Journal of Advanced Zoology
ISSN: 0253-7214
Volume 44 Issue S6 Year 2023 Page 2198-2204

Effectiveness And Safety Measures Of Benazepril Hydrochloride On Diabetic Nephropathy

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Accepted:

Abstract

One of the most common chronic microvascular consequences of diabetes, diabetic nephropathy (DN) affects a significant number of individuals globally. The International Diabetes Federation (IDF) reports that there are 37 million diabetes people globally, with around 4.6 million of them passing away in 2011. The current review was based on the effectiveness and toxicity of Benazepril Hydrochloride on Diabetic Nephropathy. Benazepril is a prodrug that consists of an extremely low inhibitory action ethyl ester, a carboxylic acid group, and the benzepine nucleus with a phenyl-propyl side chain. The FDA has approved benazepril hydrochloride for the treatment of hypertension, either by itself or in conjunction with other antihypertensive medications. Anaphylactoid reactions and angioedema, which can include tongue edema and laryngeal angioedema, are examples of sensitivity reactions that have the potential to be lethal. Renal dysfunction and electrolyte imbalances are linked to hypotension. In the second and third trimesters of pregnancy, the use of medications that affect the renin-angiotensin system decreases fetal renal function and increases morbidity and mortality in the fetus and newborn. The most prevalent indicator of toxicity is low blood pressure. In additions, lack of energy, increased salivation, elevated heart rate, vomiting, diarrhoea, weakness, coughing, bronchospasms, and kidney malfunction are other indicators of toxicity. In conclusion, in the management of diabetic nephropathy combination therapy- benazepril with spironolactone or diuretic is recommended. It heals the nephrons which have been affected due to the toxicity of various drugs or infections.

Keywords: Diabetic Nephropathy, Benazepril Hydrochloride, effectiveness, toxicity, nephrons.

INTRODUCTION

One of the most common chronic microvascular consequences of diabetes, diabetic nephropathy (DN) affects a significant number of individuals globally [1]. With diabetes growing at an accelerated rate every year, DN incidence is rising, and it is now a leading cause of end-stage renal disease (ESRD) [2][3]. The International Diabetes Federation (IDF) reports that there are 37 million diabetes people globally, with around 4.6 million of them passing away in 2011. Moreover, China and other emerging nations are experiencing a sharp rise in the prevalence of diabetes, which is placing a significant financial and social burden on them. DN is now the first significant illness that needs dialysis care, and it comes with high associated expenditures [4][5].
The first clinical manifestation of DN is typically microalbuminuria, which also accelerates the disease's progression. Kidney failure eventually results from elevated proteinuria levels that are not effectively treated [6]. Not only does proteinuria indicate the severity of DN, but it is also strongly linked to the advancement of DN [7]. The first clinical manifestation of DN is typically microalbuminuria, which also accelerates the disease's progression. Kidney failure eventually results from elevated proteinuria levels that are not effectively treated [8]. Proteinuria is directly linked to the advancement of DN in addition to serving as a marker for its severity.
Benazepril is a prodrug that consists of an extremely low inhibitory action ethyl ester, a carboxylic acid group, and the benzepine nucleus with a phenyl-propyl side chain. Benazepril's main metabolite, the diacid benazeprilat, a strong ACE inhibitor, is produced when the ethyl ester is broken down following injection and absorption [9]. But because of its low absorption, benazeprilat is not suited for oral use. A popular medication for the clinical treatment of DN is benazepril hydrochloride (BH), which lowers blood pressure and proteinuria simultaneously.

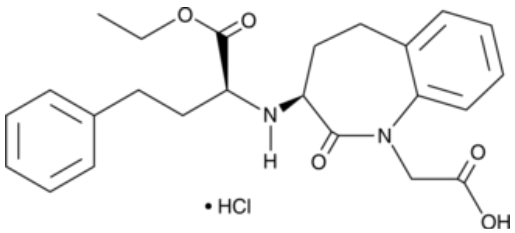

Fig 1. **Structure of Benazepril hydrochloride**

The FDA has approved benazepril hydrochloride for the treatment of hypertension, either by itself or in conjunction with other antihypertensive medications. It is possible to combine thiazide diuretics with benazepril. As benazepril decreases blood pressure, it lowers the risk of cardiovascular events that can be deadly or nonfatal, particularly myocardial infarctions and strokes [10].

