ANNALS OF HEPATOLOGY

Volume 2 *Number* 1 *January-March* 2003

Artículo:

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Annals of Hepatology 2003; 2(1): January-March: 36-40

Annals of Hepatology

Original Article

A randomized study of losartan *vs* propranolol: Effects on hepatic and systemic hemodynamics in cirrhotic patients

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Abstract

Background & aims: **The potential use of losartan, an angiotensin II type 1 receptor blocker, in the treatment of portal hypertension is still under debate. This randomized controlled trial compared the effects of losartan vs. propranolol on portal and systemic hemodynamics in patients with cirrhosis. *Methods*: Twenty-seven compensated patients were randomized to receive losartan 25 mg/day (n = 17) or propranolol (n = 10). Hepatic venous pressure gradient (HVPG), portal blood flow (Doppler duplex ultrasound) and systemic hemodynamics were measured at baseline and after 12-week treatment. Portal resistance was calculated as HVPG/portal blood flow. *Results*: Propranolol induced a reduction in cardiac output (p 0.002), heart rate (p 0.0001) and HVPG [from 16.4 (± 4.1) to 13.1 (± 3.6) mmHg (p 0.07)]; six patients showed a reduction equal or greater than 20% and were considered responders. Losartan caused a decrease in HVPG [from 15.6 (± 4.2) to 11.8 (± 3.5) mmHg (p 0.002)], without changes in portal blood flow and systemic hemodynamics. Changes in HVPG correlated with variations in portal resistance (r 0.88, p < 0.0001). Losartan induced a reduction in HVPG between 10 and 19% in 5/17 patients, and 20% or more in 8/17. Five out of eight patients who respond to losartan showed severe portal hypertension, with higher baseline HVPG (equal or greater than 16 mmHg). *Conclusions*: the administration of losartan in a doses of 25 mg per day may be effective in lowering portal pressure in patients with compensated cirrhosis, particularly in those with more severe portal hypertension.**

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Key words: Cirrhosis, portal hypertension, hemodynamic, propranolol, losartan, angiotensin II, angiotensin II receptor: randomized trial, therapy, portal pressure, hepatic venous pressure gradient, portal blood flow, Doppler duplex ultrasound.

Introduction

Portal hypertension represents one of the main clinical complications of chronic liver diseases. Its consequences, variceal bleeding, ascites and hepatic encephalopathy are major causes of death and liver transplantation in patients with cirrhosis. The aim of the farmacological treatment in portal hypertension is to achieve a sustained decrease in portal pressure. A reduction in the hepatic venous pressure gradient (HVPG) by more than 20% of baseline values or below 12 mmHg by pharmacological agents has been associated with a marked reduction of the risk of variceal bleeding or rebleeding. However, these targets are achieved only in about 30% of the patients treated with nadolol or propranolol.[1-3] The presence of adverse effects or contraindications to β-blockers and the low efficacy of this therapy have stimulated the search of alternative pharmacological treatments for portal hypertension.

The effect of the blockade of the renin-angiotensin system in the treatment of portal hypertension at different levels, with saralasin or angiotensin convertase enzyme inhibitors, has been studied since two decades.[4,5] However, severe arterial hypotension was frequently observed. With the development of non-peptide, orally active angiotensin II type 1 receptor (AT1) antagonists, a new chapter in the inhibition of the bioenzimatic cascade was started. In 1999, Schneider et al. reported that the administration of 25 mg per day of losartan caused an important decrease in portal pressure in patients with portal hypertension without clinically significant arterial hypotension.[6]

Conversely, recent studies were unsuccessful in corroborating this initial results.[7,8] For instance, in the study of González-Abraldes et al, the administration of higher doses of losartan caused arterial hypotension without changes in HVPG.[7] Hence, the potential use of losartan in the treatment of portal hypertension is still under debate.

The aim of the present randomized controlled study was to evaluate the effects on portal and systemic hemodynam-

ics of long term losartan administration (25 mg/day) *versus* propranolol in cirrhotic patients with portal hypertension.

