STUDY OF THE RENAL RESPONSE TO RAMIPRIL AND VALSARTAN IN RATS WITH LIVER CIRRHOSIS AND ASCITES

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ABSTRACT

This study was designed to examine the effects of combined administration of the angiotensin receptor blocker (AT1RB), valsartan & the angiotensin converting enzyme inhibitor (ACEI), ramipril on renal function in rats with liver cirrhosis. This animal model was induced by giving gradually increased intra-gastric doses of carbon tetrachloride (CCl₄).

Thirty male albino rats weighing 150-200 grams were used through this study. Rats were divided as the following:

Group (I) : formed of 6 non-cirrhotic control rats.

Group (II) : comprised 6 cirrhotic ascitic control rats.

Group (III) : Cirrhotic ascitic rats treated with ramipril in a dose of 2.5mg/kg/day for 2

weeks.

Group (IV) : Cirrhotic ascitic rats treated with valsartan in a dose of 20mg/kg/day for 2 weeks.

Group (V) : Cirrhotic ascitic rats treated with ramipril & valsartan combination for 2 weeks.

Daily urine volume & body weight were assessed to follow up the development & progress of ascites. Urinary & plasma sodium & potassium were measured. In addition plasma renin activity (PRA) & serum creatinine were estimated. In cirrhotic ascitic rats combination therapy with ramipril & valsartan was more efficacious than either monotherapy in improving kidney function & salt & water retention. Ramipril is as equally effective as valsartan at ameliorating the decline in renal function & salt

& water retention.

These results indicate that in rats with liver cirrhosis & ascites, the renal protective effect afforded by combined RAS (renin- angiotensin system) blockade in this model adds further support to the involvement of a tissue based RAS. Although the present study reveals elevation in PRA either in association with monotherapy or combined therapy, RAS blockade improved renal function which indicating that a local RAS confers renoprotective effect. The enhancing effects of ramipril & valsartan combination on renal electrolyte & volume excretion may reduce the need for diuretics & thus attenuates the risk of their induced electrolyte disturbances.

INTRODUCTION

In liver cirrhosis & ascites, the renin angiotensin system is usually activated. Such a correlation supports the hypothesis that activation of the RAS plays role in the pathogenesis of ascites in liver cirrhosis (1). PRA is increased in hepatic cirrhosis & is correlated with hepatic venous pressure gradient (2). Angiotensin II(Ang-II) is an important mediator of portal hypertension (3). Therefore, blockade of

RAS by ACEI/Ang II receptor antagonists should be beneficial for improvement of ascites, fluid & salt excretion(4). Consequently, intensive research has focused over the years on developing drugs, such as ACEI, renin inhibitors & AngII receptor antagonists that interfere with RAS at different levels (5).

The antihypertensive effect of ACEI has been mainly attributed to diminished formation of both plasma & tissue Ang II & due to accumulation of endogenous vasodilator kinins (6), as ACE catalyzes both the conversion of AngI to Ang II & the degradation of bradykinins & related kinins (7).

Although the administration of ACEIs results in a fall in plasma AngII levels the efficacy of ACEI is probably limited by their inability to completely block ACE activity & the generation of Ang II through other enzymatic pathways (8,9). Longterm ACEI use associated with a return in circulating Ang II following a reactive rise in plasma renin & Ang I due to interruption of Ang II feedback on renin release (10). On the other hand angiotensin receptor blockers do not affect production of bradykinin & should theoretically block the action of Ang II

chronically at the receptor level. Angiotensin receptors exist in two main forms, angiotensin receptors type -I (AT1) & type-2 (AT2) receptors. The main target for angiotensin receptor blocker is the AT1 receptors, which mediate AngII-induced vasoconstriction & electrolyte homeostasis.⁽¹¹⁾

Ramipril was selected among several analogs because of its unique physicochemical properties. It is a non-sulfhydryl ACE inhibitor, & after oral absorption it is transformed in the liver into its active metabolite ramiprilate, which is at least 23 times more lipophilic than enalaprilate & 47 times than for captopril.

Furthermore, the in vitro affinity of ramiprilate for the enzyme is higher than for enalaprilate & captopril by several times. The ramiprilate-ACE complex is therefore very stable & dissociates 6 times more slowly than the enalaprilate ACE complex & 22 times more slowly than the captopril ACE complex. In addition ramipril possesses a favorable pharmacokinetic profile as a consequence of its physicochemical properties; its higher potency allows the use of very low dose & the slow dissociation of the

ramipril-ACE complex explains the long duration of its action permitting a once-daily treatment⁽¹²⁾.

