The Effect of Valsartan, an Angiotensin II Receptor Antagonist, on Portal and Systemic Hemodynamics and on Renal Function in Liver Cirrhosis

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Abstract

Aim. The aim of the study was to assess the effects of valsartan, a new generation angiotensin II receptor antagonist, on portal and systemic hemodynamics and on renal function in cirrhosis. Methods. Eighty patients with cirrhosis and portal hypertension were divided into two groups as follows: group I - 40 patients who received valsartan (Diovan) 80 mg/day for 7 days and group II - 40 patients who received placebo. All the patients had hemodynamic, endocrine and renal parameters measured on day 0 and 7. The following were assessed: creatinine clearance, lithium clearance, plasma renin activity, concentration of plasma aldosteron and sodium homeostasis. Hemodynamic effects were assessed sonographically by portal flow volume and velocity evaluation, and mean arterial blood pressure. Results. Valsartan increased the portal blood flow and the portal velocity (p<0.01). These changes occurred without any significant changes in blood pressure and renal function or the glomerular filtration rate, compared with controls (p>0.05). Valsartan also reduced the concentration of plasma aldosteron (p < 0.01) and increased the urinary sodium excretion (p < 0.001). Conclusion. A one week treatment with valsartan in cirrhotic patients with portal hypertension determines an increase in natriuresis, which could be regarded as beneficial, and in addition, changes in the portal hemodynamics which might be speculated to represent a reduction of portal resistance.

Key words

Valsartan - portal blood flow - systemic hemodynamics - Doppler ultrasound - liver cirrhosis

Introduction

Portal hypertension is a major complication of chronic liver disease and is defined by an elevation in portal pressure. It is associated with hemodynamic changes characterized by a hyperdynamic circulation in the splanchnic and systemic territories. Its main clinical consequence, esophageal variceal bleeding, is the most important life threatening complication.

Several studies have shown that effective protection against the risk of variceal bleeding is achieved by a decrease in the portal pressure less than 12 mmHg or at least by 20% of the baseline values. Non-selective β blockers have been used prophylactically as the first drug of choice, because they provide a reduction in the incidence of variceal bleeding (1). However a decrease in portal pressure has been achieved only in one third of the cases. Combination therapy associating β blockers with nitrovasodilators has been introduced to overcome this limitation (2-5). Indeed, vasodilators, such as isosorbide-5-mononitrate (2,4,5) reduce the portal pressure, and may enhance the effect of β blockers, by decreasing the porto-hepatic vascular resistance. However, treatment with nitrates alone is not recommended as an alternative to β blockers, since they decrease portal pressure, but at the same time appear to increase mortality, possibly as a consequence of deleterious effects on renal circulation. The increase in portal pressure is also triggered and maintained through the activation of the renin-angiotensin-aldosterone system and consequent fluid retention. Blocking the vasoconstricting action of angiotensin and the effect on fluid retention might have a beneficial effect on portal pressure, as it has been shown in some preliminary work with ACE-inhibitor and angiotensin receptor inhibitor.

The aim of this study was to assess whether valsartan treatment might influence portal and systemic hemodynamics in patients with cirrhosis and also to evaluate its effects on renal function.

Methods

We studied 80 cirrhotic patients with endoscopic signs...
of portal hypertension admitted to the University Hospital in Bucharest for abnormal liver function between 1998 and 2002.

The group comprised 52 males and 28 females with ages ranging from 37 to 68 years. Ten patients were diagnosed by liver biopsy, but the diagnosis of cirrhosis was made by clinical status and by laboratory and sonographic findings for the rest of the patients.

Inclusion criteria comprised:
- endoscopic signs of portal hypertension (esophageal and/or gastric varices and or hypertensive gastropathy);
- no alcohol consumption for at least three months;
- no history of variceal bleeding four weeks previously;
- discontinuation of β blocker or any other vasodilator drugs 7 days before the study;
- any diuretic treatment stopped three days before the renal investigation and resumed after each renal function measurement. The dose of diuretics had to be stable for one month before inclusion in the study and throughout the study.

We excluded the patients who had:
- severe liver failure: bilirubinemia >5 mg/dl, INR >2, hepatic encephalopathy;
- presence of renal failure (serum creatinine >1.5mg/dl);
- hypotension (systolic blood pressure <90mmHg).

All the patients were informed about the protocol and they gave their consent prior to the study.

The severity of liver disease was graded according to Child Pugh’s score. The patients were maintained on a sodium restricted diet (60-80mmol/day) and randomly divided into two equal groups, each group comprising 40 patients.