MOA of benazepril [11]

- An essential part of the renin-angiotensin-aldosterone pathway is played by the enzyme angiotensin-converting enzyme (ACE). Vasoconstriction, elevated sympathetic activity, and Na+ retention are the end products of this route, which also raises blood pressure and promotes water retention. The ACE enzyme catalyses the conversion of angiotensin I to angiotensin II, which is one stage in this process. As a result, by stopping this stage in the renin-angiotensin pathway, ACE inhibitors lower systemic arterial blood pressure and increase the excretion of Na+ in the urine.
- ACE inhibitors are involved in the metabolism of bradykinin as well. ACE enzymes break down the natural vasodilator bradykinin into inactive metabolites. But because the ACE enzyme is suppressed, the blood pressure-lowering effects of this vasodilator are maintained.
- Renin-angiotensin-aldosterone system (RAAS) activation results in decreased renal artery perfusion in heart failure patients because of inadequate cardiac output. By increasing intravascular volume and activating the RAAS pathway, it raises blood pressure, which raises cardiac output through the Frank-Starling mechanism.

Indication

Benazepril comes in dosage forms of 10, 20, and 40 milligrams for oral tablets. Patients can take it with or without meals, and it should be taken once or twice a day at regular intervals [12]. The morning and afternoon dosages exhibit varying degrees of efficacy, with the early dose producing a more prolonged impact (effectiveness lasting about 19 hours). It has not been studied to take more than 80 mg daily in total. To measure

peak (2 to 6 hours after treatment) and trough responses, dosage modification should be carried out. A higher dosage or divided administration should be taken into consideration if a single daily dose delivery regimen is unable to provide a sufficient trough response. A diuretic can be added if benazepril is insufficient to manage blood pressure. Benazepril should be started at a dose of 5 mg while a patient is receiving diuretics to prevent severe hypotension [13].

Toxicity [14][15]

Benazepril is an ACE (angiotensin converting enzyme) inhibitor that is nonsulfydryl. It is used to treat hypertension and manage heart failure in both human and animal patients.
Human Studies:

- Anaphylactoid reactions and angioedema, which can include tongue edema and laryngeal angioedema, are examples of sensitivity reactions that have the potential to be lethal.
- Airway obstruction may arise from head and neck angioedema that affects the tongue, glottis, or larynx.
- This uncommon ACE inhibitor-associated clinical condition, which first appears as cholestatic jaundice, has the potential to be lethal and progresses to fulminant hepatic necrosis.
- Individuals on an ACE inhibitor, such as benazepril, who experience jaundice or noticeably elevated liver enzymes should stop taking the medication and get the necessary monitoring.
- There have not been any reports of benazepril overdoses in humans, although the most typical symptom is probably hypotension, for which intravenous infusion of normal saline solution is the standard course of therapy.
- Renal dysfunction and electrolyte imbalances are linked to hypotension. In the second and third trimesters of pregnancy, the use of medications that affect the renin-angiotensin system decreases fetal renal function and increases morbidity and mortality in the fetus and newborn.
- The resulting oligohydramnios may cause skeletal malformations and fetal lung hypoplasia. Anuria, hypotension, renal failure, skull hypoplasia, and even death are possible newborn side effects.
- Similar to other ACE inhibitors, benazepril has also been linked to a low incidence of elevated serum aminotransferases.

The most prevalent indicator of toxicity is low blood pressure. Lack of energy, increased salivation, elevated heart rate, vomiting, diarrhoea, weakness, coughing, bronchospasms, and kidney malfunction are other indicators of toxicity. The specific ACE inhibitor taken will determine when symptoms start and how long they last.

Preclinical

- Benazepril at a single oral dosage of 3 g/kg was linked to a considerable mortality rate in mice. However, single oral dosages up to 6 g/kg were tolerated by rats. In rats, reduced activity was observed at 5g/kg and in mice at 1g/kg. Benazepril did not negatively impact either male or female rats' ability to reproduce when administered in doses ranging from 50 to 500mg/kg/day. Benazepril was given to rats and mice for up to two years at levels of up to 150 mg/kg/day with no indication that it was carcinogenic.
- In vitro tests for forward mutations in cultured mammalian cells, the Ames test in bacteria (with or without metabolic stimulation), and the nucleus anomaly test did not reveal any mutagenic activity.

