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Short term effects of valsartan on portal blood flow in cirrhotic patients

Sirotik hastalarda, valsartanm portal kan akımı üzerine kısa dönem etkileri

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Background/aims: *Portal hypertension is a common syndrome characterized by a chronic increase of the portal pressure and is the most frequent clinical manifestation of cirrhosis. In this study short term effects of Valsartan, an angiotensin II receptor antagonist, upon portal blood flow in 36 cirrhotic patients was determined by Doppler ultrasonography.* ***Methods:*** *Patients were divided into three groups of 12 according to Child-Pugh classification. They (18 women and 18 men with a mean age of 50+14 years) received a daily dose of 80 rag valsartan for one week after which the effects upon hemodynamic changes were evaluated by colored Doppler ultrasonography. Hemodynamic measurements were performed 24 hours prior to valsartan administration and then four and eight days after administration. The following parameters were evaluated: for hemodynamic changes: peak systolic flow velocity, diastolic flow velocity, peak systolic flow velocity / diastolic flow velocity ratio, resistive index and pulsatility index were evaluated in hepatic, superior mesenteric and right and left renal arteries. In the portal vein, diameter, mean flow velocity and flow volume were evaluated. Results are expressed as means±SD.* ***Results:*** *Hemodynamic parameters showed no significant change during the measurement in hepatic, superior and right and left renal arteries. Valsartan induced a significant decrease ($p<0.05$) in portal vein diameter, in portal vein maximal flow velocity and in portal vein flow volume. The decrease in portal vein flow volume was 11.7% on day four and 24.4% on day eight. In two patients, a symptomatic hypotensive attack occurred. Serum potassium levels were increased significantly ($p<0.05$).* ***Conclusions:*** *These results indicate that valsartan can be used in portal hypertension safely.*

Keywords: Portal hypertension, valsartan, portal blood flow, Doppler ultrasonograhy

Amaç: *Portal hipertansiyon, portal basınçta kronik artış ile karakterize olan, sık görülen bir sendromdur ve sirozun en sık klinik manifestasyonudur. Bu çalışmada, 36 sirotik hastada bir anjiotensin II reseptör antagonisti olan Valsartanm, portal kan akımı üzerine kısa dönem etkilerini Doppler ultrasonografi ile inceledik.* ***Yöntem:*** *Hastalar, Child-Pugh sınıflamasına göre her grupta 12 hasta olacak şekilde üç gruba ayrıldı. Yaş ortalaması 50±14 olan, 18 kadın ve 18 erkek hasta, bir hafta boyunca günlük 80 mg Valsartan aldı ve hemodinamik parametreler üzerindeki etkiler, renkli Doppler ultrasonografi ile değerlendirildi. Hemodinamik ölçümler, Valsartan kullanmaya başlamadan 24 saat önce, kullanmaya başladıktan sonra dördüncü gün ve tedavinin sonunda (sekizinci gün) yapıldı. Hemodinamik değişiklikler için şu parametreler incelendi: Hepatik, süperiyor mezenterik, sağ ve sol renal arterlerde; Pik Sistolik Akım Hızı, Diyastolik Akım Hızı, Pik Sistolik Akım Hızı IDiyastolik Akım Hızı Oranı, Rezistivite indeksi ve Pulsatilite İndeksi değerlendirildi. Portal vends; Çap, Ortalama Akım Hızı ve Akım Hacmi (Debi) incelendi. Sonuçlar ortalama±SD olarak gösterildi.* ***Bulgular:*** *Hepatik, süperiyor mezenterik, sağ ve sol renal arterlerde yapılan ölçümlerde hemodinamik parametrelerde anlamlı bir değişiklik meydana gelmedi. Valsartan, portal ven çapı, portal ven maksimal akım hızı ve portal ven debisinde istatistiki olarak anlamlı ($p<0.05$) bir azalmaya neden oldu. Portal ven debisindeki azalma dördüncü günde %11.7, tedavi sonunda (sekizinci gün) ise %24.4 idi. iki hastada semptomatik hipotansif atak meydana geldi. Serum potasyum seviyeleri anlmalı olarak arttı (p was <0.05).* ***Sonuç:*** *Portal hipertansiyon tedavisinde güvenle kullanılabileceğini göstermektedir.*