Valsartan is a highly selective, orally available angiotensin receptor (AT1), antagonist. Experimental studies have confirmed the abolition or attenuation of Ang II related effects, such as vasoconstriction, cell growth promotion & aldosterone release. In humans valsartan is rapidly absorbed with maximal plasma concentration occurring 1-2 hours after oral administration ⁽¹³⁾. Valsartan does not need to be metabolized to be effective. There is only one inactive metabolite. Since any AT receptor blockers-induced rise in Ang II should be attenuated by parallel ACE1 administration. The present study aimed to determine if a combination of ramipril & valsartan confer greater benefit than single therapy alone in liver cirrhosis with ascites in rats.

MATERIAL & METHODS

Drugs-used :

- Tritace tablets (each tab. contains 2.5 mg ramipril) produced by Hoechst Co.
- Diovan tab. (valsartan, 160mg (tab.) supplied by Novartis Co.
- Carbon-tetra chloride (CCl₄) pro-

duced by adwic Co.; each ml contains 1gram CCl_4 .

- Phenobarbitone powder: Alexandria Co.

The experimental protocol:

Thirty male albino rats weighing between 150-200grams. The animals were housed in a controlled environment. The animals were allowed free access to food & water.

Liver cirrhosis was induced by weekly intra gastric administration of CCl_4 (starting with 40ul/week & increasing progressively up to 300-400uL/week, along with Phenobarbital in the drinking water (0.35gram/L) accelerate induction of hepatic cirrhosis as previously described (14). The onset of ascites was detected by rapid weight gain associated with bulging of the flanks. When ascites developed, rats were given lower doses of CCl_4 (80ul/ week) for 2 weeks & then discontinued. This method was chosen to avoid spontaneous disappearance of ascites that may occur if CCl_4 is stopped immediately after appearance of ascites (15). Liver cirrhosis started to appear 5-6 weeks after CCl_4 administration. Sodium retention was detected about one week after the evidence of cirrhosis.(16,17).

After occurrence of ascites, animals were housed individually in metabolic cages. Measurement of water, food intake, body weight & urine volume were recorded daily. Urine specimens were collected daily & frozen at -70°C for later analysis. At the end of the experiment the rats were killed by decapitation. The diagnosis of cirrhosis was confirmed by visual examination at laparotomy. Blood samples were collected under ice in tubes containing EDTA & the separated plasma was stored at -70°C until the assessment of the following parameters:

- PRA by radioimmunoassay (18).
- Plasma & urine sodium & potassium by ion selective electrode electrolyte analyzer (avL988-Switzerland) (19).
- Serum & urine creatinine by using the modified Jaffe method with (20) deproteinization utilizing Boehringer-Mannheim kits.

Animal grouping :

Thirty male albino rats were used in this study. The animals were randomly divided into 5 equal groups:

Group (I) : Non-cirrhotic control animals, treated with 0.5ml saline intragastrically for 2 weeks .

Group (II) : Cirrhotic ascitic control rats treated with 0.5 ml saline for 2 weeks intragastrically.

Group (III) : Cirrhotic ascitic control rats treated with ramipril 2.5mg/kg/day (21), intragastrically for 2 weeks.

Group (IV) : Cirrhotic ascitic control rats treated with valsartan (22), 20 mg/kg/day intragastrically for 2 weeks.

Group (V) : Cirrhotic ascitic control rats treated with combination of ramipril & valsartan in same previous route, doses for 2 weeks.

in body weight as compared to noncirrhotic animals as illustrated in table (1). Cirrhotic untreated rats developed marked sodium & water retention associated with increased urinary potassium excretion & serum creatinine, but without changes in plasma potassium level as illustrated in table (1&2).

Administration of ramipril to cirrhotic rats with ascites induced significant decrease in body weight & urinary potassium excretion & serum creatinine levels, but it produced a significant increase in plasma potassium, urine volume & urinary sodium excretion as compared to cirrhotic non-treated rats (tab.1&2).

STATISTICAL ANALYSIS

The result were carried out according to Pipkin (23), using the student "t" test. P values < 0.05 were considered to be significant.

All values are expressed as mean $\pm$ standard error of the mean (SEM).

RESULTS

The diagnosis of cirrhosis was confirmed by visual examination at laporatomy. At the time of study all the cirrhotic animals showed marked ascites. Experimental induction of cirrhosis produced a significant increase

Administration of valsartan in a dose of 20 mg/kg/day for 2 weeks to cirrhotic rats with ascites produced similar changes as previously mentioned with ramipril treatment.

