The Effect of Benazepril on Cats with Chronic Renal Failure

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Abstract. The study was carried out on 12 outpatient cats, age between 4 and 16 years, 7 males and 5 females, that were diagnosed with chronic renal insufficiency. In the first week, benazepril was administered orally, in dose of 0.25 mg/kg/day, after that the dose was increased to 0.5 mg/kg/day. Before and after 1, 4 and 12 weeks of benazepril administration, the blood pressure was measured by oscillometric method. For each cat, the systemic blood pressure value was calculated as the mean of five consecutive measurements. Blood and urine sample were collected before and after four and 12 weeks of the initiation of benazepril administration. After four weeks of benazepril administration, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and proteinuria, assessed by the urine protein-to-creatinine ratio, were all significantly lower (p<0.05) then the values recorded before the administration of benazepril. Benazepril had no significant influences concerning the blood biochemical parameters of renal profile.

Keywords: blood pressure, proteinuria, benazepril

INTRODUCTION

Chronic renal failure (CRF) is characterized by gradual and irreversible decrease of glomerular filtration rate, result of gradual loss of the renal functional mass. In compensation, the remaining nephrons suffer structural and functional changes in order to maintain the filtration rate constant. The functional adaptation refers to hyperfiltration, which is produced by an increase in the glomerular capillaries blood flow and pressure, following dilatation of the afferent arteriole (Verdier-Fontaine and Priymenko, 2003). The glomerular capillary pressure can be emphasized by the efferent arteriole constriction, produced by angiotensine II. The angiotensine II activity is increased in most of the chronic renal diseases. Increase in the glomerular capillary pressure is, in the long run, deleterious to kidney structure and function. Elevated pressure leads to proteinuria, increased shear stress and local production of cytokines, which cause progressive renal injury. Therefore, decreasing the glomerular capillary pressure and consecutive proteinuria are key factors in slowing down the progression to end stage of chronic renal failure (Brown, 2003, Lefebvre and Toutain, 2004). Renoprotection can be defined as any dietary or pharmacologic intervention to delay progression of CRF. The angiotensine converting enzyme inhibitors (ACEI) may lower glomerular pressure by decreasing systemic blood pressure and inhibiting the formation of angiotensin II which induces vasoconstriction of the efferent arteriole (Lefebvre and Toutain, 2004). On the available ACE inhibitors, benazepril hydrochloride is different in that is excreted in urine and bile. Pharmacokinetic studies showed that in cats, the active metabolite of benazepril, benazeprilat, is eliminated principally (approximately 85%) via biliary excretion (King et al., 2006). Because of this property, benazepril does not accumulate in the
body of animals with renal diseases, indicating its potential as a safe therapeutic means for chronic renal failure of small animals (Watanabe and Mishina, 2007; King et al., 2006).

The purpose of this study is to evaluate therapeutic effects of benazepril in cats with spontaneously occurring chronic renal insufficiency.

**MATERIALS AND METHODS**

The study was carried out on 12 outpatient cats, age between 4 and 16 years, 7 males and 5 females, that were diagnosed with chronic renal insufficiency at Timisoara University Veterinary Clinics. Chronic renal failure was diagnosed by physical examination, clinical signs and elevated level of serum creatinine. In this study were included cats with serum creatinine concentration ≥ 2 mg/dl, that were determined twice before the study to establish the diagnosis of renal failure. It is recommended that all cats to be fed a commercial renal support diets.

In the first week, benazepril was administered orally, in dose of 0.25 mg/kg/day, after that, the dose was increased to 0.5 mg/kg/day. Before and after 1, 4 and 12 weeks of benazepril administration, the blood pressure was measured using oscillometric blood pressure monitor (Cardell Model 9401) that was previously validated for use in dog and cats. This automatic oscillometric device indirectly measures systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse frequency. The inflatable cuff was positioned around the forelimb, between the elbow and carpus, at the level on the median artery. For each cat, a cuff width of between 30-40% of the limb circumference was chosen. Blood pressure was measured in the owner’s presence, after a period of acclimatization, before the physical examination, to reduce the magnitude of “white coat” hypertension. For each cat, the systemic blood pressure value was calculated as the mean of five consecutive measurements.