Patients fulfilling inclusion criteria were randomized, single blind, to receive either valsartan (Diovan - 80 mg orally) (Group I), or placebo (Group II) once daily at 9 a.m. every day. The treatment was maintained for 7 days. Informed consent was obtained from all patients and the study was approved by the local Ethics Committee.

The methodology used was the same for all patients. Before and after the treatment (day 0 and day 8) the patients underwent the following procedures:
- routine laboratory tests: creatinine, glucose, ALT, AST, alkaline phosphatase, total bilirubin, albumin, INR, in the blood samples;
- creatinine clearance (Cr.CI);
- lithium clearance (Li.CI) - as an index of sodium proximal tubular reabsorption;
- plasma renin activity (PRA);
- plasma aldosteron concentration;
- urinary sodium excretion/24h (U Na);
- urinary metanephrine concentration (U.Me);
- systemic hemodynamics: heart rate (HR) and mean arterial pressure (MAP);
- hepatic hemodynamics: portal flow volume (P volume) and portal flow velocity (P velocity).

Blood samples were taken at 8:00 a.m. from the right antecubital vein with the patients in resting position (for liver tests, sodium, potassium, lithium, creatinine, renin and aldosterone concentrations). The 24-hour urine samples were collected every day for assessing creatinine and sodium excretion. For lithium clearance, patients received 600 mg lithium carbonate the evening before starting the study (at 10.00 p.m.) and the last evening (before day 8). After an overnight fast spent supine, the following morning urine collection started at 8.00 a.m. Urine was collected by spontaneous voiding. The collection period lasted 4 hours. Water intake was fixed at 1 liter over the 4 hours. Blood samples at the beginning (8.00 a.m.) and at the end of clearance period (12.00) were analysed for plasma concentration of sodium and lithium. Urine volume was recorded and samples were assayed for lithium and sodium concentrations during the whole of the 4 hour clearance period (6). The subjects were kept in a horizontal position during the investigations except during the voiding of urine.

The creatinine clearance was calculated from the serum creatinine concentration in men as: $$\text{Cl Cr} = (140 - \text{age [yr]} \times (\text{body wt [kg]}/(72) \times (\text{serum creatinine [mg/dl]}).$$ In women, the calculated values were multiplied by 0.85.

Lithium clearance (Li.Cl) was calculated from the concentration of lithium in urine (U Li), urinary flow rate (V) and plasma concentration of lithium (P Li) as: $$\text{Li Cl} = \text{U Li} \times V / \text{P Li}.$$ Lithium in plasma and urine was measured by spectrophotometry. For measurement of renin and aldosteron, blood was sampled from the venous catheter and the radiimunoassay method was used. Metanephrines (catecholamine metabolites) were measured in urine (enzyme immunoassay) as an index of serum catecholamine levels (7).

During the study period starting at day 0, auscultatory arterial blood pressure and heart rate were assessed 4 times daily (8 a.m., 12 a.m., 4.p.m. 8.p.m.). Blood pressure was measured on the left arm with a standard mercury sphygmomanometer.

The study of portal hemodynamics was performed using an ultrasonic Duplex Doppler system consisting of an Aloka machine; the frequency of the B mode transducer was 3.5 MHz and a pulsed Doppler device operated at a center frequency of 3.52 MHz and pulse repetition frequency of 2.2 kHz. All measurements were performed at 8.15 a.m. at the beginning and at the end of treatment (day 0 and day 8) in the patients, after 15 minutes of resting. They had been fasting one night prior to the procedure. The Doppler US measurements were obtained by the intercostal approach at a location 2-3 cm in distance from the portal vein bifurcation (8) along its longitudinal axis and with a Doppler probe at a fixed angle (<60°) during suspended quiet respiration and supine position. The sample volume was set in the middle of the portal vein trunk. We measured the mean portal velocity and the diameter of the portal vein.

We calculated the following Doppler hemodynamic parameters:
- cross sectional area of the portal vein (A). $$A = \pi r^2 (r = \text{radius of the portal vein});$$
- portal flow volume = the mean portal velocity multiplied by the cross sectional area of the portal vein.

Auscultatory arterial blood pressure was measured on the left arm with a standard mercury sphygmomanometer and the heart rate was derived from electrocardiogram monitoring. Mean arterial pressure was calculated by the formula: MAP = diastolic arterial pressure + 1/3 pulse pressure, where pulse pressure=systolic arterial pressure - diastolic arterial pressure.