Patients and methods

Patients

Twenty-seven outpatients were selected among those who had been referred to the Liver Unit of the hospital, and were included in the study. The inclusion criteria were: presence of cirrhosis, endoscopically proven esophageal varices and permeability of portal vein assessed by Doppler duplex ultrasound. The diagnosis of cirrhosis was based on liver biopsy and/or compatible clinical, ultrasonographic and analytical findings. The exclusion criteria were: age < 18 or > 75 years, active alcoholism, presence of hepatocellular carcinoma, Child-Pough score >12, contraindications to β-blockers and renal failure (serum creatinine level > 2 mg/dL). All the patients had compensated cirrhosis and had abstained from alcohol for at least 6 months. Seven patients had history of variceal hemorrhage and eleven of ascites. The severity of liver disease was graded according to Pough's criteria. Additional data are given in *Table I*.

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethical Commitee of the Hospital. Written informed consent was obtained in every case. The study was performed in the Liver Unit and the Hemodynamic Unit of Hospital Argerich, dependent from the Government of the City Of Buenos Aires.

Study Design

The study was a randomized trial of losartan *vs*. propranolol. Patients were randomized with a ratio 2:1 to receive either losartan or propranolol. Randomization was carried out in blocks of five using random numbers stratified according to the severity of portal hypertension, arbitrary defined as moderate (baseline HVPG less than 16 mmHg) or severe (equal or greater than 16 mmHg). The sample size was calculated in 27 patients for a power to detect an increase of response from an estimated 37% in the propranolol group[3] to 95% in the losartan group (Schneider et al. reported 98% of response in their study)[6] with an α-error of 0.05 and a β-error of 0.20.[9]

Splanchnic and systemic hemodynamics and Doppler duplex ultrasound were performed at baseline and after 3 months of continued therapy. Laboratory analysis including hematologic tests (hemoglobin, leukocyte, neutrophil and platelet count) and biochemical tests (alanin aminotransferase, alkaline-phosphatase, gammaglutamyltransferase, creatinine, blood urea nitrogen, albumin and prothrombin time), were performed at baseline and every 4 weeks by the local laboratory. Any therapy with vasoactive drugs was withdrawn at least seven days before baseline measurements.

Once the baseline measurements were completed, patients were randomly allocated to one of the two treatment groups. Ten patients (five with moderate and five with severe portal hypertension) received propranolol therapy with an initial dose of 20 mg per day. This dosage was increased stepwise until the heart rate

Table I. Clinical characteristics of the patients.

	Propranolol	*Losartan*	*p*
n	10	17	
Age (years)	42.8 (21-72)	53.1 (19-70)	NS
Sex (male/female)	4/6	10/7	
Etiology			
HCV	4	6	NS
Alcohol and hepatitis C	1	0	NS
Alcohol	2	5	NS
Other diseases*	3	6	NS
Presence of ascites (n)	2	2	NS
Esophageal varices (I/ II-III**)	2/8	3/14	NS
History of variceal bleeding (n)	4	3	NS
Spleen size (cm)	14.7 (± 3.3)	14.6 (± 2.4)	NS
HVPG (mmHg)	16.4 (± 4.1)	15.6 (± 4.2)	NS
Portal vein diameter (cm)	12.4 (± 1.7)	12.3 (± 3.3)	NS
Serum bilirrubin (mg/dL)	1.77 (± 0,8)	1.61 (± 0,81)	NS
Serum ALT (IU/l)	73 (± 69)	73 (± 77)	NS
Serum albumin (mg/dL)	3.5 (± 0.5)	3.6 (± 0.5)	NS
Prothrombin time (%)	64 (± 12)	70 (± 14)	NS
Creatinine (mg/dL)	0.78 (0.19)	0.88 (± 0.21)	NS
Child- Pough class (A/B)	8/2	17/0	NS
Child-Pough score	5.9 (± 1.7)	5.3 (± 0.5)	NS
Response to the drug	6	8	NS

* Hepatitis B, Autoimmune hepatitis, primary biliary cirrhosis or Criptogenic.

** Japanese Resarch Society for Portal Hypertension (Chairman: R. Inokuchi). The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg 1980; 10: 84-87.

was reduced by 20% or to less than 55 beats/min. Seventeen patients (nine with moderate and eight with severe portal hypertension) received losartan 25 mg/day. The patients were enrolled and assigned to the groups by G.C.