Blood and urine sample were collected before and after 4 and 12 weeks of the initiation of benazepril administration. Biochemical blood parameters (creatinine, urea, phosphorus, potassium, total protein and albumin) were determined by usualy methods, on Vet-Screen biochemical analyzer. Urine was collected by cystocentesis or urethral catheterization and proteinuria was estimated by urine protein to creatinine ratio. Total protein concentration in the urine was measured by using a colorimetric pyrogallol red method and urine creatinine was determined by Jaffe method.

The data obtained were analyzed by Mann-Witney test and the differences were considered significant at p<0.05.

**RESULTS AND DISCUSSIONS**

After one week of treatment with benazepril the values of SBP, DBP and MAP were lower with 3.94%, 9.08% and 6.85% than initially value (table 1). In the 8th day, the benazepril dose was increased to 0.5 mg/kg/day and at the evaluation of 4 weeks, the mean values of the SAP, DAP and MAP were lower with 7.23%, 14.28% respectively 11.31% than those registered before administration of benazepril. After 12 weeks of treatment with benazepril, the blood pressure measured has shown appropriate values with those taken at 4 weeks (table 1).

The differences between SBP, DBP and MAP values measured before and after the first week of treatment were statistically insignificant (p>0.05). Instead, at 4 and 12 weeks,
the values of SBP, DBP and MAP were significantly lower (p<0.05) than the values recorded prior of the benazepril administration. The dynamic of the mean values of the blood pressure during the treatment with benazepril, in the cats taken in this study, were appropriate with the cats with CRF experimentally induced. (Brown et al., 2001; Watanabe and Mishina, 2007) Therefore, in the literature there is less data concerning the ACEIs, respectively of benazepril, over the blood pressure in cats.

Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before benazepril administration</th>
<th>During benazepril administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 week</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>152.0 ± 12.0</td>
<td>146.0 ± 5.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>105.7 ± 13.3</td>
<td>96.1 ± 7.3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>121.1 ± 12.6</td>
<td>112.8 ± 6.5</td>
</tr>
<tr>
<td>Pulse frequency</td>
<td>135 ± 10.7</td>
<td>136.4 ± 8.2</td>
</tr>
</tbody>
</table>

¹ Values are mean ± standard deviation

The most studies were done over the cats CRF surgically induced by ablation of 7/8 of total renal masses. The enalapril administrated in dose of 0.5 mg/kg/day for 1 week induced a decrease in blood pressure for 15 – 17 hours in cats with polycistic kidney disease, but the decrease in systolic blood pressure was only 16 mmHg (Miller et al., 1999). Similarly, in cats with experimental renal failure and mild hypertension, treatment with benazepril induced a mean decrease of between 5-11% in systolic blood pressure compared with placebo treated animals (Brown et al., 2001). Watanabe and Mishina (2007), have obtained a significant reduction (value of 10-15% lower) of SBP, DBP and MAP in cats with experimentally induced CRF, after one week of treatment with benazepril at doses between 0.92 and 2 mg/kg/day.

The effect of the benazepril over the renal function has been appreciated through the changes of the blood biochemical parameter of the renal profile. Plasma creatinine concentration is an important variable for tolerability assessment in cats with CKD. The mean values of the serum creatinine measured at 4 and 12 weeks of treatment with benazepril were lower with 10.1% respectively 14%, but the differences were not statistically significant. This dynamics of serum creatinine concentration could be explained by the fact that benazepril induces a mild decrease of systemic blood pressure and, by the other hand, increases the glomerular filtration rate. (Brown et al., 2001)

The value of serum creatinine obtained in the study of 5 cats with spontaneously CRF which have received increasing doses of benazepril (0.25 mg/kg/day in the initial week, 0.5 mg/kg/day in the second week and 1.0 mg/kg/day in the third week and thereafter) was significantly lower since the 12th week compared with cats placebo group. (Watanabe and Mishina, 2007)

