Diabetic Nephropathy Prevention and the Role of Managed Care Pharmacists

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OBJECTIVE:

To demonstrate the practical value of the managed care pharmacist in drug selection. The managed care pharmacist can provide valid scientific data to the physician that will turn aid in appropriate drug selection for each patient as an individual.

DATA SOURCES:

Scientific journals and texts.

STUDY SELECTION:

Not applicable.

DATA EXTRACTION:

Not applicable.

DATA SYNTHESIS:

Managed care activities are receiving increased publicity, most of which is negative in nature. Managed care pharmacists can

generate a refreshingly positive demonstration of managed care. Their usefulness in drug selection can be effective whether care is concurrent, retrospective or prospective. Managed care pharmacists can use drug use data, disease state, and therapy knowledge to make a positive impact on how drugs are selected. Each patient is an individual with his or her own set of risks and experiences. Barriers are present to true participation in drug selection responsibilities but pharmacists can offer viable unbiased information on new drugs and drug selection.

CONCLUSION:

Prevention of diabetes complications, namely diabetic nephropathy, has a role for the managed care pharmacist. The intervention by the pharmacist can potentially

improve therapy as well as prevent other drug therapies that would be needed as the diabetic kidney fails leading to end stage renal disease. This intervention to better therapy has a dual benefit. The more expensive and inappropriate calcium antagonist used in patients with diabetes can be exchanged for better therapy in the ACE inhibitors, which is also much less expensive. Pharmacists need only to take the initiative and make an effort to promote "good therapy."

KEY WORDS:

Diabetic nephropathy, Managed care, ACE inhibitors, Calcium channel blockers, Disease management

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Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States. Diabetic nephropathy affects about 40% of patients with type I diabetes who have had diabetes for 20 years or more and 4%-20% of patients with type II diabetes.¹ According to Bakris and Stein,² 35% of all patients with diabetes will develop diabetic nephropathy sometime during their lifetime. Clearly, it is important to recognize the earliest stages of diabetic nephropathy, namely the detection of microalbuminuria, and start appropriate therapy.¹ Clinical studies²⁻³¹ have looked at calcium antagonists and ACE inhibitors as possible agents to treat, as well as prevent, diabetic nephropathy. This article will discuss and compare these two drug classes in terms of their roles in treating and preventing diabetic nephropathy.

PATHOPHYSIOLOGY

Diabetes affects the kidneys in many ways; diabetic nephropathy encompasses all the structure changes, i.e., lesions within the kidney and the changes in kidney functioning such as renal blood flow (RBF) regulation and glomerular filtration rate (GFR) as measured by creatinine clearance (CrCl).

At the onset of type I diabetes, RBF and GFR generally are elevated with no apparent histological abnormalities. Glycemic control is a major determining factor in the time required to produce histological changes such as glomerular basement membrane thickening and increased mesangial matrix material build-up. These two changes also cause renal

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hypertrophy. Progressive histological damage may continue over about a 10-year period and lead to renal hyperfiltration. The persistent increase in filtration rate leads to an increase in intraglomerular capillary pressure; the initial build-up of glomerular material causes a subsequent morphological change in kidney size. This hypertrophic stage is slowly reversed due to the constant pressure on the filtering system. The damage caused by renal hyperfiltration with increased intraglomerular capillary pressure slowly causes irreversible damage to the kidney nephron cells, to a point where the kidneys start to lose form and function. These histological changes are grossly manifested as a reduction in kidney size from hypertrophy to atrophy. DeFronzo¹ has estimated that it may take approximately 10 years to progress to kidney hypertrophy and another 15 years to kidney atrophy. Some time during this 15 years albuminuria is detected through a laboratory test used to indicate the first signs of kidney damage. Eventually, the elevated RBF and GFR return to normal. This last sign indicates the point of no return in preventing the onset and progression of ESRD.¹ The constant pressure on the mesangial matrix, along with hyperfiltration, eventually causes the deterioration of the filtering membranes and destruction of both kidney function and tissue. Development of microalbuminuria may take 20–25 years. Anderson et al.³ give a time line of 6–9 years, but this may not represent the years diabetes went undiagnosed. Other nonhistological changes include an increase in sodium (Na) retention by the kidney and increased vascular reactivity in the presence of vasoconstrictors such as norepinephrine and angiotensin-II. Also noted at this time is the absence of myogenic reflex control of efferent arteriolar tone and subsequent blood flow into the glomerular capillaries.²

The onset of microalbuminuria (30–300 mg/24 hr) is the point at which drug therapy is started by most physicians, but this critical danger sign often is not detected because it is not routinely measured. Urine dipsticks detect gross protein measurements called macroproteinuria (>300 mg/24 hr). Microalbuminuria and macroproteinuria should not be compared for this measurable difference because the disease process is more advanced with the presence of macroproteinuria.⁴ Tight glycemic control (i.e., maintenance of postprandial glucose less than 140 mg/dL), may prevent the onset of microalbuminuria.^{5,6} The Diabetes Control and Complication Trial⁷ showed that tight glycemic control vs. conventional control had no significant effect on the progression of existing microalbuminuria. Risk factors for development of diabetic nephropathy include a family history of cardiovascular disease,⁸ a history of HbA_{1c} > 9.5,⁹ and the presence of microalbuminuria.