**Statistical analysis**

The data are presented as means ± SD. Paired Student t test was used to assess the significance of comparing pre and post treatment values with respect to renal, neurohumoral and hemodynamics parameters within the same group. Unpaired Student t test compared the results between groups. The significance was established at p <0.05.

**Results**

The characteristics of the two groups of patients are presented in Table I.

### Table I Clinical and laboratory data in the patients studied

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology of cirrhosis (alcoholic/ viral/ cryptogenic)</td>
<td>20/15/5</td>
<td>18/16/6</td>
</tr>
<tr>
<td>Child Pugh’s class (A/B/C )</td>
<td>12/18/10</td>
<td>12/19/9</td>
</tr>
<tr>
<td>Ascites (Yes/No )</td>
<td>21/19</td>
<td>23/17</td>
</tr>
<tr>
<td>Esophageal and / or gastric varices (Yes/ No)</td>
<td>40/0</td>
<td>40/0</td>
</tr>
<tr>
<td>Variceal bleeding in the history (Yes/ No)</td>
<td>22/18</td>
<td>25/15</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>29±2</td>
<td>28±3</td>
</tr>
<tr>
<td>INR</td>
<td>1.63±0.7</td>
<td>1.68±0.8</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.93±0.05</td>
<td>0.94±0.04</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24h)</td>
<td>94.5±19.2</td>
<td>90.3±16.3</td>
</tr>
</tbody>
</table>

There were no differences between the two groups for any variable.

**The renal function**

After administration of valsartan a statistically significant increase in the urinary sodium excretion was observed compared to the original values. This parameter was strongly correlated with an increase of Li Cl (Table II, Fig.1). After valsartan treatment, urinary sodium excretion was significantly higher than basal: in Child A group, by 28% (140.9 vs 110, p <0.01), in Child B group, 19% (130.4 vs105, p <0.05) and in Child C group, 18% (110.5 vs 90, 3 p <0.05). In patients without ascites (n=19), valsartan induced a higher natriuresis: 141.5 vs 98.2 (30%) than in those with ascites (n=21): 116.7 vs 92.2 (21%) (p <0.05).

![Fig.1 Renal response after valsartan:](image)

We found an increase in the creatinine clearance compared with the original values, but this increase was not statistically significant.

**The neurohumoral response**

With regard to the vasoactive effect, valsartan caused an effective blockade of A, receptors reflected by a decrease in plasma aldosteron concentration. As expected, valsartan induced more than a 4 fold increase in plasma renin concentration, whereas urinary metanephrines were not significantly modified by valsartan (Table III, Fig. 2).

**Portal and systemic hemodynamics**

Concerning the systemic hemodynamics, mean arterial pressure decreased in patients who received valsartan especially in those with Child C cirrhosis, but the reduction was not statistically significant and was not accompanied by significant changes in renal or liver function parameters. Valsartan caused a significant increase of the portal velocity and portal flow volume in the hepatic hemodynamics in comparison with the original values (Table IV, Fig. 3).

With regard to the Child groups, the changes in portal hemodynamics between pre and post valsartan treatment were as follows: in Child A: portal flow velocity: 13.2 vs 17.6 (24%), portal flow volume: 0.61 vs 0.98 (37%). In Child B patients, portal flow velocity: 12.4 vs 17.3 (28%), portal flow volume: 0.56 vs 0.96 (42%) and in Child C patients, portal flow velocity: 11.6 vs. 16.5 (30%), portal flow volume: 0.49 vs. 0.88 (45%). Valsartan treatment induced more
important changes on portal hemodynamics in Child C patients.

There were no significant differences in the portal hemodynamics after valsartan between patients with respect to the history of variceal bleeding: portal flow velocity: (mean values) 17.3 vs 17.4 cm/sec and portal volume 0.88 vs 0.99 l/min (p=ns).

The comparison between valsartan and placebo groups (after 7 days of treatment) with respect to neurohumoral, renal and hemodynamics parameters is shown in Table V.

Regarding the tolerability and adverse events of valsartan, five patients did not tolerate it because of a significant fall in the mean arterial pressure (18% of the baseline values). Arterial hypotension was accompanied by dizziness and vertigo, but without deterioration of renal function. These patients discontinued the treatment and dropped out of the study. These side effects completely disappeared one day after withdrawal from the treatment.

