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A1166C Angiotensin II Type 1 Receptor Gene Polymorphism May Predict Hemodynamic Response to Losartan in Patients with Cirrhosis and Portal Hypertension

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OBJECTIVE: Losartan, a dose of 25 mg/day, has been found to be effective in 50% of patients with portal hypertension without adverse effects. We evaluated the relationship between genetic polymorphisms of the renin-angiotensin system (A1166C angiotensin II type 1 receptor (AT1R), angiotensinogen T174M and M235T, and angiotensin-converting enzyme I/D) and the effects of losartan on portal and systemic hemodynamic in patients with cirrhosis and portal hypertension.

METHODS: We performed a longitudinal study that included 23 consecutive patients with cirrhosis and esophageal varices who received 25 mg/day of losartan during 12 wk. Hepatic venous pressure gradient (HVPG) and systemic hemodynamic were measured at baseline and after treatment. Genomic DNA was extracted from peripheral blood leukocytes; genetic polymorphisms of the renin-angiotensin system were investigated by polymerase chain reaction and restriction fragment length polymorphisms.

RESULTS: The homozygous patients for AT1R A allele showed higher pulmonary-wedged and free hepatic venous pressure on baseline. After treatment, they showed a higher decrease of HVPG (32.5% $\pm$ 19.2) in comparison with patients with AC/CC genotype (2.4% $\pm$18.9), $p < 0.01$. Ten of 15 patients with AA genotype were responders, while only one of eight with AC/CC genotype ($p < 0.002$); genotype AA showed a positive predictive value of 66.6% and negative predictive value of 87.5%.

CONCLUSIONS: These results suggest that there is a relationship between the AT1R A1166C polymorphisms and the therapeutic response to losartan. The genetic testing may be used as a predictive factor of this response.

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INTRODUCTION

Portal hypertension is 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 pharmacological treatment in portal hypertension is to achieve a sustained decrease in portal pressure since a reduction in the hepatic venous pressure gradient (HVPG) by more than 20% of baseline values or below 12 mmHg has been associated with a marked reduction in the risk of variceal bleeding or rebleeding (1). Although propranolol is the standard therapy, these goals are achieved only in about 30% of the treated patients (2). Besides, adverse effects and contraindications to β-blockers have stimulated the search of alternative pharmacological treatments.

The effects of the renin-angiotensin-system (RAS) blockade at different levels have been studied during the last two decades since it has been shown that angiotensin II (AngII) may play a central role in the pathogenesis of portal hypertension. AngII stimulates stellate cell contraction by angiotensin II type 1 receptor (AT1R), a G-protein-coupled receptor expressed by many cells, therefore, worsening portal hypertension by increasing hepatic sinusoidal resistance (3). Moreover, AngII levels are elevated in cirrhosis (3). These data support the rationale for treating portal hypertension with AT1R blockers. In 1999, Schneider *et al.* found that the administration of 25 mg per day of losartan, a nonpeptide AT1R antagonist, caused an important decrease in portal pressure of patients with portal hypertension, without significant arterial hypotension (4). Recently, two randomized controlled trials have shown that losartan had equal or greater effect

in lowering portal pressure than propranolol, without serious adverse effects (5, 6). These studies also pointed out that a significant proportion of the patients remained unresponsive, suggesting the existence of individual factors underlying the different pharmacological efficacy of the angiotensin II antagonism in patients with portal hypertension.

Polymorphisms of the genes encoding the components of the renin-angiotensin system have attracted a great deal of attention as genetic markers for various cardiovascular diseases. The angiotensin-converting enzyme (ACE) gene was mapped to human chromosome 17q23, and an insertion/deletion (I/D) polymorphism resulting from the presence/absence of a 287 base pair (bp) fragment in the 16th intron has been identified (7). The ACE genotype with two deletion alleles (DD genotype) was reported to have association with high serum ACE activity and also with several cardiovascular diseases (8).

Recent studies have suggested a direct correlation between angiotensinogen AGT and blood pressure (9). The AGT gene was mapped to chromosome 1q42–43 and bears a polymorphism at codon 235 in exon 2, constituting the thymine-cytosine transition at nucleotide 704, which results in a methionine to threonine substitution at amino acid 235 (M235T) (10). The T/T genotype of AGT gene codon 235 has been found to be associated with a higher plasma AGT concentration in several conditions (11, 12). Another polymorphism in the same exon of the AGT gene occurs at codon 174. This molecular variant of AGT also constitutes the cytosine–thymine transition at nucleotide 521, which causes a sense mutation from threonine to methionine at amino acid 174 (T174M). The M allele of AGT codon 174 has also been reported to be associated with essential hypertension (10).