Coadministration of ramipril and valsartan to cirrhotic rats with ascites produced additive decrease in body weight, urinary potassium excretion serum creatinine & plasma sodium levels as compared to single drug administration. In contrast administration of the two drugs simultaneously developed a significant increase in urinary volume output, PRA & urinary sodium excretion (table 1 & 2).

Table (1): Effect of intragastric administration of ramipril and valsartan on body weight, urine volume, urinary sodium and potassium excretion in cirrhotic ascitic rats (Mean $\pm$ SE).

Animal group N=6	Bodyweight (gm)	Urinary sodium (m mol/L)	Urinary potassium (m mol/L)	Urine volume (ml/d)
Non-cirrhotic control	240 $\pm$ 5.1	220 $\pm$ 6.3	145 $\pm$ 4.6	8.8 $\pm$ 0.3
Cirrhotic ascitic control	320 $\pm$ 10.5 P1<0.001	191 $\pm$ 4.5 P1<0.05	178 $\pm$ 1.8 P1<0.05	4.5 $\pm$ 0.2 P1<0.05
Cirrhotic rats treated with ramipril (2.5mg/kg/day) for 2 week	280 $\pm$ 9.1 P2<0.05	210 $\pm$ 5.9 P2<0.05	155 $\pm$ 3.3 P2<0.05	5.9 $\pm$ 0.3 P2<0.05
Cirrhotic rats treated with valsartan (20 mg/kg/day) for 2 week	283 $\pm$ 8.4 P3<0.05	213 $\pm$ 4.8 P3<0.05	156 $\pm$ 4.2 P3<0.05	6.1 $\pm$ 0.4 P3<0.05
Cirrhotic rats treated with combined ramipril & valsartan in previous doses for 2 week (2.5mg/kg/day)	266 $\pm$ 9.3 P4<0.05	218 $\pm$ 6.8 P4<0.05	150 $\pm$ 6.1 P4<0.05	7.3 $\pm$ 0.1 P4<0.05

SE= standard error.

P1= test of significance between cirrhotic ascitic non-treated vs non-cirrhotic control rats.

P2= test of significance between cirrhotic ascitic rats treated with ramipril vs cirrhotic control.

P3= test of significance between cirrhotic rats treated with valsartan vs cirrhotic control.

P4= test of significance between cirrhotic rats treated with combination of ramipril & valsartan vs cirrhotic control rats.

Table (2): Effect of intragastric administration of ramipril and valsartan on plasma sodium, potassium, serum creatinine & plasma renin activity (Mean $\pm$ SE).

Animal group N=6	Plasma sodium (m mol/L)	Plasma potassium (m mol/L)	Serum creatinine (mg/dl)	PRA ng/ml/hour
Non-cirrhotic control	143 $\pm$ 0.5	4.4 $\pm$ 0.1	0.9 $\pm$ 0.01	5.6 $\pm$ 0.1
Cirrhotic ascitic control	210 $\pm$ 0.8 P1<0.001	4.5 $\pm$ 0.2 P1>0.05	3.6 $\pm$ 0.08 P1<0.001	8.5 $\pm$ 0.5 P1<0.001
Cirrhotic rats treated with ramipril (2.5mg/kg/day) for 2 week	180 $\pm$ 0.9 P2< 0.001	5.3 $\pm$ 0.1 P2<0.05	2.5 $\pm$ 0.02 P2<0.05	12.5 $\pm$ 0.6 P2<0.01
Cirrhotic rats treated with valsartan (20 mg/kg/day) for 2 week	175 $\pm$ 0.8 P3<0.001	5.1 $\pm$ 0.2 P3<0.05	2.1 $\pm$ 0.01 P3<0.05	12.1 $\pm$ 0.3 P3<0.05
Cirrhotic rats treated with combined ramipril & valsartan in previous doses for 2 week (2.5mg/kg/day)	160 $\pm$ 0.7 P4<0.001	5.3 $\pm$ 0.3 P4<0.05	1.8 $\pm$ 0.03 P4<0.001	12.8 $\pm$ 0.4 P4<0.05

SE= standard error.

P1= test of significance between cirrhotic ascitic non-treated vs non-cirrhotic control rats.

P2= test of significance between cirrhotic ascetic rats treated with ramipril vs cirrhotic control.