Table III Variables of the neurohumoral response in the studied patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I Baseline</th>
<th>Group II Baseline</th>
<th>p</th>
<th>Group I Valsartan</th>
<th>Group II Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosteron (ng/dl)</td>
<td>20.4±14.2</td>
<td>18.2±15</td>
<td>&lt;0.01</td>
<td>18.2±15</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>12.1±0.5</td>
<td>11.9±0.7</td>
<td>&lt;0.01</td>
<td>11.9±0.7</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Urinary metanephrines (µg/mg/creatinine)</td>
<td>7.1±1.8</td>
<td>6.9±2</td>
<td>ns</td>
<td>6.8±2</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

Table IV Variables of the portal and systemic hemodynamics in the cirrhotic patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I Baseline</th>
<th>Group II Baseline</th>
<th>p</th>
<th>Group I Valsartan</th>
<th>Group II Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>79 ± 6</td>
<td>81 ± 9</td>
<td>ns</td>
<td>83 ±8</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>84.6± 4</td>
<td>81.6±2</td>
<td>ns</td>
<td>83 ±2.7</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Portal flow velocity (cm/sec)</td>
<td>12.2±1.4</td>
<td>13.1±2.2</td>
<td>&lt;0.01</td>
<td>13.5±1.6</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Portal flow volume (l/min)</td>
<td>0.56± 0.2</td>
<td>0.65±0.1</td>
<td>&lt;0.001</td>
<td>0.65±0.1</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

Table V Portal and systemic hemodynamics, neurohumoral response and renal function after treatment in the two groups of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I Valsartan</th>
<th>Group II Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>48.2 ± 0.2</td>
<td>11.9± 0.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aldosteron (ng/dl)</td>
<td>9.2± 8.1</td>
<td>18.2±15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24 h)</td>
<td>134.2 ± 26.7</td>
<td>92 ± 15.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Li Cl (ml/min)</td>
<td>33.4± 5.2</td>
<td>22.2± 5.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cr Cl (ml/min)</td>
<td>95 ± 31</td>
<td>91 ± 24</td>
<td>ns</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.95± 0.04</td>
<td>0.95 ± 0.02</td>
<td>ns</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>84 ± 6</td>
<td>83 ±8</td>
<td>ns</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>80.1 ± 3.6</td>
<td>83 ±2.7</td>
<td>ns</td>
</tr>
<tr>
<td>Portal flow velocity (cm/sec)</td>
<td>17.3 ± 2.1</td>
<td>13.5 ± 1.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Portal flow volume (l/min)</td>
<td>0.96± 0.3</td>
<td>0.65±0.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Discussion

The initial mechanism leading to portal hypertension is an increase in hepatic resistance; later an increase in portal blood flow maintains and exacerbates portal hypertension unless portosystemic collaterals develop. Although morphologic changes in cirrhosis are the most important factors in the increase in hepatic resistance, functional factors lead to increased vascular tone contributing to increased hepatic resistance in cirrhosis. This has a therapeutic relevance since it sets the rationale for the treatment of portal hypertension with vasodilators (9-11).
Two angiotensin II receptor subtypes, AT₁ and AT₂, have been described and cloned. The AT₁ receptors primarily located in a vascular smooth layer, kidney, brain, lung, adrenal cortex and the pituitary gland, are responsible for the most, if not all, of the known biological effects of angiotensin II (9,10,12). Increase in angiotensin II level is the result of the activation of the renin-angiotensin system (RAS) which is commonly evidenced in patients with cirrhosis and has been shown to correlate with portal hypertension. Angiotensin II increases hepatic resistance (and portal hypertension) and decreases hepatic blood flow in patients with cirrhosis (13,14). These effects are probably caused by the contraction of the vascular smooth muscle as well as by hepatic stellate cells (9,13).

Activation of the RAS may also aggravate portal hypertension due to increased liver fibrogenesis. All this suggests that preventing the activation of RAS or blocking the activity of angiotensin II may have beneficial effects in lowering portal pressure (9,12).

In our study, we tried to assess whether valsartan, a new generation of angiotensin II receptor antagonists, influences portal and systemic hemodynamics parameters and the renal function in cirrhotic patients with portal hypertension (15,16). We used valsartan due to its pharmacokinetic characteristics (17-19):

- it is a non peptide inhibitor antagonist of the angiotensin II receptors:
  - it is orally active;
  - it is a specific competitive angiotensin II antagonist of the AT₁ receptor subtype;
  - following a single oral dose, plasma valsartan concentration increases rapidly reaching a maximum concentration in about 2-3 hours in most subjects;
  - 94 - 97% of the circulating valsartan is bound to serum proteins, mainly albumin;
  - no clinically significant drug-drug interaction has been observed between valsartan and other drugs including diuretics;
  - valsartan undergoes little metabolic conversion. Its clearance is about 83% in the feces and 13% by urine in an unchanged form;
  - there is no change in the kinetics of the drug with repeated dosage, and cumulation is minimal when given once daily;
  - there is no correlation between renal function and systemic clearance of valsartan; adjustment in patients with impaired renal function is therefore not considered necessary.

