clinical Trials with 50,000 patients, indicated that low dose thiazides (diuretics) and β-blockers are more effective as compared to other agents in reducing total mortality, cardiovascular mortality, stroke and myocardial infarction in individuals with hypertension. The results of this meta-analysis make β-blockers potentially a drug of choice among diabetic individuals with hypertension. Prospective studies have, however, indicated an increased risk of mortality in diabetic patients treated with diuretics[12,13]. As a result of these findings, the use of diuretics as the first line treatment for hypertension in diabetes mellitus has not been recommended[14].

This commentary aims to critically assess the common misconceptions held regarding the use of β-blockers among diabetic hypertensive patients and to explore the recent literature on use of β-blockers among hypertensive diabetic patients.

Misconceptions

A review of the relevant literature shows that the most common misconceptions about the use of β-blockers among diabetic hypertensive patients are (1) fear of developing Insulin resistance or hyperglycemia (2) masking of hypoglycemic symptoms and (3) development of lipid abnormalities.

Insulin resistance or hyperglycemia

Increased insulin resistance with subsequent increased blood glucose levels are frequently cited as an argument in favor of withholding β-blockers from patients with diabetes mellitus. This impression is usually based on two major studies conducted in early eighties; MRC Mild Hypertensive Study[15] and Beta Blocker Heart Attack Trial Research Group (BHAT)[16]. MRC Mild Hypertensive Study[15] indicated that non-selective β-blockers tend to cause a small increase in blood glucose while Beta Blocker Heart Attack Trial Research Group (BHAT)[16] reported an increased prescription of hypoglycemic agents in the Propranalol treated group. This resistance appears to be the result of decreased β_2-stimulated insulin secretion and partly by reduced peripheral uptake of glucose[17]. This effect is diminished with the use of beta selective agents[18], especially if concomitant changes in potassium and weight are avoided[19]. Although this effect seems potentially important, there is little evidence that it is clinical problem. Jonas et al followed a prospective cohort of 2,723 patients with diabetes mellitus and established Coronary Artery Disease (CAD), and found that patients on β-blockers achieved the same levels of glycemic control and had a lower mortality, as compared to diabetics not using β-blockers[20]. The UK Prospective Diabetes Study Group (UKPDS), whose results were published in 1998, has shown no difference in HbA_1C levels between Atenelol (β-blockers) and Captopril (ACE Inhibitor) groups, indicating comparable glycemic control[21].

Masking of hypoglycemic symptoms

One of the most widely used reason for withholding beta blockers for use in diabetic patients is that it may mask the symptoms of hypoglycemia, which may prove fatal[11, 13, 14, 18]. This action is mainly a characteristic of non-selective β-blockers by delaying the return of low blood glucose to normal, along with modifying hypoglycemic signs and symptoms[23]. However, the fact is ignored that hypoglycemic unawareness to a level that may prove dangerous is a problem only in a small number of patients with IDDM. Apart from this, the use of selective β_1-blockers reduces this concern further[5, 13, 18]. A prospective study of 778 elderly diabetic patients with hypertension and CAD found no

increased risk of hypoglycemia with use of beta-blocker [24]. UKPDS also, in a nine-year follow-up comparing the efficacy of Propranalol with Captopril, found no difference between the number and severity of hypoglycemic events in either treatment arms[21], which should be a sufficient evidence to clear this misconception.

Lipid abnormalities

Changes in plasma lipid levels are also one of the grounds for withholding β-blockers in diabetic patients. β-blockers have little effect on LDL cholesterol, but do increase plasma VLDL as well triglyceride levels, along with lowering HDL concentration[25]. Kasiske et al, in a meta-analysis that included 474 trials found that use of β-blockers is associated with an increase of triglycerides by 30mg/dl and decrease of HDL cholesterol by 4 mg/dl on average[26]. This negative surrogate end point (a lab measurement or a physical sign used as a substitute to a clinical endpoint) has been a strong argument used to withhold β-blockers in diabetic patients. These changes are more apparent with non-selective beta-blockers, which may be due to the interference with peripheral lipoprotein lipase, an enzyme responsible for the removal of endogenous triglycerides[13]. However, the clinical significance of β_2-blockade on changing lipid levels is not clear, as non-selective agents such as Timolol and Propranalol have been found very effective in reducing post-MI mortality and re-infarction[27], a benefit that is undiminished in the presence of adverse changes in lipid levels[28]. Samuelsson et al in a prospective study of 686 hypertensives, of which 76% used β-blockers, found that although baseline triglyceride level elevation predicted future CVD events, treatment induced hypertriglycedemia (>15 years of follow-up) did not add to the initial risk[29]. However, even if this argument cannot eliminate the concern regarding these adverse surrogate endpoints, the newer β-blockers such as Labetalol, Acebutalol, Carvedilol and Bisprolol could be considered. It has been observed that blood lipid level changes with these agents are minimal or absent[30, 31]. The use of these agents is favored since β_1- blockade appears to be the active ingredient in cardiovascular protection, and their use can also prevent the emergence of the adverse surrogate endpoints by non selective beta blockade.

