ABSTRACT

BACKGROUND: Many diabetics develop hypertension, and it is a major risk factor for cardiovascular and microvascular complications.

OBJECTIVE: To review a case study of a patient with poorly controlled hypertension and diabetes.

SUMMARY: Further assessment of this case study shows that the patient has poorly controlled hypertension, despite multiple medications. The patient also has metabolic syndrome complicated by diabetes, microalbuminuria and peripheral arterial disease. The patient’s hypertension treatment options must be evaluated in light of the fact that polypharmacy has made it more difficult for her to achieve glycemic control. A panoply of drugs and drug classes are available from which to choose: diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists. New vasodilatory beta-blockers reduce adverse drug reactions and produce beneficial effects on arterial vasculature. Various beta-blockers’ effects on insulin sensitivity are compared.

CONCLUSION: Older beta-blockers have been shown to have detrimental effects on glucose or lipid parameters. Newer agents such as nebivolol do not impact lipid, glucose, insulin, or high-density lipoproteins. Instead, nebivolol stimulates endothelial nitric oxide release in renal arteries and improves renal function.

KEYWORDS: Hypertension, Diabetes, Beta-Blockers, Nebivolol, Third-generation beta-blockers, Patient assessment

J Manag Care Pharm. 2007;13(5):S17-S19

Case Study: The Link Between Hypertension and Diabetes

George L. Bakris, MD, FACP, FAHA, FASN, and Edgar R. Gonzalez, PharmD, FASHP, FASCP

M any diabetics develop hypertension. It is a major risk factor for cardiovascular and microvascular complications and often results from nephropathy in type 1 diabetes. Hypertension may be present as part of metabolic syndrome (i.e., obesity, hyperglycemia, and dyslipidemia), which contributes to higher rates of cardiovascular disease in type 2 diabetics. Clinical trials confirm that lowering blood pressure (BP) to less than 140/80 mm Hg in diabetic patients reduces cardiac events, stroke, and nephropathy. When treating hypertension in diabetics, clinicians target a lower BP—130/80 mm Hg—in an attempt to reduce the likelihood of cardiac events and stroke.1

For many years, clinicians believed beta-blockade should be avoided in diabetics. A 1990 study published in the European Heart Journal compared diabetic patients with nondiabetic patients to determine the effect of beta-blocker therapy following acute myocardial infarction (MI). Their large multicenter cohort (N=2,024) included 340 diabetics, 281 of whom survived hospitalization. One year later, the mortality rate was 10% for nondiabetics, and 7% and 13% for those taking and not taking beta-blockers, respectively. For diabetics overall, mortality was 17%, but diabetics discharged on beta-blockers had a mortality of 10%, compared with 23% for diabetics not on beta-blockers. In diabetics, pulmonary congestion was more prevalent than in nondiabetics, regardless of whether they were taking beta-blockers. Beta-blocker use independently predicted 1-year cardiac survival following hospital discharge for all diabetics. These data began to highlight the importance of using beta-blockade among diabetic patients after acute MI.2

In this case study, assessment shows that patient RM has poorly controlled hypertension, despite multiple medications. RM has metabolic syndrome complicated by diabetes, microalbuminuria, and peripheral artery disease. Her antihypertensive treatment options must be evaluated in light of the fact that RM has complained that the addition of metoprolol XL made it more difficult for her to achieve glycemic control. A panoply of drugs and drug classes are available from which to choose: diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists account for more than 130 antihypertensive medications. The new beta-blockers must fit into this crowded field. Traditional beta-blockers, while reducing cardiovascular events, may have unwanted metabolic effects. New vasodilatory beta-blockers reduce adverse drug reactions and produce beneficial effects on arterial vasculature. Carvedilol has alpha-blocking actions; nebivolol stimulates nitric oxide (NO). These new agents may be especially useful in heart failure; carvedilol is indicated for both acute and chronic heart failure.3

The double-blind, randomized Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives
(GEMINI) trial looked at carvedilol’s possible metabolic effects, comparing it with immediate-release metoprolol tartrate. Both drugs were administered twice daily to 1,235 patients with hypertension and type 2 diabetics receiving an ACEI or an ARB. Thus, renin angiotensin system inhibition was ubiquitous. Study subjects’ BPs were in the prehypertensive to hypertensive range, and glycated hemoglobins (A1Cs) were between 6.5% and 8.5%. Metoprolol doses were initiated at 50 mg and carvedilol was administered at 6.25 mg, each twice daily. Both drugs were titrated up as necessary; the mean daily dose of metoprolol was 256 mg and carvedilol was 35 mg. The trial’s primary endpoint was the difference in the change from baseline in A1C at 5 months. Although both groups’ BPs were similar, mean A1C increased with metoprolol, but not with carvedilol. Carvedilol-treated patients also had improved insulin sensitivity, but metoprolol-treated patients did not, with more than two thirds of study subjects achieving a BP of ≤130/80 mm Hg. Progression to microalbuminuria was less frequent with carvedilol than with metoprolol.

Beta-blockers are used less in hypertensive patients with diabetes, kidney disease, and stroke. Older beta-blockers like atenolol and metoprolol have been shown to have detrimental effects on glucose or lipid parameters. Nebivolol does not affect lipid, glucose, insulin, or high-density lipoprotein cholesterol (HDL-C). It stimulates endothelial NO release in renal arteries and improves renal function.

**Metabolic Effects of Beta-Blockers**

The figure compares various beta-blockers’ effects on insulin sensitivity. Celiprolol, carvedilol, and dilevalol all improve insulin sensitivity. The traditional, vasoconstricting beta-blockers do not.