Anahtar kelimeler: Portal hipertansiyon, Valsartan, portal kan akımı, Doppler ultrasonografi

INTRODUCTION:

Portal hypertension (PH) is a common syndrome characterized by a chronic increase in portal pressure (1,2) and is the most frequent clinical manifestation of cirrhosis (2). Massive upper gastrointestinal bleeding from ruptured esophageal varices is the main complication of PH, and represents one of the leading causes of death in patients with cirrhosis (1).

The pharmacologic treatment of PH is based on the assumption that a sustained reduction in portal pressure reduces the incidence of hypertensive complications (1-4). Lowering of the elevated pressure essential for the treatment and prevention of acute or recurrent variceal hemorrhage (1-4).

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Non-selective beta-blockers have proved effective in reducing portal pressure by lowering splanchnic blood flow (5), and are used in primary and secondary prevention of variceal bleeding (6,7). However, the mean decrease in portal pressure in response to propranolol is only approximately 15% (8) and one third of cirrhotic patients do not respond despite adequate blockade (9).

During the last decade, marked progress in knowledge of the pathophysiology of PH has opened the scene to pharmacological treatments, resulting in a dramatic change in the therapeutic approach to portal hypertension (3).

Angiotensin II (A-II) is considered a potential mediator of intrahepatic PH because its plasma level is elevated in cirrhosis (10-11) and infusion of A-II induces a rise in portal pressure (12). Enhancement of the adrenergic vasoconstrictor influence on the portal system (13), direct contractile influence on activated stellate cells (14,15) and sodium and fluid retention induced by stimulation of aldosterone secretion (16) are possible mechanisms that contribute to the portal effects of A-II.

Hence, in theory, blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin converting enzyme (ACE) inhibitors/A-II receptor antagonists should be benefical for improvement of fluid and salt secretion and reduce portal pressure in cirrhotic patients (17).

Orally active A-II receptor antagonists represent the most recent therapeutic development in the inhibition of RAAS (18). Recently, the A-II receptor antagonists losartan (19) and arbesetran (20) have been studied in portal hypertensive patients with promising results.

Valsartan is an oral antagonist for A-II that competes with A-II for the ATI-receptor and is being developed as an antihypertensive agent (21).

The recently developed non-invasive method of assessing portal hemodynamics, namely duplex-Doppler ultrasonography (USG), has produced a large amount of data on blood velocity and flow in portal vein (22,23). Several effects of pharmacologic agents which are used in the treatment of PH can be evaluated by Doppler USG (24,25). Moreover, this method is more useful in the measurement of acute, fast and dramatic changes rather than the monitoring of chronic changes in portal hemodynamics (26).

In this study, hemodynamic changes in portal blood flow after short term valsartan administration were evaluated by the non-invasive method of Doppler USG.

MATERIALS AND METHODS

A total of 36 consecutive patients with biopsy confirmed cirrhosis who were admitted to Fırat University Internal Medicine Clinic between April 1999 and May 2000 were evaluated. There were 18 male and 18 female patients with a mean age of 50±14 (14-70) years.

The patients were divided into three groups according to Child-Pugh classification.

Informed consent was obtained from all patients and the study was approved by the local ethics committee.

Patients with severe ascites (in whom accurate measurements by doppler US are not possible), portal vein thrombosis, blood pressure less than 80 mmHg , congestive heart failure, drug allergy history, beta blocker usage, advanced age and who were pregnant, were not included in the study. Patients already receiving antihypertensive treatment and those with bleeding from esophageal varices within the previous four weeks were also excluded. In patients receiving diuretics, the dosage was required to be constant for four weeks prior to baseline measurement, otherwise they were also excluded. Routine medication was continued during the study without modification.