Methods

Doppler duplex ultrasound. After an overnight fast, a Doppler duplex ultrasound study was performed according to a previously described procedure[10,11] (Aloka SS1700, with color Doppler and a 3.5 MHz sector electronic probe). Briefly, the portal vein was longitudinally scanned and the sample volume was positioned in the middle of the portal trunk; the isoniation angle was equal or lower than 55°. Portal diameter and mean flow velocity were measured and portal blood flow was automatically calculated.[12] The final value of all measurements was the mean of at least three determinations. All these studies were performed by the same observer (G.C.).

Splanchnic and systemic hemodynamics. After the ultrasound study was performed, the patients were transferred to hemodynamic Unit. Then, under fluoroscopic guidance, a 7F balloon catheter was advanced into the main right hepatic vein to measure the free and wedged hepatic venous pressures, and a Swan-Ganz catheter was advanced into the pulmonary artery to measure cardiopulmonary pressures, as previously described.[10,13] Portal pressure was determined by the HVPG, which is obtained by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. Systolic, diastolic and mean arterial pressures were measured by using an automatic sphygmomanometer (VR 12, Electronics for Medicine). Systemic vascular resistance was calculated as [(Mean Arterial Pressure- Right Atrial Pressure)/Cardiac Output] X 80. Total arterial compliance was calculated as stroke volume/pulse pressure; where stroke volume = cardiac output/heart rate; and pulse pressure = systolic – diastolic pressure.[14,15] Portal resistance was calculated as HVPG/portal blood flow and expressed as mm Hg X minute/liter.[16] The final value of all measurements was the mean of at least three determinations. All these studies were performed by the same observer (P.V.), who was blinded to group assignment.

Statistical analysis

Results were expressed as mean $\pm$ SD. Shapiro-Wilk's *W* of normality was performed. Differences between proportions were analyzed by χ^2 test and the Fisher's exact test. Differences between groups were analyzed by paired and unpaired Student's *t* test, and by Mann-Whitney *U* or Wilcoxon matched paired tests, according to the distribution. Significance was established at $p < 0.05$. Pearson's *r* coefficient was utilized for correlations.

Results

A total of 27 patients were randomized to receive losartan (n = 17) or propranolol (n = 10). Recruitment started in September 1999 and ended in October 2001. All the patients completed the study, and none of them was excluded from analysis. Both drugs were well tolerated and no important adverse effect was recorded. There were no differences between the two groups in clinical, laboratory or hemodynamic baseline characteristics *(Tables I and II)*. No significant difference was found in the proportion of responders between the groups. No significant changes were observed in liver or renal function tests after propranolol or losartan administration.

Propranolol administration

Propranolol induced a statistically significant reduction of cardiac output and heart rate *(Table II)*. Propranolol caused a decrease in HVPG from 16.4 ($\pm$ 4.1) to 13.1 ($\pm$ 3.6) mmHg (p 0.07), without changes in portal blood flow or portal resistance. Six out of 10 patients showed a reduction equal or greater than 20% in HVPG and were considered responders. The five patients with severe portal hypertension were responders, *versus* 1/5 patients with moderate portal hypertension (p 0.048)

Losartan administration

No significant difference was observed after losartan administration in any parameter of the systemic hemodynamics. After losartan administration, the HVPG decreased from 15.6 ($\pm$ 4.2) to 11.8 ($\pm$ 3.5) mmHg (p 0.002), with a reduction in portal resistance from 13.7 ($\pm$ 5.7) to 10.9 ($\pm$ 5.8) mmHg . min/L (p 0.049), without changes in portal blood flow. A significant correlation was found between changes in HVPG and portal resistance (r 0.88; $p < 0.0001$).

A decrease in HVPG between 10 and 19% from baseline was found in 5/17. Eight patients showed a reduction of 20% or more in HVPG and were considered responders.

Responder patients to losartan had a higher mean arterial pressure (105 $\pm$ 12 *vs* 89 $\pm$ 9 mmHg; p 0.01), pulmonary wedged pressure (16 $\pm$ 7.2 *vs* 8.2 $\pm$ 3.2 mmHg; p 0.01) and wedged hepatic vein pressure (26.9 $\pm$ 5 *vs* 21.4 $\pm$ 3.2 mmHg; p 0.02) than non responders.