Insulin-dependent diabetes mellitus (IDDM) patients with microalbuminuria that progresses to clinical proteinuria have a cardiovascular disease mortality rate that is 37 times higher than the general population.^{10,11} Jensen et al.¹² showed that blood pressure did not correlate with the presence or absence of microalbuminuria. This indicates that hypertension (HTN) is a consequence and not a cause of diabetic renal disease. However, hypertension is an important factor in the progression of renal disease.¹³

The pathologic hallmark of diabetic renal disease is mesangial matrix expansion with thickened glomerular basement mem-

brane. However, about one in five IDDM patients without hypertension or microalbuminuria have mesangial matrix expansion. This may indicate that progression to diabetic nephropathy can occur in the absence of clinical signs and symptoms.¹⁴ The duration of diabetes correlates poorly with the degree of mesangial matrix expansion;^{15,16} however, this is only an indirect factor if glycemic control is poor.

Angiotensin-II, endothelin, and vasopressin are all associated with mesangial cell proliferation and matrix expansion. Angiotensin-II is the primary problem in the pathophysiologic progression of diabetic nephropathy.^{17,18}

TREATMENT WITH CALCIUM ANTAGONISTS

Intracellular calcium concentrations are elevated in the hypertensive patient. This, in turn, leads to an increase in vasoconstriction responsiveness to vasoactive hormones such as angiotensin-II and norepinephrine in vascular smooth muscle and mesangial cells. This pathophysiologic abnormality provides the rationale for the use of calcium antagonists. If the calcium is blocked, its effects on angiotensin-II also are eliminated. Unfortunately, not all of the calcium antagonists work. For instance, Hill et al.¹⁹ offered evidence suggesting that more than an increase in systolic calcium is responsible for cell proliferation.

The dihydropyridines-class calcium antagonists do not appear to be consistent in their ability to preserve renal function. Dihydropyridines may increase renin secretion which, in turn, increases angiotensin-II production, leading to continued expansion of mesangial matrix.²⁰ Also, the lack of dihydropyridine calcium channels on the efferent arteriole leads to a more pronounced effect of angiotensin-II.²¹ This effect causes an increase in GFR, as well as an increase in urinary albumin excretion (UAE).^{22–24} The dihydropyridine lack of protection against diabetic nephropathy development is evidenced again by the total lack of effect on glomerulosclerosis, a precursor to diabetic nephropathy.^{25–27} Nicardipine, which has a side chain in its chemical structure that is similar to the verapamil configuration, may be an exception. More studies are needed to verify the effectiveness of nicardipine.^{28,29}

Verapamil and diltiazem are the only calcium antagonists with definitive proof of renal preservation effects; several studies document the renal hemodynamics of these compounds. For example, Raji et al.³⁰ demonstrated a decrease in mesangial uptake of macromolecules due to a decreased mesangial membrane permeability and pore size. Several studies^{31–33} also indicate that the mechanism(s) responsible for autoregulation of renal blood flow are inhibited by calcium antagonists. Verapamil and diltiazem have been shown to effectively decrease UAE in several studies.^{30,34,35} This result was due to a decrease in intraglomerular volume rather than intraglomerular pressure.³⁶ Mesangial matrix expansion is decreased^{37–39} due to the predominant mechanism of action afforded to calcium antagonists. This calcium channel blockage decreases the effects of angiotensin-II which, in turn, reduces the cell proliferation of

mesangial cells. Lastly, verapamil and diltiazem were shown to slow the progression of glomerulosclerosis.^{39,40}

Only verapamil and diltiazem calcium channel blockers blunt the intrarenal efferent arteriolar effects of angiotensin-II.⁴¹ Verapamil and diltiazem seem to be about as effective as the ACE inhibitors in patients with both diabetes and hypertension. Studies with normotensive patients are less clear in the practical use of calcium antagonists.

