Off-Label Drug Uses

Benazepril: Nephropathy (Non-diabetic)

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

Data from controlled trials support the use of benazepril for non-diabetic nephropathy, demonstrating significant reductions in proteinuria and lowering the risk of chronic kidney disease (CKD) progression.

The KDIGO guidelines for the Evaluation and Management of CKD and Management of Blood Pressure in CKD recommend therapy with an ACE-inhibitor (ACE-I) or angiotensin renin blocker (ARB) in diabetic and non-diabetic adult patients with CKD and urine albumin excretion of 4,300 mg per 24 hours (or equivalent). There is insufficient evidence to recommend the combination of an ACE-I with ARBs for the prevention of CKD progression.

The Eighth Joint National Committee (JNC-8) Guideline for the Management of Blood Pressure in Adults recommends the use of an ACE-I or ARB as antihypertensive regimens to improve kidney outcomes in all adults with CKD and hypertension regardless of race, proteinuria, or diabetes status.

RATIONALE

Nephropathy, damage to or disease of the kidney, may lead to CKD, which has been defined as abnormalities of kidney structure or function, present for longer than 3 months, with implications for

health. Nephropathy may be caused by a variety of conditions, most commonly diabetes mellitus, hypertension, glomerulonephritis, and polycystic kidney disease. After diagnosis of CKD, uncontrolled blood pressure and proteinuria are the crucial factors associated with the potential decline in renal function and development of end stage renal disease (ESRD). Both factors are influenced by angiotensin II, a potent vasoconstrictor that causes an increase in blood pressure, as well as glomerular hypertension. Glomerular hypertension leads to proteinuria and, ultimately, to a reduced glomerular filtration rate.

There is strong evidence that blockade of the renin-angiotensin aldosterone system (RAAS) is a blood pressure (BP)-lowering strategy that may also be effective in reducing the risk of kidney and cardiovascular disease in the presence of albuminuria. ACE-Is, including benazepril, inhibit the production of angiotensin II in order to decrease systemic blood pressure and glomerular pressure.^{1,2}

POPULATION

Adults with nondiabetic nephropathy

DOSING STUDIED

Oral: Initial: 10 mg once daily. If tolerated well, may increase to 10 mg twice daily.^{3,4}

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DISCUSSION

Guidelines

Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of CKD; KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD

The KDIGO guidelines note that the management of CKD progression is influenced by the multiple factors associated with the disease. Thus, strategies for management include general lifestyle measures aimed at improving cardiovascular health, blood pressure control, and the interruption of the renin-angiotensin aldosterone system. The guidelines provide a strong recommendation based on moderate quality evidence for therapy with an ACE-I or ARB in diabetic and non-diabetic adult patients with CKD and urine albumin excretion of 4,300 mg per 24 hours (or equivalent). Based on very low quality evidence, they suggest the use of an ARB or ACE-I in diabetic adult patients with CKD and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent). There is insufficient evidence to recommend the combination of an ACE-I with ARBs for the prevention of CKD progression.¹ These guideline statements were created to be consistent with the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in CKD, which provide the rationale and support for the statements.² Both ACE-Is and ARBs have been shown to reduce urine albumin levels; microalbuminuria (excretion of 30 to 300 mg per 24 hours) and macroalbuminuria (>300 mg per 24 hours) are known risk factors for the progression of cardiovascular and CKD progression. Data from RCTs suggest that these drugs may help reduce the progression of CKD and possibly CVD in patients with microalbuminuria and prevent “hard outcomes” (eg, doubling of serum creatinine [SCr], kidney failure, or death) in patients with macroalbuminuria.

Eighth Joint National Committee (JNC-8) Guideline for the Management of Blood Pressure in Adults

For all adults with CKD and hypertension (regardless of race, proteinuria, or diabetes status), JNC-8 guidelines recommend that an ACE-I or ARB should be included in antihypertensive regimens to improve kidney outcomes. This recommendation is based primarily on data reporting beneficial kidney outcomes, as there is less evidence favoring ACE-Is or ARBs for cardiovascular outcomes in patients with CKD. Neither ACE-Is nor ARBs improved cardiovascular

outcomes for CKD patients compared with a β -blocker or calcium channel blockers. There were no RCTs in the evidence review that directly compared ACE-Is to ARBs for any cardiovascular outcome. However, both are renin-angiotensin system inhibitors and have been shown to have similar effects on kidney outcomes.⁵