Because of its physiological role, the AT1R gene is a candidate gene for hypertension. Bonnardeaux *et al.* (13) have screened exon 5 and the 3′ untranslated region (UTR) for mutations in 50 hypertensive subjects and identified several frequent polymorphisms. One of these, an A/C transition at nucleotide position 1166 in the 3′ UTR, was found to be associated with hypertension. Since this initial study, conflicting results have been obtained concerning the association of the AT1R 1166 A/C polymorphism with hypertension (14, 15) or with preeclampsia (16).

In the present study, we hypothesized that RAS polymorphisms, particularly the A1166C polymorphism of the AT1R gene, may explain the heterogeneous response to angiotensin II inhibition in portal hypertension, and consequently, we studied whether there was a relationship between RAS component gene polymorphisms and the hemodynamic response to losartan in cirrhotic patients with portal hypertension.

To investigate whether different losartan pharmacokinetic profiles may explain the interindividual variation in drug efficacy we measured plasma losartan levels. Since losartan is metabolized by the hepatic cytochrome p450 complex, CYP2C9 (17), we also investigated the contribution of the polymorphisms at the CYP2C9 gene to the therapeutic response.

METHODS

For testing this hypothesis, we performed a longitudinal study that involved 23 consecutive patients with cirrhosis and esophageal varices between September 2003 and March 2004.

Patients were selected from among those who had been referred as outpatients to the Liver Unit of the Hospital for the evaluation of portal hypertension. The inclusion criteria were the 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 as follows: age <18 or >75 yr, active alcoholism, the presence of hepatocellular carcinoma, Child-Pugh score >12 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.

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of our Institutions. Written informed consent was obtained in every case.

Hemodynamic Study

All patients were evaluated at baseline and after 12 wk of losartan 25 mg/day (Losacor, donated by Roemmers, Buenos Aires, Argentina). The hemodynamic procedure was described elsewhere (17, 18); briefly, systemic hemodynamic and hepatic vein pressures were obtained by catheterization.

Doppler duplex ultrasound (Aloka SS1700, 3.5 MHz sector electronic probe) was performed with measurements of portal diameter and mean flow velocity, automatically calculating portal blood flow. Patients were transferred to the hemodynamic unit where, 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 into the pulmonary artery to measure cardiopulmonary pressures. Portal pressure was estimated 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 obtained by an automatic sphygmomanometer (VR 12, Electronics for Medicine). Systemic vascular resistance was calculated as 0 (Mean Arterial Pressure−Right Atrial Pressure)/Cardiac Output] $\times$ 80. Portal resistance was calculated as HVPG/portal blood flow and expressed as mmHg min/L (19). The final value of each variable of a patient was the mean of at least three determinations.

Patients who showed a decrease in HVPG equal or greater than 20% under losartan treatment were considered responders.

Genetic Studies

Genomic DNA was extracted from white blood cells by a standard method as previously described (20) and genetic polymorphisms of the RAS components were investigated

as described elsewhere (21). Genetic polymorphisms were detected by hot-start Polymerase Chain Reactions (PCR) using Molecular Biology grade reagent from Sigma Co. (St. Louis, MO) and a Robocycler 96 thermal cycler (Stratagene, La Jolla, CA). All primers were from Life Technologies (Rockville, MD) (Table 1).

The I/D polymorphism of the ACE was detected using a previously published method (7) with minor modifications. Preferential amplification of the D allele was excluded by the addition of an insertion-specific primer (C) (Table 1), which produced an amplicon of 300 bp in the presence of the I allele.

For typing the AGT variants in codons 174 and 235, the exon 2 of the AGT gene was amplified using a modification of the method of Jeneumaitre *et al.* (10). For T174M polymorphism genotyping, 20 μl of the PCR product was digested with 1 U of Nco I restriction endonuclease (New England Biolabs, Beverly, MA) overnight at 37°C according to Caulfied *et al.* (22). Digested fragments were detected by electrophoresis in 3% agarose gel containing ethidium bromide. Following digestion, the homozygous threonine genotype (T/T) appears as a single band of 354 bp and the M/M genotype as a 260 bp and 94 bp.