P3= test of significance between cirrhotic rats treated with valsartan vs cirrhotic control.

P4= test of significance between cirrhotic rats treated with combination of ramipril & valsartan vs cirrhotic control rats.

DISCUSSION

In the present study cirrhosis induced by CCl_4 was followed by a significant decrease in both urinary output & urinary sodium excretion as well as significant increase in body weight and urinary potassium excretion. Furthermore cirrhotic rats showed increased serum creatinine & PRA. These findings were in accord with Lopez-Novoa et al. (24), where they reported that rats with liver cirrhosis & ascites were unable to excrete salt & water promptly. However, the cause of the renal sodium & water retention not completely elucidated, there are many theories about its pathogenesis (25,26). It has been proposed that the major initiating factor is the peripheral arterial vasodilatation in the splanchnic circulation that activates baroreceptors mediated vasoconstriction, antinatriuretic & anti-diuretic response to counterregulate the underfilling of arterial circulation. This counter regulation in compensated cirrhosis is associated with an increased plasma volume but without ascites. However, when the cirrhosis progresses, decompensation occurs as defined by ascites formation.

Many liver diseases including various types of liver cirrhosis may be

complicated by ascites. Conventional treatment of ascites with diuretics is frequently complicated by renal dysfunction & electrolyte disturbances (27). A brisk diuresis results in contraction of extracellular fluid volume. Therefore, the use of angiotensin converting enzyme blocker may share in solving some of the above mentioned problems.

The present study reports that in a model of liver cirrhosis with ascites & renal impairment, combination therapy with ramipril & valsartan was more efficacious than either monotherapy in improving kidney function & sodium & water retention. Ramipril is as equally effective as valsartan at ameliorating the decline in renal function & sodium & water retention. A similarity in the renoprotective effects AT1 receptor blocker & ACEI has been reported in a variety of studies that have been compared monotherapy vs combined therapy (28). The studies that have compared monotherapy vs combined AT receptor blocker & ACEI have reported no additional benefit of combined therapy on renal structure & function in the 5/6 mass ablation models (29), cyclosporine induced interstitial fibrosis (30) and unineph-

rectomized STZ diabetic spontaneously hypertensive rats (31).

In present study there are the attenuation of the decline in renal function in cirrhotic ascitic rats treated by combined valsartan & ramipril. These findings are supported by studies of Willeinson et al. (24), they reported that combined valsartan & perindopril treatment reduced albuminuria & attenuated the decline in GFR (glomerular filtration rate) to similar extent as monotherapy in diabetic nephropathy.

The present study was performed in rats with liver cirrhosis & ascites, which overexpresses various components of the RAS, including renin. These added reno protective effects afforded by combined RAS blockade in this model adds further support to the involvement of a tissue-based RAS. A number of studies suggested that an enhanced RAS may induce local injury (29,31,32). Although the present study reveals elevation of PRA in either monotherapy or combined therapy, however RAS blockade improved renal function, indicating that local RAS blockades confers renoprotective effect.

Osteopontin (OPN) mediates progressive renal injury in various renal diseases by attracting macrophages, and its expression is regulated by the RAS(33). Up regulation of OPN expression may play a role in tubulointerstitial injury & blockade of RAS by ramipril may confer renoprotective effect by decreasing OPN expression (33). It was suggested that valsartan has some renal protective effect in rats through down regulating tumour transforming growth factor beta-1 (TGF beta-1) expression & reducing deposition of glomerular extracellular matrix (34). Furthermore, Nagasawa et al. (34), reported that AngII has a direct effect on connective tissue cells & their ability to produce extracellular matrix proteins. The direct effect of the renin-angiotensin system on the activity of interstitial cells was further proven by molecular biology techniques showing an up regulation of transcription for collagen I & II which was prevented by ACE inhibitor. (35).

CONCLUSIONS

Combination therapy of an AT₁ receptor blocker (valsartan) & ACE1 (ramipril) appears to be approach for developing effective natriuresis & decreased deterioration in renal

function associated with liver cirrhosis and ascites.

The enhancing effects of ramipril & valsartan combination on renal electrolyte & volume excretion may reduce the need for diuretics & thus attenuated the risk of their induced electrolyte disturbance. These findings provide a rationale for applying such combination regimens in the prevention of hepatorenal syndrome. However this phenomenon may not occur in humans & therefore one must be cautious in extrapolating these findings in humans.