TREATMENT WITH ACE INHIBITORS

Angiotensin Converting Enzyme (ACE) inhibitors have been accepted as the "gold standard" for the treatment of diabetic kidney disease. However, the antiproteinuric response to ACE inhibitors is not uniform. About 60% of diabetic patients respond with a reduction in microproteinuria and proteinuria, whereas the remaining 40% do not respond at all.⁴²

A decrease in serum albumin levels is an indication that albumin is being lost. Normal serum albumin levels are approximately 3.5–5.5g/dL. Praga et al.⁴³ showed that patients with serum albumin levels of 3.5g/dL or higher had an average reduction in protein excretion of about 50%, whereas patients with serum albumin levels of 3.0 or less did not respond. This suggests that the number of patients responding to ACE inhibitors is probably greater than 60% if treatment is started within the first few months after microalbuminuria is detected. There is also increased interest in using ACE inhibitors early in the course of renal disease. Starting an ACE inhibitor before the development of overt nephropathy whose first sign is the presence of microalbuminuria has much support.^{44,45}

Materson⁴⁶ points out that diabetologists seem to be treating a majority of their patients with ACE inhibitors, although it remains unclear whether or not all types of diabetes should be treated with these compounds. Ravid et al.⁴⁷ proved that the antiproteinuric effect of ACE inhibitors is beneficial in normotensive diabetics as well. Blood pressure reduction in normotensive diabetics has been minor. Two studies^{48,49} have concluded that the ACE inhibitors' renal effects are independent of blood pressure reduction. The renal hemodynamics of ACE inhibitors have been shown to be due to their selective effects on efferent arteriole resistance. This consequently decreases intraglomerular pressure, as well as slows the diabetic renal disease process to an extent greater than simple blood pressure control alone.^{50,51}

Two studies by DeFronzo^{52,53} have shown that ACE inhibitors decrease peripheral vascular resistance by inhibiting the production of angiotensin-II. GFR also is relatively unaffected, whereas RBF is increased and the filtration fraction is decreased. These studies also showed that ACE inhibitors decrease proteinuria and microalbuminuria. However, ACE inhibitors also decrease mesangial matrix expansion. This is probably due to the direct effects on angiotensin-II.

Other beneficial effects of ACE inhibitors, which are seen in most of the calcium antagonists, include increased insulin sensitivity, lack of affect on blood glucose, and effectiveness in

treating dyslipidemia.^{54,55} Hirsh⁵⁶ points out that even low levels of microalbuminuria worsens dyslipidemia and that albumin is directly toxic to renal cells.

Materson⁴⁶ suggests that the renoprotective effect of ACE inhibitors is generalizable to patients with diabetes. However, there have been preliminary data on specific tissue-level ACE inhibition activity that shows differences among the ACE inhibitors. Further research is needed to clarify this issue.⁵⁷

COMPARISON OF ACE INHIBITORS TO CALCIUM ANTAGONISTS

Studies^{2,31} have shown verapamil and diltiazem are equivalent to ACE inhibitors. Combination therapy using both a calcium antagonist and an ACE inhibitor has a synergistic reduction in UAE. However, even with long-term treatment, research has shown no significance for multiple drug therapy in slowing of the disease process.⁵⁸

DISCUSSION

Many published clinical trials indicate that an ACE inhibitor should be a drug of choice in diabetic patients for treatment and/or prevention of diabetic nephropathy.^{2,31} An ACE inhibitor should be started when microalbuminuria is detected.^{44,45} ACE inhibitor use in diabetic patients that have high risk for the development of diabetic nephropathy also is beneficial.

Physicians should still monitor for microalbuminuria on an annual basis. At greatest risk are those patients who have a 10-year-or-longer history of diabetes, a significant history of poor glycemic control demonstrated by a consistent HbA_{1c} > 9.5, a family history of cardiovascular disease, and an elevated CrCL of > 120cc/min.

Clinical and laboratory results are not routinely available to pharmacists. However, managed care pharmacists can easily identify diabetic patients by insulin and/or oral hypoglycemic use. With a routine review of the patients profile, they can make a determination of possible hypertension and help improve treatment. For example, if the patient is not on an ACE inhibitor, the pharmacist might suggest this course of treatment to the physician. If the ACE inhibitor fails, denoted by development or worsening of increased urinary albumin excretion, a calcium antagonist of either verapamil or diltiazem class can be used. Nicardipine is not recommended as an alternative choice by the authors at this time.

The cost of drug therapy for all patients with diabetes is minor compared to the cost of treatment for diabetic nephropathy. If drug cost is a major budget concern, the number of patients with diabetes can be reduced by first treating high risk patients. Additional savings result from the differences in cost of an ACE inhibitor and calcium antagonist. Proper treatment may reduce or reverse the progression of kidney damage in high-risk patients and enable them to live a healthier life for years.