The competitive allele-specific oligonucleotide hybridization of Morgan *et al.* (23) was used for genotyping the M235T polymorphism; 20 μl of the amplified product was denatured in 125 μl of 0.2 N NaOH, 2 × SSC, and spotted in duplicate onto nylon membranes (Hybond N+) (Dupont, Boston, MA). Fluorescein 5′ end-labeled oligonucleotides corresponding to wild type and mutant sequences at each site (Table 1) were synthesized (Life Technologies) and purified by HPLC. Each membrane was prehybridized for 1 h at 52°C in 10 ml SSPE, 1% SDS containing 30 pmoles of unlabeled oligonucleotide corresponding to either the wild-type or mutant sequence opposite to the allele recognized by the labeled oligonucleotide, then hybridized for 1 h at 52°C in 10 ml 5 × SSPE, 1% SDS containing 3 pmoles of the allele-specific fluorescein 5′ end-labeled allele-specific oligonucleotide. Dot detection was performed by using a chemiluminiscence kit (Life Science, Boston, MA) according to the manufacturer's recommendations. The determination of genotypes for the A1166C variant of the AT1R gene was performed according to the mismatch PCR/RFLP technique of Wang *et al.* (15). The PCR products digested with the Afl II restriction endonuclease (New England Biolabs, Beverly, MA).

CYP2C9 genotyping was performed according to Sullivan *et al.* (24). The CYP2C9∗2 and CYP2C9∗3 alleles include single nucleotide polymorphisms in exon 3 and exon 7 that cause amino acid substitutions Arg144Cys and Ile359Leu, respectively. The CYP2C9∗2 allele was analyzed by amplification of a fragment including an AvaII restriction site in the wild type allele but absent in the CYP2C9∗2 allele because of the $C_{416} \rightarrow T$ mutation. For the analysis of the CYP2C9∗3 allele, amplification of a fragment including an NsiI restriction site in the wild type allele ($A_{1061} \rightarrow C$) was performed. Primers are shown in Table 1. Aliquots of each PCR product were subjected to restriction enzyme analysis with 5 U of either AvaII or NsiI (New England Biolabs, Boston, MA). After overnight incubation at 37°, nucleotide fragments were visualized by electrophoresis in 3% agarose gel containing ethidium bromide.

Table 1. Primers used for PCR Detection of Genetic Polymorphisms

Gene Variants	Primers (5′–3′)
ACE I/D	Upper (A): CTG GAG ACC ACT CCC ATC CTT TCT
	Lower (B): GAT GTG GCC ATC ACA TTC GTC AGA T
	Insertion-specific (C): TGG GAC CAC AGC GCC CGC CAC TAC
AGT exon2	Upper: GCC AGC AGA GAG GTT TGC CT
	Lower: GAT GCG CAC AAG GTC CTG TC
	ASO M235: TCC CTG ATG GGA GCC AG
	ASO 235T: TCC CTG ACG GGA GCC AG
AT1R A1166C	Upper: ATA ATG TAA GCT CAT CCA CCA AGA AG
	Lower: TCT CCT TCA ATT CTG AAA AGT ACT TAA
CYP2C9∗2	Upper: TAC AAA TAC AAT GAA AAT ATC ATG
	Lower: CTA ACA ACC AGA CTC ATA ATG
CYP2C9∗3	Upper: AAT AAT ATG CAC GAG GTC CAG AGA TGC
	Lower: GAT ACT ATG AAT TTG GGA CTT C

The underlined letters indicate mismatched nucleotides in order to create a restriction site. ACE, angiotensin-converting enzyme; AGT, angiotensinogen; AT1R, angiotensin II type 1 receptor.

Determination of Plasma Losartan Levels by High Performance Liquid Chromatography (HPLC)

For this substudy, we randomly selected 14 subjects receiving 25 mg of losartan (Losacor) daily for at least 2 wk. For the determination of losartan, after an overnight fast, venous blood samples (10 ml) were obtained before (0 hour) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 10 h after oral drug intake. The samples were collected in heparinized Vacutainer blood-collecting tubes and centrifuged. Plasma was separated and stored at −20°C until analysis. Losartan was supplied by Merck & Company, Inc. (Rahway, NJ). Plasma samples were analyzed for losartan mainly as described by Ritter *et al.* (25). In brief, 1 ml plasma was extracted with 8 ml methyl *t*-butyl ether, followed by the evaporation of the organic phase. The residue containing losartan was resuspended in 200 μl of mobile phase. A 100 μl aliquot was injected into an HPLC through a LichroCart, Lichrospher RP-8 column (5 μl, 4 mm internal diameter × 125 mm long) (Merck, Argentina) and a Lichrospher RP-18 precolumn (4×4) (Merck, Argentina). The mobile phase consisted of 10-mmol/L ammonium acetate at pH 3, acetonitrile and methanol (66:24:10) [vol/vol]), with a flow rate of 1 ml/min. The compounds were detected by UV detection at 245 nm. Standard curves were analyzed in the range from 25 to 8000 nmol/L for both losartan and E-3174 in plasma. The limits of quantification for losartan

and E-3174 were 10 nmol/L and 5 nmol/L. The coefficients of variation calculated for the 50 and 500 nmol/L concentrations for losartan and E-3174 were less than 10% and 6%, respectively.