Effectiveness of Benazepril Hydrochloride on Diabetic Nephropathy

Xue et al. (2017) examined the effects of benazepril hydrochloride (BH) on proteinuria and ANGPTL-4 expression in rat model. Three groups- normal control, DN group, and BH treatment (BH) group) were randomly assigned to a total of 72 Wistar male rats. STZ, or streptozotocin, was used to induce the DN model. We looked at weight, hyperglycaemia, proteinuria, biochemical markers, and the kidney weight index at eight, twelve, and sixteen weeks. Additionally, qRT-PCR and immunohistochemistry were used to measure the expressions of the ANGPTL-4 mRNA and protein. Spearman analysis was used to look into the relationships between ANGPTL-4 and biochemical markers. In comparison to the NC group, the DN and BH groups had significantly lower weights but significantly higher glucose levels ($P < 0.05$). After BH treatment, triglycerides, albumin, proteinuria, urea, creatinine, and total cholesterol levels were all lower than in the DN group. BH also decreased renal volume and improved the histological alterations linked to DN. Following BH therapy, ANGPTL-4 expression was dramatically reduced, and there was a strong positive correlation ($P< 0.05$)

between ANGPTL-4 expression and DN biochemical markers. In conclusion, by lowering the expression of ANGPTL-4, benazepril hydrochloride improves DN and reduces proteinuria [16] *Huo et al. (2006)* Renal outcomes (such as the time to the first event in the composite end point of a doubling of SCr level, ESRD, or death) were improved with benazepril treatment compared with placebo among patients with the higher baseline creatinine levels (group two). Additionally, fewer patients reached the prespecified end points, such as the progression of kidney disease or death (n = 44 vs 66; p = 0.004). As would be predicted, whether or not they received ACEis, patients getting benazepril and having lower baseline SCr levels (group one) had better clinical outcomes than patients taking the medication and having higher baseline SCr levels (group two) (Figure 1). Remarkably, benazepril's renoprotective benefits didn't seem to depend on blood pressure regulation. The risk of doubling SCr was 51% lower in patients with more advanced chronic kidney disease (CKD) who got benazepril compared to those who received a placebo, according to an analysis of the various renal end point components (p = 0.02). Additionally, benazepril decreased the chance of ESRD by 40% (p = 0.02) [17]. *Shoda et al. (2006)* Benazepril's renoprotective benefits have also been shown in comparison to those of other antihypertensive medications. In a small, long-term (5-year) research involving 68 nondiabetic individuals with renal insufficiency, benazepril (or trandolapril) showed a higher reduction in GFR decline rate and a decreased demand for dialysis compared with ARB (candesartan or losartan) medication [18]. Additional research has confirmed these results, demonstrating that while CCBs and RAAS antagonists both reduce blood pressure, their effects on renal disease progression are not as great [19][20]. *Tomasz et al. (2011)* The GUARD (Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension) trial showed that benazepril/hydrochlorothiazide was more effective than amlodipine combined with benazepril in reducing baseline urinary albumin:creatinine ratio and normalizing urinary albumin: creatinine ratio in patients with baseline microalbuminuria, although this effect was accompanied by a greater decrease in glomerular filtration rate than with benazepril/amlodipine. In the ACCOMPLISH (Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial, patients who received benazepril in combination with amlodipine experienced better CV outcomes and renoprotective effects.