Analyzing the variations in hemodynamic parameters according to the severity of portal hypertension, patients with severe portal hypertension showed higher baseline mean arterial pressure, HVPG, wedged hepatic venous pressure and portal resistance *(Table III)*, and showed a significant reduction in HVPG and portal resistance after treatment. Three out of nine patients with moderate portal hypertension were responders to losartan vs. 5/8 patients with severe portal hypertension (NS).

Table II. Systemic and hepatic hemodynamics at baseline and after 3 month treatment.

	Propranolol			Losartan		
	Baseline	3 months	*p*	Baseline	3 months	*p*
Mean arterial pressure (mmHg)	86 (± 12.5)	83.3 (± 11.65)	NS	96.6 (± 13.2)	93.9 (± 15.9)	NS
Arterial compliance (L/mmHg.10^{-3})	2.17 (± 1.1)	2.9 (± 1.4)	NS	1.8 (± 1)	2.02 (± 0.9)	NS
Cardiac output (L/min)	6.7 (± 1.8)	5.6 (± 1.8)	0.002	7.2 (± 2.4)	7.4 (± 2.6)	NS
Cardiac index (L/min/m^2)	3.7 (± 0.7)	3.1 (± 1)	0.03	3.8 (± 1.7)	4 (± 1.2)	NS
Systemic vascular resistance (din/seg/cm^{-5})	1038 (± 403)	1246 (± 581)	0.06	1108 (± 410)	1039 (± 394)	NS
Heart rate (beats/min)	81.6 (± 9.2)	63.2 (± 3.0)	0.0001	78.1 (± 11.8)	75.8 (± 15.2)	NS
Pulmonary capillary wedged pressure (mmHg)	9.1 (± 5)	11.2 (± 6.2)	NS	11.9 (± 6.6)	12.3 (± 6.2)	NS
Mean pulmonary artery pressure (mmHg)	17.4 (± 9)	19 (± 12.1)	NS	20.1 (± 7.9)	20.3 (± 7.2)	NS
HVPG (mmHg)	16.4 (± 4.1)	13.1 (± 3.6)	0.07	15.6 (± 4.2)	11.8 (± 3.5)	0.002
Portal blood flow (mL/min)	1274 (± 628)	1160 (± 662)	NS	1279 (± 495)	1266 (± 578)	NS
Portal resistance (mmHg . min/L)	16.2 (± 9.7)	14.5 (± 8)	NS	13.7 (± 5.7)	10.9 (± 5.8)	0.049

Table III. Systemic and hepatic hemodynamics according to the severity of portal hypertension at baseline and after 3 month treatment with losartan.

	Moderate portal hypertension HVPG < 16 mmHg (n = 9)			Severe portal hypertension HVPG equal or >16 mmHg (n = 8)			*
	Baseline	*3 months*	*p*	*Baseline*	*3 months*	*p*	
Mean arterial pressure (mmHg)	89 (± 9)	93 (± 17)	NS	105 (± 12)	95 (± 15)	NS	0.01
Cardiac index (L/min/m^2)	3.9 (± 1)	4.2 (± 1)	NS	3.8 (± 1.4)	3.9 (± 1.3)	NS	NS
Systemic vascular resistance (din/seg/cm^{-5})	949 (± 314)	979 (± 359)	NS	1286 (± 451)	1107 (± 445)	NS	NS
Mean pulmonary arterial pressure (mmHg)	21.2 (± 9)	20.3 (± 7.9)	NS	18.8 (± 7.5)	20.3 (± 6.8)	NS	NS
HVPG (mmHg)	12.6 (± 2.5)	10.8 (± 3.1)	NS	19 (± 2.8)	12.9 (± 3.7)	0.01	0.000
Free hepatic venous pressure (mmHg)	8.9 (± 4.3)	10.3 (± 4.9)	NS	7.9 (± 3)	10.5 (± 3.5)	0.05	NS
Wedged hepatic venous pressure (mmHg)	21.4 (± 4.3)	21.1 (± 4.9)	NS	26.9 (± 4)	23.4 (± 4.4)	0.01	0.02
Portal blood flow (mL/min)	1324 (± 635)	1228 (± 717)	NS	1222 (± 263)	1314 (± 382)	NS	NS
Portal resistance (mmHg . min/L)	11.4 (± 5.6)	11.4 (± 6.8)	NS	16.5 (± 4.5)	10.3 (± 4.4)	0.01	0.05
N° of responders		3**			5**		