Triglyceride elevation and low-density lipoprotein cholesterol elevations do occur with propranolol, atenolol, and metoprolol. A study by Rizos et al. conducted in Europe and published in 2003 compared 2 beta-blockers (nebivolol and atenolol) in combination with a statin (pravastatin) to determine if interference with lipid metabolism differed. Thirty hyperlipidemic patients with concurrent hypertension were treated with either atenolol 50 mg daily (n = 15), or nebivolol therapy 5 mg daily (n = 15). After 12 weeks of therapy, each group added pravastatin 40 mg daily. Atenolol increased triglyceride levels by 19%, nebivolol increased HDL-C by 8% and decreased triglyceride levels by 5%, but these findings were not significant. Triglycerides kill the beta-cells in the pancreas and are thus important.

Fibrinogen levels were equally and not significantly decreased in both groups by 9% and 7%, respectively. Serum high-sensitivity C-reactive protein levels also fell in atenolol patients by 14% and in nebivolol patients by 15%. In the nebivolol group, glucose levels remained the same, while insulin levels were reduced by 10% and the homeostasis model assessment index (a model of insulin sensitivity calculated using fasting glucose levels multiplied by fasting insulin levels and divided by 22.5) was reduced by 20%. Measures of inflammation, homocysteine levels, and C-reactive protein fell 17% and 43%, respectively.

Pooled analysis of 3 pivotal trials looked at the effects of nebivolol on glucose and lipid levels. At the probable maximum dose of 10 mg, no significant change in triglycerides was found.

**Other Effects of Nebivolol**

Researchers have looked at many of the other effects of nebivolol compared with older beta-blockers, often using animal studies. They have found the following:

- Several beta-blockers, including nebivolol, exert their vasodilatory action through the 5-HT1A receptor/NO pathway and that treatment with these beta-blockers may protect against renal endothelial injury in hypertension.
- With respect to renal plasma flow, in the presence of a NO blocker, vasodilation does not occur. But in its absence, renal blood flow increases.

Erectile dysfunction (ED) is a serious concern and can affect adherence to medications. In a recent study, 44 men aged 31 to 65 years with essential hypertension received atenolol, metoprolol, or bisoprolol for 6 months or more. Results of the International Index for Erectile Function questionnaire revealed that 65.9% experienced beta-blocker-induced ED. After switching to an equipotent dose of nebivolol for 3 months, 11 of the 44 (65.9%) reported their erectile function had normalized. This outcome may be due to increased NO availability.

Use of beta-blockers in the elderly also raises special concerns, especially with regard to left ventricular function. Numerous trials (the U.S. Carvedilol Trials, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure [MERIT-HF], Cardiac Insufficiency Bisoprolol Study [CIBIS], and Carvedilol Prospective
DISCLOSURES

This article is based on a presentation funded by an educational grant from Forest Pharmaceuticals. The authors disclose that they have received honoraria from Forest Pharmaceuticals for participation in this supplement. George L. Bakris discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: AstraZeneca, Abbott, Boehringer-Ingelheim, BMS/Sanofi-Aventis, Kos, GlaxoSmithKline, Merck, Novartis, Lilly, Walgreens (Formulary Committee), NIH (NIDDK/NHLBI), and Atlas Foundation. Edgar R. Gonzalez discloses the following commercial/financial relationships through grant/research support, consultant services, speakers bureaus, and/or advisory boards: Amgen and King Pharmaceuticals.

REFERENCES


Case Study: The Link Between Hypertension and Diabetes

Randomized Cumulative Survival Study Group [COPERNICUS]14 have used different beta-blockers. In patients with heart failure, beta-blockers represent a clear benefit for reducing mortality. Nebivolol’s utility in senior populations was addressed directly in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial15; its 2,128 study participants were all older than 70 years (mean age 76 years) and had heart failure. This study more closely approximated a real-world population of heart-failure patients than did previous beta-blocker studies because its participants tended to be older. Most were male, and two thirds of them had clear systolic dysfunction. Most of them had been prescribed ACE inhibitors and diuretics, and approximately 40% were taking digoxin. Approximately 25% were also taking aldosterone antagonists.

The primary outcome measure—all-cause mortality or cardiovascular hospitalizations—was chosen to reflect quality of life in the elderly. Nebivolol dramatically reduced the risk for all-cause mortality and cardiovascular hospitalizations. Beneficial effects appeared after 6 months and were sustained with longer treatment durations. In participants younger than 75 years, nebivolol conferred clear benefit even when ejection fraction exceeded 35%. Nebivolol is effective and well tolerated in elderly patients with heart failure.15

Dr. Gonzalez: Microalbuminuria is a marker for endothelial dysfunction. What do you believe nebivolol’s effect on microalbuminuria would be?

Dr. Bakris: Studies have not been done, but my opinion based on what I have seen to date is that its benefit would probably be more profound than that seen with carvedilol. Its antioxidant effect in combination with its NO effect should reduce microalbuminuria independent of blood pressure dramatically compared with other beta-blockers. It needs to be tested also against an ACEI. Its utility may be for the elderly who, if they have elevated creatinine levels, cannot take an ACEI, but we must wait for controlled studies to confirm this.

Dr. Gonzalez: Our patient RM said when she presented that her glucose became more difficult to control after starting metoprolol XL. What message is in her insistence on this point?

Dr. Bakris: We should listen to patients. Because, in fact, some of the best ideas I’ve had to build my career came from patients.