The ACCOMPLISH trial is the largest investigation to date to demonstrate the additional advantage of combining ACE inhibitors with calcium-channel blockers in renal protection, even though the patients in this study did not have overt renal impairment (instead, they had serious cardiovascular conditions) [21]. *Piero et al. (2019)* In patients with type 2 diabetes and overt nephropathy, to determine whether combination therapy with angiotensin-converting enzyme (ACE) inhibitor and angiotensin II receptor blocker is more nephroprotective than either agent alone. The Italian Drug Agency supported this phase III trial, which was prospective, randomized, open, blind-endpoint, and involved 103 consenting patients with type 2 diabetes who were over 40 years old, had serum creatinine levels between 159 and 309μmol/L, and had a spot morning urinary albumin-creatinine ratio > 1000 mg/g (or > 500 mg/g if they were on ACE inhibitor or ARB therapy at inclusion). The patients were stratified by center and randomly assigned to receive treatment for 4.5 years with valsartan (320mg/d), benazepril (20mg/d) (n = 34), or half dosages of both drugs (n= 33). End-stage renal disease was the main outcome. Analyses using modified intention-to-treat were carried out. Between June 2007 and February 2013, there were ten recruitment centres in Italy and one in Slovenia. 26 people withdrew from the study before its completion, leaving 77 participants overall. Twelve people on benazepril (35.3%) and nine on combination therapy (27.3%) advanced to end-stage renal disease (ESRD) over a median (interquartile range) of forty-one (18-54) months, compared to five on valsartan (13.9%). Even after adjusting for age, gender, and baseline serum creatinine, systolic blood pressure, and 24-hour proteinuria (HR 5.16, 95% CI 1.50–17.75, P = 0.009 and HR 4.75, 95% CI 1.01–22.39, P = 0.049, respectively), there were still significant differences between benazepril (hazard ratio [HR] 3.59, 95% confidence interval [CI] 1.25–10.30; P = 0.018) or combination therapy (HR 3.28, 95% CI 1.07–10.0; P = 0.038) and valsartan. The groups' respective distributions of adverse events were comparable. Compared to benazepril (20 mg/d) or halving the dosages of both drugs, valsartan (320 mg/d) safely delayed end-stage renal disease (ESRD) in individuals with type 2 diabetes who also had nephropathy [22]. *Peng et al. (2014)* studied that how benazepril affected the renal tubular epithelial cells' ability to transdifferentiate in diabetic rats. In this investigation, thirty male Sprague-Dawley rats were used. The diabetic rat model was made up of the remaining 22 rats, who received injections of streptozotocin (STZ), while the remaining eight rats, chosen at random, constituted the normal control group (N group). Diabetic rats were randomized into two groups: the B group, which received benazepril, and the DM group, which did not. The course ran for a total of twelve weeks. At the beginning and conclusion of the trial, measurements were made of blood glucose, body weight, kidney/body weight, 24-hour urine protein, serum creatinine, and blood urea nitrogen. We utilized immunohistochemistry and western blotting to identify the expression of α-smooth muscle actin (α-SMA) in renal tissue in addition to observing the tubulointerstitial

pathological alterations. The DM group had significantly greater levels of blood glucose, kidney/body weight, tubulointerstitial damage index (TII), serum creatinine, blood urea nitrogen, and 24hour urine protein than the N group ($p<0.01$). With the exception of blood glucose and kidney/body weight, all other indicators showed a significant difference ($p<0.01$) between the B group and DM group. Western blot analysis showed that the expression of α-SMA in diabetic renal tissue increased 3.27-fold compared with that of the N group, while the expression of α-SMA in the B group decreased 45% compared with that in the DM group. Immunohistochemical staining results showed the expression of α-SMA in renal tubular epithelial cells to be significantly higher in the DM and B groups compared with the control group ($p<0.01$). In conclusion, benazepril blocked the transdifferentiation of renal tubular epithelial cells produced from diabetic rats, greatly reduced the expression of α-SMA in these cells, and played a crucial role in protecting the kidneys [23]. *Duan et al. (2022)* investigated the potential therapeutic benefits of combining benazepril and spironolactone for treating diabetic nephropathy, as well as the impact of this combination on serum levels of TNF-α, CRP, and IL-6, 100 patients with diabetic nephropathy who were admitted to The Affiliated Hospital of Inner Mongolia Medical University between April 2019 and October 2020 were randomly selected and split into two groups, E and F, using a drawing lot (n=50 for each). Group F was given a combination treatment of benazepril and spironolactone, while Group E was given benazepril alone. The study examined the therapeutic efficacy, incidence of adverse medication responses, renal function following treatment, and blood levels of TNF-α, CRP, and IL-6 before and after treatment. In addition, fasting blood glucose (FBG) levels were assessed prior to treatment, as well as seven and fourteen days after drug administration. While post-treatment incidence of adverse medication responses and expression levels of CRP, IL-6, and TNFα were significantly lower in group F compared to group E ($p < 0.05$), therapeutic efficacy and renal functions were significantly better in group F than in group E. Both groups' levels of inflammatory factors dropped after therapy. Patients with diabetic nephropathy who get both benazepril and spironolactone experience a greater degree of therapy response compared to those who just receive benazepril. For the treatment of patients with diabetic nephropathy, combination therapy is advised [24]. *Singh et al. (2006)* It is preferable to use angiotensin receptor blockers (ARB) and angiotensin converting enzyme (ACE) inhibitors to slow the course of diabetes mellitus. In an animal model of diabetic nephropathy, the preventive renal effects of benazepril (5 mg/kg, p.o.), an ACE inhibitor that partially inhibits the synthesis of angiotensin II, and telmisartan (10 mg/kg, p.o.), an ARB that totally blocks the action of angiotensin, were compared in this study. In male albino rats, DN was induced by a single intraperitoneal injection of streptozotocin (50 mg/kg). After four weeks, the biochemical parameters (blood urea, urine protein, and creatinine clearance) in diabetic rats were considerably ($p<0.01$) changed. In diabetic rats, therapy with telmisartan (10 mg/kg, p.o.) and benazepril (5 mg/kg, p.o.) significantly ($p<0.01$) decreased the increased levels of blood urea and urine protein. Following eight weeks of diabetes, there was a discernible difference in the blood urea decrease between the groups treated with benazepril and telmisartan. There was no significant difference in the reduction of proteinuria between benazepril and telmisartan. The difference in creatinine clearance improvement between benazepril and telmisartan was likewise not statistically significant ($p>0.05$).