The mean values of the serum concentration of urea and phosphate were lower in the 4th and 12th week of evaluation, but the differences were not significant (p>0.05). During the treatment with benazepril, the mean values of serum concentration of total protein, albumine and potassium were improved but the differences toward the values prior to benazepril administration, were insignificant (p>0.05).
In clinical studies made on cats with spontaneously occurring CRF and in experimental induced renal failure, no effect on plasma biochemistry and hematology were observed following long-term treatment with benazepril. (Brown et al., 2006; King et al., 2006; Watanabe and Mishina, 2007)

**Table 2.**

Blood biochemical parameters and UPC ratio before and during benazepril administration in cats with CRF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before benazepril administration</th>
<th>During benazepril administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before administration</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.77 ± 0.73</td>
<td>2.49 ± 0.49</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>83.0 ± 27.79</td>
<td>74.0 ± 15.92</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.90 ± 0.49</td>
<td>2.99 ± 0.41</td>
</tr>
<tr>
<td>Total Proteine (g/dl)</td>
<td>7.38 ± 0.63</td>
<td>7.40 ± 0.51</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>5.29 ± 1.93</td>
<td>5.09 ± 1.05</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.11 ± 1.00</td>
<td>4.49 ± 0.64</td>
</tr>
<tr>
<td>UPC (mg/dl)</td>
<td>0.42 ± 0.25</td>
<td>0.24 ± 0.13*</td>
</tr>
</tbody>
</table>

¹ Values are mean ± standard deviation  
* p<0.05 vs. before benazepril administration

The urine samples analysis have proved that proteinuria appreciated by UPC ratio was the only biochemical variable which has significantly decreased after 4th weeks of benazepril treatment (table 2). The evaluation made at 12 weeks showed that the UPC ratios were significant decreased compared with those recorded before initiation of benazepril administration.

Proteinuria is not only a marker of glomerular damage, but also a major cause of progression of renal failure. The data available in cats, reveal an inverse relationship between magnitude of proteinuria and survival time in cats with CRF. (Syme et al., 2006; King et al., 2006; King et al, 2007, Lees et al., 2004). Increased UPC ratio was an independent risk factor associated with shorter renal survival time in cats with CRF. (King et al., 2007) Probable mechanisms for proteinuria in cats with CRF are glomerular capillary hypertension, systemic hypertension or both. (Brown et al., 2001; King et al., 2006; Lefebvre and Toutain, 2004) Other causes that can be involved include incomplete covering of the glomerular surface area by podocytes in the presence of glomerular hypertrophy or lesions caused by toxins or immunoreactants (Lefebvre and Toutain, 2004). Reduction of proteinuria with benazepril treatment has been reported previously in clinical and experimental study in cats. (King et al, 2006; Brown et al., 2001) The mechanism of action is attributed to a reduction in filtration pressure secondary to reduced glomerular hypertension (Brown et al., 2001). The ACEI may lower glomerular pressure by decreasing systemic blood pressure and inhibiting the formation of angiotensin II which induces vasoconstriction of the efferent arteriole (Lefebvre and Toutain, 2004). This effect has been investigated in cats and dogs with experimental CRF using renal micropuncture techniques. In cats, benazepril (0.25 – 2 mg/kg, p.o., q24 h) given for approximately 6.5 months induced a decrease in mean glomerular capillary pressure by 12 – 14 mmHg. The ratio of efferent to afferent arteriolar resistance was decreased by benazepril, and the rate of elimination of ultrafiltration was increased about two- to threefold. No significant treatment associated changes in single nephron glomerular filtration rate were observed. The arteriolar vascular effect of ACEI, and not the systemic hypotensive effect, was demonstrated to be the primary factor contributing to the decrease in glomerular hypertension (Brown et al., 2001)
In a clinical study on cats with spontaneously occurring CRF, the administration of benazepril in dose of 0.5 – 1.0 mg/kg/day produced a significant reduction of proteinuria, assessed by the urine UPC ratio, and this effect was present in all subgroups tested, including cats with UPC<0.2, although the effect was largest in cats with higher UPCs. (King et al., 2006)

CONCLUSIONS

The treatment with benazepril, by decreasing proteinuria and systemic arterial hypertension may have favourable effects in treatment of chronic renal insufficiency in cats.

Benazepril had no significant influences concerning the blood biochemical parameters of renal profile

REFERENCES