DISCUSSION

Apart from blood pressure lowering effect, β-blockers have anti-anginal, anti ischemic and anti-arrhythmic properties, which have been effective in reducing CHD events and deaths as shown by a number of studies[32, 33, 34]. Yusuf et al in a meta-analysis demonstrated 20-25% reduction in recurrent CHD events and mortality in post-MI patients[27]. Interestingly Gunderson et al showed a greater benefit derived by diabetic patients in a secondary prevention trial of myocardial infarction as compared to non-diabetics[35]. Such evidence is compelling to re-think that the potential role of β-blockers in treatment of diabetic hypertensive patents.

Few would now disagree that β-blockers have a useful role in the treatment role of heart failure, which was regarded a contraindication until fairly recent times. However, the role of beta-blockers regarding the treatment of hypertensive diabetics is still emerging. There has been a long held bias against the use of β-blockers in diabetes, especially in favor of ACE- inhibitors. The more frequent and liberal use of ACE inhibitors in diabetes mellitus is mainly due to a) their insignificant effects on triglcerides, HDL and LDL levels[36], b) delayed diabetic nephropathy[37] which appears to be an independent effect of blood pressure control[38], and c) ability to reduce insulin resistance[36]. Thus, it has been advocated that ACE inhibitors should be the first line therapy for hypertension in diabetic patients, due to the lack of ACE inhibitors effecting the above mentioned surrogate end-points. Study results favoring more liberal use of beta-blockers in type II diabetics come from the UKPDS[21, 39]. The UKPDS study has shown that tight control of hypertension in diabetic patients resulted in fewer cardiovascular events and is more important than glycemic control in reducing CVD events and mortality. Importantly, β-blockers were as effective as ACE inhibitors, and there were trends favoring the use of β-blockers, such as fewer myocardial infarctions, fewer strokes and micro vascular diseases, and lower total mortality[21] in β-blockers. β_1 selective blockade appeared to be the active ingredient for these benefits[40].

This review does not advocate the use of β-blockers in every hypertensive diabetic. Reviewing the results of the HANE study[41] in 886 young to middle aged men and women (21-70 years) and the Veteran Affairs Cooperative study in 1105 men[42], Atenolol was found to be best for younger individuals (<60 years) while hydrocholorothiazide and dialtizam were best for older individuals with hypertension. As a result β-blockers should not be the first line therapy for older hypertensives. These conclusions also apply to elderly hypertensive diabetic patients.

In the UKPDS study the most common reason for non-compliance with Atenelol was brochoconstriction[21]; a risk which is greatest with the use of non-selective agents without intrinsic symptomatic activity[23]. Although this risk is minimized with the use of highly selective β_1 blockers, but patients are not totally safe from reversible airway changes[43]. In hypertensive diabetic patients with severe airway conditions, alternative therapy should be offered. Similarly in those patients with IDDM who suffer from hypoglycemic symptom unawareness, β-blockers may be contraindicated with an ACE inhibitor or calcium channel blocker considered[12-14]. In patients with diabetic nephropathy (mainly seen in IDDM patients), ACE inhibitors are recommended to delay the onset of end stage renal-disease[44, 45]. However β-blockers can now be considered for the same role as the results of SOLVD Heart Failure

Study[46] indicated that β-blockers offered more reno-protection as compared to ACE inhibitor. Finally among patients with autonomic dysfunction, the use of β-blockers may be challenginge[13, 14].

An important aspect to consider is the quality of life for the patient. Hypertension in most cases, even associated with type II diabetes is asymptomatic. Thus it is very important to ensure compliance, which can be significantly enhanced with agents that do not produce side effects that impairs quality of life[40]. Although Croog et al looking into quality of life with antihypertensives demonstrated that propranalol, but not captopril decreased quality of life[47], many similar studies comparing beta selective agents with ACE inhibitors found no difference between their effects on quality of life[48-50].

Anticipation of surrogate end points has lead to hesitancy for using beta-blockers in diabetic hypertensives. Despite widely held beliefs, the literature supports the notion that β-blockers should be among the preferred therapy for hypertensive diabetic patients. They cause the reduction of the most important complications of diabetes with hypertension, such as CVD events, strokes and mortality. This paper calls on practitioners to reconsider the role of β-blockers on their menu of options for hypertensive diabetics.

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