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β-BLOCKERS IN HYPERTENSION, DIABETES AND HEART FAILURE

Dr. I. S. Anand, Suman Chaudhary*, Dr. P. H. Prajapati, Dr. D. J. Sen and Dhiren Chaudhary

Department of Clinical Pharmacy, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India.

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***Corresponding Author**
Suman Chaudhary
Department of Clinical Pharmacy, Shri Sarvajanik Pharmacy College, Gujarat Technological University, Arvind Baug, Mehsana-384001, Gujarat, India.

ABSTRACT

β-Blockers (BBs) are an essential class of cardiovascular medications for reducing morbidity and mortality in patients with heart failure (HF). However, a large body of data indicates that BBs should not be used as first-line therapy for hypertension (HTN). Additionally, new data have questioned the role of BBs in the treatment of stable coronary heart disease (CHD). However, these trials mainly tested the non-vasodilating β1 selective BBs (atenolol and metoprolol) which are still the most commonly prescribed BBs in the USA. Newer generation BBs, such as the vasodilating BBs carvedilol and nebivolol, have been shown not only to be better tolerated than non-vasodilating BBs, but also these agents do not increase the risk of diabetes mellitus (DM), atherogenic dyslipidaemia or weight gain. Moreover, carvedilol has the most evidence for reducing morbidity and mortality in patients with HF and those who have experienced an acute myocardial infarction (AMI). This review discusses the cornerstone clinical trials that have tested BBs in the settings of HTN, HF and AMI. Large randomised trials in the settings of HTN, DM and stable CHD are still needed to establish the role of BBs in these diseases, as well as to determine whether vasodilating BBs are exempt from the disadvantages of non-vasodilating BBs.

KEYWORDS: β-Blockers, heart failure, therapy for hypertension, coronary heart disease, atenolol and metoprolol, diabetes mellitus, myocardial infarction.

Hypertension and diabetes

Hypertension (HTN) is a largely asymptomatic disease affecting around 50 million Americans and one billion people worldwide.[1–3] Patients with HTN are at an increased risk for heart failure (HF), stroke, renal disease and acute myocardial infarction (AMI).[1,3] Although HTN is the most common primary care diagnosis in the USA, it remains undertreated.[3]

Pharmacological treatment of HTN includes the class of medications known as β-blockers (BBs). The various agents in this class differ substantially in their pharmacological properties. Atenolol, metoprolol, bisoprolol and nebivolol are β_1 selective BBs, preferentially inhibiting cardiac β_1 receptors as opposed to β_2 receptors. Carvedilol, in contrast, inhibits β_1, β_2 (postsynaptic and presynaptic) and α_1 receptors, upregulates cardiac muscarinic M_2 receptors and possesses antioxidant effects.[4–7] Additionally, nebivolol (which is highly selective for the β_1 receptor) also has vasodilating properties due to its ability to increase the endogenous production and release of endothelial nitric oxide (NO).

Atenolol

The Medical Research Council (MRC) elderly HTN treatment trial was a placebo-controlled, single-blind trial that randomised 4396 patients between the age of 65–74 years to receive either hydrochlorothiazide (HCTZ; plus amiloride), atenolol or placebo.[9] Despite the fact that atenolol reduced blood pressure (BP) to levels below that of placebo (approximately −10/7 mm Hg over 60 months), patients receiving atenolol, compared with patients assigned to placebo, did not have a significant reduction in any cardiovascular (CV) end point during 5.8 years of the study (stroke (relative risk (RR) 0.82, 95% CI 0.60 to 1.14, p=0.25); coronary heart disease (CHD; RR=0.97, 95% CI 0.73 to 1.30, p=0.85); CV events (RR=0.96, 95% CI 0.77 to 1.19, p=0.69); CV death (RR=1.06, 95% CI 0.81 to 1.39, p=0.66) and total death (RR=1.08, 95% CI 0.88 to 1.34, p=0.46)). On the other hand, patients receiving HCTZ plus amiloride had a significantly reduced risk of stroke (31%, 95% CI 3% to 51%, p=0.04); CHD events (44%, 95% CI 21% to 60%, p=0.0009) and all CV events (35%, 95% CI 17% to 49%, p=0.0005). Even after adjusting for lower than atenolol-induced BP changes, HCTZ plus amiloride still led to a lower risk of CV events (p=0.01) than atenolol. Despite this fact, both the HCTZ plus amiloride and the atenolol groups compared with placebo had significantly increased withdrawals per 1000 patient years due to impaired glucose tolerance 6.9 (HCTZ)

versus 2.7 (placebo) per 1000 patient years and 5.8 (atenolol) versus 2.7 (placebo) per 1000 patient years.