Statistical Analysis

Results were expressed as mean ±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 unpaired Student's t test or analysis of variance (ANOVA) with repeated measurements. Significance was established at $p < 0.05$.

RESULTS

There was no difference in clinical, demographics, and liver function test at baseline between responders and nonresponders to losartan except for spleen size, which was larger in nonresponder patients (Table 2). All the patients had a Child-pugh grade A.

In the entire population, there was a significant reduction in the HVPG (15.5 ± 3.7 to 12.5 ± 3.8, $p < 0.001$) and wedged hepatic venous pressure (24.6 ±4.2 to 22.3±5.2 mmHg; $p < 0.002$) after 3 months of treatment with losartan, without variations in systemic hemodynamic. Eleven patients were considered responders.

To study the genetic basis of differences in losartan responses, we evaluated genotype frequencies of variants of the RAS component genes. ACE I/D, angiotensinogen T174M and M235T, and AT1R genotype distributions were compatible with the Hardy-Weinberg expectations (data not shown). Neither the ACE ID nor angiotensinogen T174M and M235T polymorphisms were associated with losartan therapeutic response.

However, as can be seen in Table 3, homozygous patients for the AT1R A1166 allele had higher pulmonary-wedged pressure and free hepatic venous pressure on baseline. After treatment, AT1R AA patients showed a higher decrease of the HVPG in comparison with patients with AC/CC genotype (32.5 ± 19.2% *vs* 2.4 ± 18.9%; $p < 0.01$). Then, 10 of 15 patients with the AA genotype while only one of eight patients with the AC/CC genotype were responders ($p < 0.01$). Therefore, the positive and negative predictive values for genotype AA were 66.6 and 87.5%, respectively. As a whole sample, AT1R genotype frequencies (AA: 65% and AC/CC: 35%) were similar to that we observed in a matched healthy adult population (AA: 72% and AC/CC: 28%, n = 175).

Losartan plasma levels as assayed by HPLC were similar between responders and nonresponders, thereby differences in plasma drug concentration seemed not to explain differences in drug response (Fig. 1). This fact was consistent with a similar distribution of the variants Arg144Cys (CYP2C9∗2 allele) and Ile359Leu (CYP2C9∗3 allele) of the gene encoding the drug-metabolizing enzyme, cytochrome P450 2C9 assessed by RFLP/PCR (data not shown).

Table 2. Baseline Clinical and Biochemical Characteristics of Cirrhotic Patients According to Losartan Response

	Responders	Nonresponders	p
n	11	12	
Age (year)	49.9 (±14.3)	48.54 (±13.1)	0.760
Sex (male/female)	5/6	6/6	0.827
Esophageal varices (grade)	2.1 (±0.65)	2.09 (±0.7)	0.675
Spleen size (cm)	14.97 (±2.5)	13.24 (±1.3)	0.044
HVPG (mmHg)	16.54 (±4.6)	14.9 (±2.07)	0.302
Portal vein diameter (mm)	12.36 (±1.6)	11.14 (±4.6)	0.558
Serum bilirrubin (μmol/L)	21 (±9)	24 (±14)	0.723
Serum ALT (IU/ L)	68.09 (±77.9)	81.25 (±69.9)	0.709
Serum albumin (μmol/L)	531 (±61)	515 (±76)	0.119
Prothrombin time (%)	82.54 (±20)	72.42 (±18)	0.223
Creatinine (mmol/L)	0.073 (±0.012)	0.069 (±0.020)	0.743
Child-pough score	5.27 (±0.46)	5.28 (±0.48)	0.658

Results are expressed as mean (SD).

DISCUSSION

This study was designed to test the hypothesis that genetic factors influence the therapeutic response to losartan in cirrhotic patients with portal hypertension.

Therefore, we genotyped the patients for the A1166C AT1R polymorphism, angiotensinogen T174M–M235T, and angiotensin-converting enzyme I/D variants and analyzed the systemic and hepatic hemodynamic parameters at baseline and after losartan administration in order to see whether these genetic polymorphisms may explain the heterogenous response to losartan.