Histology showed that both medications had positive effects. This study shows that benazepril and telmisartan have similar renoprotective effects [25]. *Peter et al. (2003)* investigated whether, in type I diabetic patients with diabetic nephropathy (DN), dual blockage of the renin-angiotensin system (RAS) with both an angiotensin-converting enzyme (ACE) inhibitor (ACE-I) and an angiotensin-II receptor blocker (ARB) is preferable to either treatment alone. Eight weeks of therapy with a placebo, 20 mg of benazepril once daily, 80 mg of valsartan once daily, or a combination of 20 mg of benazepril and 80 mg of valsartan were conducted in a randomized, double-blind crossover experiment. There were twenty people with DN who had type I diabetes. We measured GFR, 24-hour blood pressure, and albuminuria at the conclusion of each treatment session. The trial was completed by eighteen patients. When compared to placebo, treatment with benazepril, valsartan, or dual blockade dramatically decreased albuminuria and blood pressure. Valsartan and benazepril both worked equally well. When compared to any form of monotherapy, dual blockade resulted in an additional reduction in albuminuria of 43% (29 to 54%), a reduction in systolic blood pressure of 6 (0 to 13) mmHg and 7 (1 to 14) mmHg (versus benazepril and valsartan, respectively), and a reduction in diastolic blood pressure of 7 (4 to 10) mmHg. Compared to monotherapy and placebo, dual blockage resulted in a reversibly lower GFR. Every treatment was well-tolerated and safe. In conclusion, in patients with type I diabetes who also have DN, dual inhibition of the RAS may provide extra protection for the kidneys and heart [26].

Compared to treatment with 20 mg/d of benazepril or halved dosages of both drugs, treatment with 320 mg/d of the ARB valsartan delayed the development of ESRD in high-risk patients with type 2 diabetes and overt

nephropathy, and it was safe. Thus, even when ACE inhibitor or ARB dosages are lowered, dual RAS blocking is not always warranted in clinical practice, as the current data support the findings of earlier research [26][27]. These results may have consequences since it is anticipated that improving patient quality and life expectancy as well as lowering direct and indirect expenses for renal replacement therapy and associated comorbidities may result from delaying or perhaps stopping the progression of diabetic renal disease to end-stage renal disease

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CONCLUSION

Trials conducted throughout the next five years should look at potential processes and directly compare hard renal outcomes in various patient populations, as evidence is mounting that renal protection with antihypertensive therapies may be caused by reasons other than blood pressure control. Benazepril is a good choice for patients with renal failure since it lowers blood pressure and delays the progression of renal disease. For patients with diabetic nephropathy, benazepril and spironolactone combination therapy is a successful treatment. Furthermore, the patient's levels of inflammatory factors are decreased and their renal function is enhanced by the combination treatment. Therefore, the management of patients with diabetic neuropathy may benefit from this therapy approach.

In conclusion, in the management of diabetic nephropathy combination therapy- benazepril with spironolactone or diuretic is recommended. It heals the nephrons which have been affected due to the toxicity of various drugs or infections.

FUNDING

Nil.

CONFLICT OF INTEREST

Authors declared for none conflict of interest.

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