We used Doppler ultrasound for evaluation of portal and systemic hemodynamics because it is a safe, painless and non invasive procedure (10,11,20). The goal of Doppler sonography was to diagnose and to appreciate the severity of portal hypertension. The variables used were mean portal velocity and portal blood flow. Previous authors assessed the relationship between portal velocity and porto hepatic venous pressure gradient or Child Pugh’s score in patients with portal hypertension. No correlation was found with Child Pugh’s score, whereas an inverse correlation was found with the hepatic venous pressure gradient. A rise in the hepatic venous pressure gradient reflects the elevation of intrahepatic resistance which induces a decrease in the mean portal velocity. Chawla et al (21) and Zoli et al (22) found that the portal flow volume and flow velocity decreased directly proportional to hepatic failure and the degree of the variceal progression.

Despite the errors due to measurements, many authors agree that Doppler sonography is suitable for monitoring diagnosis and for evaluation of the changes induced by medical treatment (1,2,10,11).

In our study, after 7 days of treatment, valsartan induced a significant increase in the portal velocity and portal flow volume in comparison with the original values and with the placebo group. Hulagu et al (23) also found a significant increase in portal velocity and portal volume after 25 mg of losartan: the US measurements were performed at 120 and 240 minutes after drug administration. Unlike our results, Yalniz et al (24) reported that 7 days of valsartan treatment induced a significant decrease in portal flow volume and flow velocity in cirrhotic patients and suggested that the drug can be used safely in portal hypertension treatment. We can not speculate on an explanation for the discordant results. Mitchell et al (cit. 11) considers that because the portal vein diameter tends to increase and portal velocity decreases with portal hypertension, portal flow tends to be main-tained in patients with cirrhosis until significant shunt development. After development of the shunts, due to portal hypertension, a significant volume of portal flow bypasses the liver. Therefore, we consider that a beneficial effect of valsartan on portal hemodynamics might be an increase in portal velocity and in portal blood volume. These parameters are decreased in cirrhosis with portal hyper-tension because of the slow flow with shunting of mesenteric and splenic flow away from the liver. The significant increase of portal velocity after valsartan treatment in our patients reflects the decreasing of hepatic resistance as a consequence of the drug effect as an antagonist of the AT₁ receptors.

As expected, valsartan induced a significant increase in plasma renin concentration caused by an effective blockade of A II receptors, reflected by a decrease in plasma aldosterone concentration. Valsartan also blocks the effects of A II both on afferent and efferent arterioles in the kidneys and thereby increases renal blood flow. In addition it interferes with sodium reabsorption via tubular transport. Previous studies have shown that the use of vasodilators in patients with cirrhosis and ascites, enhanced the activation of the endogenous vasoactive systems that produced water and sodium retention and reduction in glomerular filtration rate (4,24). In contrast to these studies, an increase in the urinary sodium excretion with a dose of 7.5 mg of losartan was reported by Girgrah et al (25). Similarly, in our study, despite a significant increase in plasma renin concentration, valsartan caused a significant increase in urinary sodium excretion mediated by a decrease in plasma aldosterone concentration and an effective blockade of A II receptors.
The decrease in the mean arterial pressure induced by valsartan represents a potential risk for long-time administration of this drug in cirrhotic patients with portal hypertension. It was found that 25 mg losartan (antagonist of AT1 receptors) given orally to cirrhotic patients for one week induced a significant reduction of the hepatic venous pressure gradient (HVPG) values and hypotension occurred as a side effect only in one patient (26). In contrast, Schepke et al (12), using irbesartan (another AT1 antagonist) reported only a moderate reduction of HVPG, but marked arterial hypotension and renal impairment in patients with advanced cirrhosis. In our study, five patients did not tolerate valsartan because of the significant fall in mean arterial pressure. This side effect completely disappeared one day after withdrawal of the drug.

In conclusion, a one week treatment with valsartan in cirrhotic patients with portal hypertension determines an increase in natriuresis, which could be regarded as beneficial, and changes in portal hemodynamics which might be speculated to represent a reduction of portal resistance. These preliminary hemodynamics results warrant further studies of valsartan in cirrhotic portal hypertension.

Conflicts of interest
None to declare.

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