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دراسة لاستجابة الكلى لتأثير اعطاء دوائى الرامبيريل والفالسرتان فى الفئران المصابة بالتليف الكبدى المصحوب بالاستسقاء

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تمت دراسة اعطاء كلام دوائى الرامبيريل (مشبط لانزيم النجيووتسين والفالسرتان) قافل لمستقبلات الانجيووتسين) كلا على وكذلك أعطائهما معاً للفئران المصابة بالتليف الكبدى المصحوب بالاستسقاء.

استخدام لاجراء هذا البحث عدد ٣٠ (ثلاثون) فأراً أبيضاً من الذكور، يتراوح وزن الواحد منهم ما بين ١٥٠ - ٢٠٠ جرام.

تم تقسيم الفئران الى خمسة مجموعات متساوية (٦ فئران فى كل مجموعة) :-

- ١- مجموعة ضابطة عادية عولجت بمحلول ملح عادى (٩.٠٪) وذلك عن طريق الفم لمدة أسبوعين.
- ٢- مجموعة ضابطة مصابة بالتليف الكبدى المصحوب بالاستسقاء عولجت بأيضاً بمحلول الملح عن طريق الفم لمدة أسبوعين.
- ٣- مجموعة مصابة بالتليف وأعطيت دواء الرامبيريل وبجرعة ٢.٥ مجم/كجم يومياً لمدة أسبوعين متتاليين وذلك عن طريق الفم .
- ٤- مجموعة مصابة بالتليف الكبدى، المصحوب بالاستسقاء وتم علاجها بدواء الفالسرتان، وذلك بجرعة تعادل ٢٠ مجم / كجم يومياً لنفس المدة السابق ذكرها وعن طريق الفم أيضاً.
- ٥- مجموعة مصابة بالتليف والاستسقاء وعولجت بإعطائها الدوائيين معاً بنفس الجرعات السابق ولنفس المدة عن طريق الفم أيضاً.

وتم تقييم تأثير استخدام هذه الأدوية بواسطة المعايير الآتية :-

- متابعة قياس وزن الجسم يومياً .
- قياس نسبة كل من الصوديوم والبوتاسيوم فى البول وكذلك فى البلازما وأيضاً قياس كمية اخراج البول خلال ٢٤ ساعة.
- قياس نشاط الرنين فى البلازما.
- قياس نسبة الكرياتينين فى المصل .

ويمكن تلخيص نتائج هذا البحث كالتالى :-

١- أعطاء الراميبريل للفئران المصابة بالتليف الكبدى المصحوب بالاستسقاء، أحدث نقص ذو دلالة إحصائية فى وزن الجسم، وكذلك فى نسبة الكرياتينين فى المصل مع حدوث تحسن ذو دلالة إحصائية فى نسبة كمية اخراج البول يومياً مع زيادة تركيز الصوديوم به وذلك عند مقارنة هذه النتائج مع المجموعة الضابطة للتليف.

٢- أعطاء دواء الفالسرات للفئران المصابة بالتليف الكبدى المصحوب بالاستسقاء بجرعة ٢٠ مجم/ك يومياً لمدة أسبوعين متتاليين وذلك عن طريق الفم، أحدث نقص ذو دلالة إحصائية فى وزن الجسم ومستوى الكرياتينين فى المصل، بالإضافة إلى زيادة كمية إخراج الصوديوم والبول يومياً، مع نقص تركيز البوتاسيوم بالبول وكذلك أحدث زيادة فى مستوى البوتاسيوم فى البلازما وأيضاً زيادة نشاط الرنين فى البلازما وذلك بالمقارنة مع المجموعة الضابطة للتليف.

٣- عند اعطاء الدوائين معاً بنفس الجرعات ولنفس المدة عن طريق الفم أيضاً أحدث تحسن فى المعايير السابقة ولكن بدرجة أفضل من تلك التى حدثت عن استخدام الدوائين على حدة.

وعلى ضوء هذه الدراسة يمكن استنتاج أن استخدام دوائى الراميبريل والفالسرات معاً له تأثير إيجابى فى علاج اضطراب وظائف الكلى المصاحب للتليف الكبدى فى الفئران المصابة وكذلك له تأثير جيد على اخراج السوائل والأملاح.

ويجدر التنبيه بأن حدوث تلك التغيرات قد لا يكون بنفس الفاعلية فى الانسان، ولذا ننصح بإجراء تجارب مماثلة فى المرضى المصابين بالتليف الكبدى المصحوب بالاستسقاء مع حدوث تغيرات فى وظائف الكلى.