Metoprolol

The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial was a post hoc analysis of the metoprolol arm of the HAPPHY study.[25] It focused on male patients between 40 and 64 years of age who had a history of HTN with an untreated diastolic BP of over 100 mm Hg and investigated the effects of metoprolol on the incidence of CHD events (sudden cardiac death (SCD) and MI) compared with thiazide diuretics. Patients receiving metoprolol were significantly less likely to experience a CHD event as compared with those on diuretics (111 vs 144 cases, p=0.001, corresponding to 14.3 vs 18.8 cases/1000 patient years; RR=0.76 at the end of the trial; 95% CI 0.58 to 0.98). Moreover, the incidence of SCD, fatal and non-fatal MI was reduced with metoprolol as compared with the diuretic treatment (p=0.024). Similarly, the risk of silent MI (p=0.016) and first definite non-fatal MI (p=0.0034, 10.6 vs 14.3 cases/1000 patient years at the end of the trial) were also lower with metoprolol. It is important to note that all baseline characteristics, including BP, were similar in the 255 participants who had a CV event versus those who did not. This suggests that the benefit demonstrated by metoprolol occurred due to something other than an anti-HTN effect. Despite these beneficial results, MAPHY should be interpreted with caution because of its post hoc subgroup design.

Meta-analyses

Almost two decades ago, conflicting meta-analyses came out, just a year apart from each other. While the first suggested BB therapy was appropriate as a first-line antihypertensive agent, another meta-analysis published a year later indicated that BBs are indeed inappropriate first-line antihypertensives in uncomplicated HTN in elderly patients.[26,27] A recent meta-analysis of 13 randomised controlled trials (RCTs) encompassing 105 951 patients with primary HTN indicated that the RR of stroke was higher for BBs than other anti-HTN medications (RR=16%; 95% CI 4% to 30%);[28] in these meta-analyses, atenolol was the most frequently utilised BB for first-line treatment of HTN. The meta-analysis concluded that BBs (mainly atenolol) increased the risk of stroke and were less effective than other antihypertensives as first-line therapy.

Another meta-analysis evaluated the effects of atenolol on morbidity and mortality in patients with HTN[29] and demonstrated that although there was a significant difference in the BP

lowering effect of atenolol and placebo, this anti-HTN effect of atenolol failed to translate into a significant reduction in the all-cause mortality (RR=1.01, 95% CI 0.89 to 1.15). Similarly, CV mortality (RR=0.99, 95% CI 0.83 to 1.18) and MI (RR=0.99, 95% CI 0.83 to 1.19) were not significantly different between the placebo and the atenolol groups. However, the risk of stroke was decreased, but not significantly, in the atenolol group as compared with placebo (RR=0.85, 95% CI 0.72 to 1.01). When compared with other anti-HTN agents, there was no significant difference in the anti-HTN effect; there was, however, a significantly higher mortality in the atenolol group (RR=1.13, 95% CI 1.02 to 1.25). Moreover, there was a higher risk of CV mortality (RR=1.16, 95% CI 1.00 to 1.34) and stroke (RR=1.30, 95% CI 1.12 to 1.50) with atenolol as compared with the other antihypertensives. Thus, this meta-analysis illustrated that although atenolol produces a marginal benefit as compared with placebo with regard to stroke prevention, it does not hold any benefit over other antihypertensives. The authors concluded that the results of this meta-analysis question whether atenolol should be used as a first-line anti-HTN agent.

Heart failure

An estimated 5 million people in the USA have HF and more than 550 000 people are diagnosed with this condition each year.[33,34] During the past two decades, based on impressive RCT data, BBs have become one of the most important pharmacological treatments for improving the CV prognosis for patients with systolic HF. It has been shown that the most frequently prescribed BBs in patients with HF in the USA and in Europe are metoprolol and atenolol.[35,36] Among 11 326 adults who survived a hospitalisation for HF, pharmacy records revealed that the most commonly prescribed BBs in descending order were metoprolol tartrate (43.2%), atenolol (38.5%), carvedilol (11.6%) and other BBs (6.7%).[36] A recent national prescription audit of BBs dispensed in the USA in 2011 indicated that the most commonly prescribed BBs in descending order are metoprolol tartrate/succinate (71.9 million), atenolol (36.3 million), carvedilol (24 million), nebivolol (15 million) and bisoprolol (9 million; figure 1). Disturbingly, these BB choices in the patients with HF are not evidence-based.