Controlled Trials

Advanced Chronic Kidney Disease

In a double-blinded, placebo-controlled study, 422 adult non-diabetic patients with advanced CKD (SCr, 1.5 to 5 mg/dL, and creatinine clearance [CrCl], 20 to 70 mL/min/1.73 m²) and persistent proteinuria (>0.3 g/day for at least 3 months) were enrolled. Patients were divided into 2 treatment arms based on SCr levels: group 1 (SCr, 1.5 to 3 mg/dL; *n* = 141) and group 2 (SCr, 3.1 to 5 mg/dL; *n* = 281). All patients entered an 8-week run-in phase during which benazepril 10 mg daily was administered for 4 weeks and increased to 10 mg twice daily for an additional 4 weeks if SCr remained unchanged or was reduced by less than 30%, serum potassium levels were below 5.6 mmol/L, and no adverse events occurred. At the end of the run-in phase, benazepril was discontinued for 3 weeks; all the patients in group 1 received benazepril (10 mg twice daily) and group 2 was randomized to receive benazepril (10 mg twice daily) or placebo. Ethics prohibited the use of placebo in group 1 as the renoprotective effect of ACE inhibitors is known in this group. All patients were advised to reduce salt intake (5 to 7 g of NaCl daily) and to eat 0.5 to 0.7 g of protein/kg of weight daily. The primary endpoint was the first event of a doubling of the SCr from baseline level, ESRD (defined as need for long-term dialysis or renal transplantation), or death. Secondary endpoints included changes in urinary protein excretion and progression of renal disease. Clinical and laboratory assessments occurred every 2 weeks for the first months and every 3 months thereafter. After the run-in phase, 104 and 224 patients entered the study phase in groups 1 and 2, respectively. Two patients in group 1 and 9 patients in group 2 (5 in the benazepril group and 4 in the placebo group) were lost to follow-up. The mean length of follow-up was 3.4 years (range, 2 to 5 years). The primary endpoint was reached in 22%, 41%, and 60% of patients receiving benazepril in groups 1 and 2 and placebo, respectively. When compared to placebo, treatment with benazepril in group 2 resulted in a 43% reduction in the risk of primary endpoint

($P = .005$). Despite receiving the same dose, benazepril-treated patients in group 2 had poorer renal outcomes than those in group 1 ($P = .003$). When individual components of the endpoint were considered, benazepril lowered the risk of doubling SCr by 51% ($P = .02$) and the risk of ESRD by 40% ($P = .02$). In group 2, a significant reduction in the level of proteinuria occurred in the benazepril group compared to placebo (52% vs 20%; $P < .001$), as well as a 23% reduced rate of decline in renal function (SCr, -0.09 dL/mg/year vs -0.11 dL/mg/year; $P = .02$). There were similar incidences of adverse effects in between benazepril and placebo patients in group 2.³

In a prospective, double-blinded, placebo-controlled, multicenter trial, 583 adult patients with chronic renal insufficiency (SCr, 1.5 to 4.0 mg/dL, and 24-hour estimated CrCl, 30 to 60 mL/min) were randomized to receive either benazepril (10 mg daily) or placebo for 3 years. Patients had CKD of various origins, including diabetic nephropathy (21 cases), interstitial nephritis (105 cases), nephrosclerosis (97 cases), polycystic kidney disease (64 cases), and miscellaneous/unknown disorders (104 cases). Severity of kidney dysfunction as measured by CrCl was defined as mild (46 to 60 mL/min) or moderate (30 to 45 mL/min). Clinical and laboratory assessment was performed every 2 weeks for the first month, monthly for 2 months, and every 3 months thereafter. The primary endpoint was the time to double the SCr or the necessity for dialysis. At the end of 3 years, 31 patients in the benazepril group and 57 in the placebo group reached the primary endpoint ($P < .001$), representing a 53% (95% confidence interval [CI], 27% to 70%) reduction in risk in the benazepril group overall, and a 71% (95% CI, 21% to 90%) and 46% (95% CI, 12% to 67%) reduction in those with mild and moderate renal dysfunction, respectively. The best results occurred in men; those with diabetic nephropathy, glomerular disease, or disease of an unknown origin; and those with a baseline urinary protein excretion above 1 g per 24 hours. The drug did not appear beneficial in patients with polycystic disease. The length of the study may not have

been long enough to identify the benefits and risks of benazepril in patients with nephrosclerosis, interstitial nephritis, or miscellaneous other nephropathies.⁴

RISK/BENEFIT CONSIDERATIONS

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Benazepril has a boxed warning regarding use in pregnancy during the second and third trimesters. ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, benazepril should be discontinued as soon as possible.

In general, benazepril is well tolerated. Some adverse reactions include hyperkalemia, dry cough, acute renal failure, and hypotension. Angioedema of the face, extremities, lips, tongue, glottis, or larynx is a rare but serious reaction requiring immediate discontinuation and medical treatment.

REFERENCES

1. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2012. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Accessed June 29, 2015.
2. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. 2012. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO_BP_GL.pdf. Accessed June 29, 2015.
3. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med*. 2006;354(2):131-140.
4. Maschio G, Alverti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med*. 1996;334(15):939-945.
5. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520 [erratum in *JAMA*. 2014;311(17):1809]. ■