PHARMACOECONOMICS

Based on 1990 statistics,⁸⁸ there were 13 million diabetic patients in the U.S. (5.2% of the general population), of which half have not been properly diagnosed. The occurrence of ESRD is stated to be in the range of 4%⁸⁸ to 21%⁸⁹ of all diabetics. Thus, for a population of 100,000, there are approximately 5,200 patients with diabetes; of these, 208–1,092 will develop ESRD requiring dialysis.

The direct cost of dialysis is \$150 per treatment, and most patients require treatment 13 times a month.⁹⁰ Additional costs include \$2,500 to \$13,000 per year for transportation to and from appointments,⁹¹ \$6,300 per year for auxiliary medications and dietary supplements,⁹¹ \$1,750 in supplies for proper control for the year (insulin, oral medications, syringes, testing equipment),⁹² and an undefined number of monthly doctor's office appointments at approximately \$45 per visit every month. The total direct cost to the health care system is between \$34,490 and \$44,990 per patient per year.

Indirect costs essentially involve the lost work time due to medical appointments. As 65% of dialysis patients are gainfully employed,⁹² this lost time results in a \$5,000–\$7,500 loss of income annually, per patient. Another indirect cost is the pharmacist's intervention in identifying a diabetic patient at risk for ESRD. Total indirect costs equal \$5,180–\$7,680 per patient per year.

Since the use of dihydropyridine-class calcium channel blockers to prevent ESRD in patients with diabetes has been shown to be ineffective, the question arises whether to treat all diabetics or diabetic patients who also have comorbid cardiovascular disease(s). This question can be answered with a cost-benefit analysis (CBA).

A benefit per patient treated with an ACE inhibitor for prevention equals the dialysis costs that are not spent (\$39,670 to \$52,670). The cost should include the continued use of supplies to control diabetes (\$1,750), the cost of the ACE inhibitor at \$360 per year, plus the potential reimbursement to the managed care pharmacist of \$15 for every fill of the ACE inhibitor (\$180 for a 12-month period). The total cost is \$2,290.

In most cases, the dollars are budgeted so a discount rate of 5% will be chosen. This reduces the benefit total to a range of \$22,089 to \$29,328. The costs are also reduced by \$1,275. The CBA results in a ratio of 17.3–23.0 to one, which means that for every dollar spent, the benefit gained is \$17.30 to \$23.00 for preventive treatment in a patient with diabetes

who will go on to develop ESRD.

How do you determine which diabetic patients to treat and which not to treat? The total cost to treat all diabetic patients is estimated to be approximately \$500 per person per year; but when this cost is discounted due to extended payments, the cost is reduced to \$300 for ACE inhibitor and managed care pharmacist's cognitive service fee. The remaining \$975 in direct and indirect cost is for treating diabetes. For a population of 100,000 lives, one would expect 5,200 diabetic patients, of which a minimum of 208 may require dialysis for ESRD.

The CBA for this 100,000-patient population would have a benefit of $208 \times (\$22,089 - \$975) = \$4,391,712$ and a cost of $5,200 \times \$300 = \$1,560,000$ resulting in a ratio of 2.8:1. This means that at the most conservative estimates the costs only marginally warrant treating all patients with diabetes. According to Health Watch,⁹⁴ hypertension affects 60%–65% of all patients with diabetes. If just those patients with diabetes and hypertension are treated, the cost is reduced to \$936,000–\$1,014,000. The CBA ratio then becomes 4.3:4.6. Depending on the number of patients with diabetes, budget considerations, and available time to implement a pharmacist intervention program, one can justify intervening for all patients with diabetes. At a minimum, intervening on behalf of patients with both diabetes and hypertension is warranted.

CONCLUSION

The managed care pharmacist can take an active role in assisting the physician by implementing protocols or screens that assess diabetic patients' drug profiles. Diabetic patients that are taking a dihydropyridine calcium antagonist should be targeted. By identifying the patients with diabetes and confirming the diagnosis of hypertension, the managed care pharmacist may intervene not only to save money but also to improve therapy with the substitution of an ACE inhibitor. Ideally, if pharmacists could identify only those patients that will develop diabetic nephropathy leading to ESRD, the cost benefit is more than \$17 saved for every \$1 spent. However, this is not feasible. By treating all patients with diabetes to prevent renal problems, the CBA is \$2.80 benefit per dollar spent. A second option is to treat just those patients with both diabetes and hypertension; the CBA here increases to \$4.30 to \$4.60 saved for every dollar spent. Renal diseases in patients with diabetes can be prevented and should be prevented with intervention from a pharmacist. ■

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