The findings of this study were interesting for several reasons. We found that 25 mg of losartan was effective in lowering portal pressure in approximately half of the patients. The different sensitivity to losartan that we and others (4–6) observed between responders and nonresponders was not significantly dependent on differences in plasma drug levels between the two groups of patients as shown by our pharmacokinetics results. Moreover, after genotyping for the genetic variants of the drug-metabolizing enzyme, CYP2C9, the similar plasma losartan levels between responders and nonresponders are not totally unexpected since both groups did not show any significant difference in the distribution of the CYP2C9 genotypes.

The effect of losartan in decreasing portal hypertension was explained by a decrease in the portal resistance. This result is in agreement with the hypothesis that angiotensin II-activated AT1R raises portal pressure by an increase in hepatic vascular resistance as a result of a contraction of activated stellate cells (3). This is in accordance with the fact that it was demonstrated by competitive binding experiments using losartan, that if the liver has AT1R and then the biological effects of AngII can be blocked by specific AT1R antagonist (26).

Table 3. Systemic and Hepatic Hemodynamic Parameters at Baseline and after Losartan Administration According to A1166C AT1R Genotype

	Genotype AA n = 15		Genotypes AC and CC n = 8	
	Baseline	Postlosartan	Baseline	Postlosartan
Systemic hemodynamic				
Mean arterial blood pressure (mm Hg)	97.6 ± 15.1	93.1 ± 14.1	96.9 ± 9.8	93.5 ± 17.7
Cardiac index (L/min/m^2)	3.7 ± 1.1	4.5 ± 1.5	4.8 ± 1.8	3.6 ± 0.9#
Systemic vascular resistance (din/seg/cm^{-5})	1160 ± 435.8	961.8 ± 400.5	947.3 ± 306.6	1134 ± 353.6
Heart rate (beats/min)	76.2 ± 10.2	77.5 ± 14.7	84.6 ± 6.6*	64.6 ± 11.6†
Pulmonary capillary wedged pressure (mm Hg)	13.9 ± 6.7	13.7 ± 6.3	7 ± 3.4*	9.9 ± 4.1
Mean pulmonary artery pressure (mm Hg)	22 ± 7.8	22.3 ± 10.7	22.4 ± 12.7	16.9 ± 8.4
Hepatic hemodynamic				
Responders/nonresponders (n)		10 / 5		1 / 7*
FHVP (mm Hg)	10.3 ± 3.4	11.3 ± 4.4	7 ± 2.6*	7.5 ± 2.3*
WHVP (mm Hg)	26.0 ± 4.4	21.9 ± 6.1††	22.9 ± 2.9	22.9 ± 3.6
HVPG (mm Hg)	15.7 ± 4.3	10.6 ± 3.4†††	15.9 ± 1.6	15.4 ± 2.8*#
Portal blood flow (ml/min)	1178.3 ± 418.5	1028.6 ± 502.2	1388.5 ± 518.4	1241.9 ± 575.1
Portal resistance (mm Hg min/L)	15.2 ± 6.9	9.4 ± 4.6††	12.5 ± 5.1	16.6 ± 6.1

FHVP, free hepatic venous pressure; WHVP, wedged hepatic venous pressure; HVPG, hepatic venous pressure gradient.
$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$, $^{\dagger\dagger\dagger}p < 0.001$ stands for statistical significance between baseline and postlosartan parameters in the same genotype group. $^{*}p < 0.05$ with respect to genotype AA at the same condition. # $p < 0.05$ for the interaction between genotype and drug effects.

In addition, we found a strong association between the therapeutic response to losartan and the A1166C AT1R gene variant. Even though an association is not definitive evidence of a cause–effect relationship, we suggest that the A1166 variant could be involved in the regulation of AT1R gene expression, which may selectively alter intrahepatic circulation sensitivity to AngII without major effect on sistemic circulation. In fact, even in basal conditions A genotype seems to influence the hemodynamic state of hepatic circulation since AA homozygote patients had higher pulmonary capillary wedged pressure and free hepatic venous pressure than C allele carriers. Besides, in the absence of losartan, there was a trend to lower systemic vascular resistance and higher cardiac index in C allele carriers that did not reach statistical significance, suggesting that this group may have a marginal peripheral vasodilation. This presumption seems to be supported by the significantly increased heart rate observed in C allele carriers.