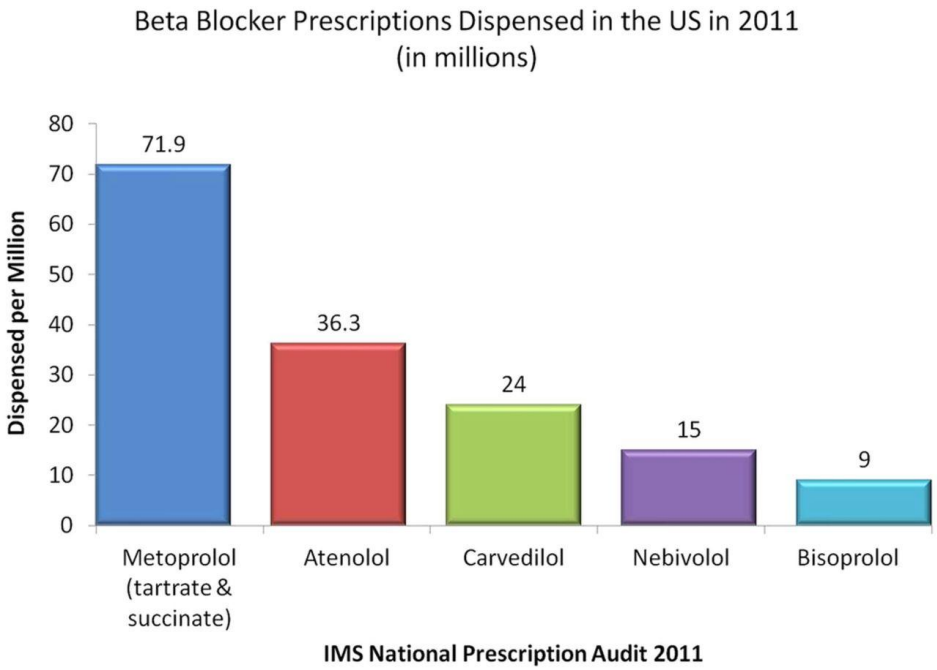

Figure 1: β-Blocker prescriptions dispensed in the USA in 2011 (in millions).

Metoprolol

Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) was a double-blind, randomised, placebo-controlled study testing metoprolol CR/XL (target dose was 200 mg once daily) in 3991 patients with chronic HF (NYHA functional class II–IV and LVEF of 40% or less).[40] Metoprolol significantly reduced all-cause mortality by 34% (RR=0.66, 95% CI 0.53 to 0.81, p=0.00009). However, there was an increase in mortality with metoprolol versus placebo in the US geographical region (HR=1.05, 95% CI 0.71 to 1.56), which included almost one-third of the mortality events in MERIT-HF. An increase in mortality with metoprolol versus placebo is also supported by the Metoprolol in Dilated Cardiomyopathy (MDC) trial, which showed an 18% increased risk of death, although not statistically significant, with metoprolol versus placebo in patients with dilated cardiomyopathy (RR=1.18, 95% CI 0.66 to 2.09, p=0.57).[41] Thus, while geographical disparity must be interpreted with caution, there does not seem to be evidence in the USA (US patients and how clinicians treat them in the USA may differ from that outside the USA) supporting the use of metoprolol in patients with HF.

Bisoprolol

The Cardiac Insufficiency Bisoprolol Study (CIBIS)-I trial was conducted in 641 patients with a history of HF and a LVEF of <40%.[42] These patients were randomised to receive either bisoprolol or placebo in addition to diuretic and vasodilator therapy. There was no

significant difference between the groups' mortality (RR=0.80, 95% CI 0.56 to 1.15, p=0.22), SCD or death due to ventricular tachycardia (VT) or ventricular fibrillation (VF). Conversely, the rate of hospitalisation for CV decompensation was lower in the group receiving bisoprolol (p<0.01). Non-lethal events, such as acute pulmonary oedema, HF without pulmonary oedema and cardiogenic shock, that is, pump failure, were less commonly seen in the bisoprolol group (p<0.001). Documented cases of VT and VF were also fewer (p=0.03) in the bisoprolol group and treatment withdrawals were similar across both groups. This study supports the beneficial effects of bisoprolol in patients with a history of HF.

CONCLUSION

Numerous trials in patients with HTN indicate that atenolol should not be used as a first-line anti-HTN agent. Further trials are required to determine the optimal BB for use in patients with HF and AMI. Until then, the evidence strongly suggests that carvedilol may have an advantage over the first generation BBs in patients with HF and AMI, as carvedilol has the greatest amount of evidence for reducing CV morbidity and mortality in these settings and is effective in HTN with less adverse effects on lipids and promotion of DM.

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