* Statistical difference between baseline parameters
** NS

Discussion

In this study we investigated the effects of twelve-week treatment with losartan 25 mg/d *versus* propranolol in patients with compensated cirrhosis and portal hypertension. We observed that chronic administration of losartan caused a significant decrease in HVPG without changes in systemic hemodynamics or renal function. Changes in HVPG strongly correlated with variations in portal resistance. Patients with higher portal hypertension and portal resistance showed a better response to losartan.

Large amount of evidence supports the hypothesis that angiotensin II plays a role in the physiopathology of portal hypertension. For instance, the renin-angiotensin system is frequently activated in patients with advanced cirrhosis and it has been observed a direct relationship between plasma renin activity and HVPG. Furthermore, angiotensin II raises portal pressure by an increase in hepatic vascular resistance[17] caused by direct contraction of activated stellate cells. Recent studies have shown that this effect is mediated by the interaction between angiotensin II and the AT1 receptor.[18]

Angiotensin II, the final active product of the renin-angiotensin system, interacts with at least two membrane receptors in humans, type1 and type 2. Physiological effects of angiotensin, such as vasoconstriction, aldosterone stimulation, salt and water homeostasis, and contraction and proliferation of hepatic activated stellate cells seem to be mediated by the stimulation of the G-protein-coupled AT1 receptor. Moreover, several studies have shown the presence of this receptors in human myofibroblast-like hepatic stellate cells.[18-20]

The variations in HVPG and portal resistance after losartan administration may be explained by the effect of the blockade of AT1 on the contractility of hepatic activated stellate cells, by means of a decrease in intrahepatic vascular resistance assuming an increased activation of the renin-angiotensin system in the hepatic circulation.[18]

Losartan is a low molecular weight non-peptide, thus orally active, without intrinsic agonist properties. This drug is well absorbed and its bioavailability unaffected by food. In the liver, by a cytochrome P450 mechanism is partially converted into a more active metabolite, EXP3174. This metabolite has about 10-fold higher affinity for the AT1 receptor than losartan and is more slowly cleared. Losartan and EXP3174 are eliminated by both, biliary and urinary excretions.[19] Consequently, reports of high losartan and EXP3174 concentrations in patients

with cirrhosis suggest that the dose should be lowered in the presence of hepatic impairment.[21]

Regarding to the systemic and portal effects of losartan, our results are in discrepancy with other authors' fidings. For instance, González-Abraldes et al found a significant decrease in mean arterial pressure and systemic vascular resistance, with renal function impairment and without changes in HVPG.[7] Nonetheless, the doses administered in this study were higher. A possible explanation to this discordance is that higher doses of losartan in patients with cirrhosis may account of marked systemic effects, specifically a reduction in arterial pressure.[22] Accordingly, arterial hypotension may enhance the activation of endogenous vasoactive systems and then counterbalance a putative local effect of the AT1 blockade.

With reference to the first study evaluating the effect of 7-day administration of losartan on portal pressure in cirrhotic patients,[6] Schneider et al found a more than 40% decrease in HVPG, without clinically important (although significant) changes in arterial blood pressure. The patients had higher baseline portal pressure and a proportion of them suffered from more advanced liver disease than those of our study. Additionally, in our series, patients with higher portal hypertension showed a better response to losartan. These clinical findings are in agreement with the observation that plasmatic angiotensin II concentrations present a two fold increase in preascitic cirrhosis versus controls, but an eight fold increase in advanced cirrhosis with refractary ascites versus controls.[23]

In conclusion, the administration of losartan in a dose of 25 mg per day was well tolerated and effective in lowering portal pressure in patients with compensated cirrhosis, particularly in those with more severe portal hypertension.

Acknowledgements

The authors are grateful to Professor Abraham Lemberg for helpful discussions.

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