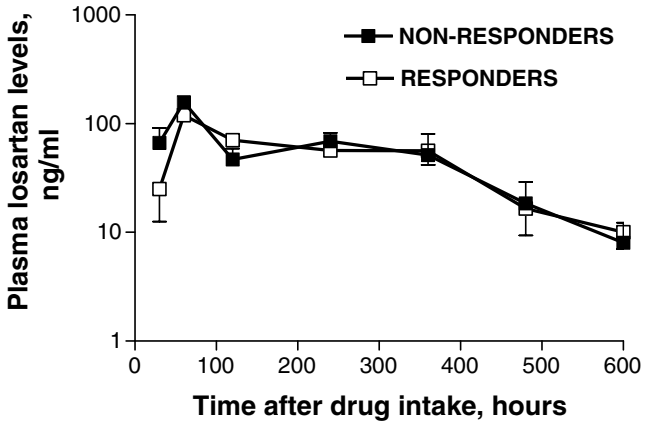

Figure 1. The determination of plasma losartan levels by HPLC in patients with portal hypertension according to the drug response.

The exquisite losartan sensitivity of AA homozygotes may be reflected in the dose dependency of the efficacy of losartan. In this regard, it is interesting to note that Gonzalez-Abraldes *et al.* failed to show any therapeutic effect of losartan on portal hypertension at a higher dose (27). Interestingly, there was no other predictor of the losartan response since responders and nonresponders showed similar clinical and hemodynamic characteristics at the beginning of the study.

Additionally, we did not observe any effect of losartan on the systemic circulation in any of the genotypes except for a weak, but significant interaction between genotypes and losartan treatment affecting cardiac index not explained by differences in baseline and losartan effect neither in AA nor in AC/CC genotypes. Conversely, the significant response observed in the intrahepatic circulation may be explained by the highest losartan and its active metabolite concentration achieved in the portal and sinusoidal bed after oral intake.

Finally, we found no association between ACE and angiotensinogen gene variants and losartan therapeutic response indicating that RAS components may play a small if any role in portal hypertension, but a note of caution should be added since additional studies with a larger number of patients should be performed until final conclusions are reached.

In summary, we demonstrated that there is an association between A1166C AT1R gene polymorphism and the hemodynamic response to losartan in patients with cirrhosis and portal hypertension. Specifically, the presence of A allele was associated with a significant decrease in HVPG, WHVP, and portal resistance after losartan administration.

This finding has the potential to provide new insights not only about the molecular mechanisms influencing drug response, but also into the role that the specific blockade of the AT1R may play in improving the medical management of portal hypertension "tailoring" the therapy depending on the patient genetic profile (28). While additional studies are necessary to confirm the relationship between AT1R polymorphism and the response of losartan in portal hypertension, our data provide the first evidence about the potential of genetic testing of A1166C AT1R polymorphisms in predicting this therapeutic response. It is worth noting that we studied a small number of patients, though many aspects about this issue should be considered. The few studies regarding the clinical efficacy of losartan in portal hypertension included a similar number of patients probably because of the complex and invasive procedure—the measurement of the HVPG by hemodynamic technique involved. We hope that our study will serve as the starting point for multicenter pharmacogenetics studies involving a large number of patients.

Certainly, it has long been suspected that interindividual variation in the efficacy and side effects of medications may be influenced by genetic factors. For that reason, selecting the most appropriate pharmacological treatment for an individual patient is a clinical challenge that we can start to deal with in the postgenome era.

WHAT IS ACCEPTED AND WHAT THIS RESEARCH ADDS

1. Losartan, a dose of 25 mg/day, has been found to be effective in 50% of patients with portal hypertension without adverse effects.
2. A significant proportion of the patients remained unresponsive, suggesting the existence of individual factors underlying the different pharmacological efficacy of angiotensin II antagonism in patients with portal hypertension.
3. We found a strong association between the therapeutic response to losartan and the A1166C AT1R gene variant, since we demonstrated that there is an association between A1166C AT1R gene polymorphism and the hemodynamic response to the drug.
4. The presence of AT1R A1166 allele was associated with a significant decrease in HVPG, Wedge Hepatic Venous Pressure, and portal resistance after losartan administration.
5. This finding has the potential to provide new insights not only about the molecular mechanisms influencing drug response, but also into the role that the specific blockade of the AT1R may play in improving the medical management of portal hypertension "tailoring" the therapy depending on the patient genetic profile.
6. Then, our data provide the first evidence about the potential of genetic testing of A1166C AT1R polymorphisms in predicting this therapeutic response.

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