Detailed disease history was obtained from all patients and physical examinations performed. Body weight, complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), y-glutamyl transferase (GGT), total bilirubin, total protein, albumin, potassium, prothrombin time and creatinine clearance were determined before and at the end of valsartan treatment. The ascites albumin level was measured and serum ascites albumin gradient was calculated in patients with ascites at the beginning of the study.

Doppler US examinations were carried out in the radiodiagnostic unit of our hospital by Toshiba Sonolayer SSH-140A machine with 3.75 mHz convex and sector electronic transducer. The doppler angle was kept at 30-60°. Patients were examined in the supine or left lateral cubitis position during deep inspiration.

To reduce the variability of results, doppler measurements were always made by the same investigator who was unaware of the patients laboratory data.

Blood flow parameters were measured at 8am after overnight fasting. The measurements were repeated three times by the same person to decrease inaccurate results and the mean of the values were accepted as real values.

Peak systolic flow velocity (PSFV), diastolic flow velocity (DFV), peak systolic flow velocity/diastolic flow velocity ratio (PSFV/DFV), resistivite index (RI= PSFV-DFV/PSFV) and pulsatility index (PI=PSFV-DFV/mean flow velocity) were measured in the renal, hepatic and superior mesenteric arteries by doppler US.

The diameter, maximal flow velocity and flow volume of the portal vein were measured. Portal vein diameter was measured fnom inner side to inner side at the point where peak flow velocities were obtained.

The flow volumes were measured by the formula of:

Flow volume (ml/min)= section area x mean flow velocity x 60.

The section areas were measured by the formula of πr^2 with the assumption of circularity of vessel section. Estimated portal vein (PV) flow velocity was calculated by using a correction factor produced from time averaged maximum velocity (Fdmax).

PV mean flow velocity= Fdmax x 0.57 (28-29)

Doppler US measurements were performed three times: at the beginning, middle (fourth day) and at the end (eighth day) of treatment. All patients were given 80 mg of valsartan (Diovan®), an AT II antagonist, following measurement and after breakfast at 8 am everyday for one week. During this one week period arterial pressure and pulses, 24 hour urine output and any side effects were monitored and recorded daily.

Statistical calculations were made using SPSS for the windows computer program. Data obtained at the end of the study was expressed as mean±SD. The Student t test for paired data was used for statistical analysis of the difference among the parameters; pre and mid, pre and post and mid and post treatment values. The results of the different groups were compared using the Student t test for unpaired data. Any significant statistical difference in the parameters among pre, mid and post treatment groups were investigated by non-parametric variance analysis test (Friedman's two variance analysis test). Minimal significance level was regarded as $p<0.05$.

RESULTS

The clinical characteristics of the patients according to Child-Pugh stage are shown in Table 1.

Table 1. Patient characteristics at presentation

	Total		Child-Pugh stage Child A		Child B		Child C	
	(n=36)		(n=12)		(n=12)		(n=12)	
	(n)	%	(n)	%	(n)	%	(n)	%
Mean age	50±14		52±16		49±14		51±12	
Male	18	50	7	58	6	50	5	42
Female	18	50	5	42	6	50	7	58
Esophageal varices	31	86.1	9	75	10	83.3	12	100
History of variceal bleeding	12	33.3	0	0	4	33	8	75
HBV	24	66.6	6	50	9	75	9	75
HCV	6	16.6	4	33	1	8	1	8
Alcohol	3	8.3	0	0	1	7	2	17
Cryptogenic	3	8.3	2	17	1	8	0	0

The relationship between baseline and post-treatment values with respect to biochemical parameters are shown in Table 2.

Post-treatment serum potassium levels were significantly higher than basal serum potassium levels ($n=36$, $p<0.001$). and these levels were also significantly higher than basal serum potassium levels with respect to Child A, B and C groups ($p<0.05$).

There was no significant difference between baseline creatinine clearance values and post-treatment valves ($p>0.05$).

Also, no significant difference was found either between preitreatment and post-treatment values of other biochemical parameters ($p>0.05$)

Parameters measured in the hepatic, superior mesenteric and right and left renal arteries in the

Table 2. Biochemical parameters at baseline and after valsartan treatment (at eihgth day) (n=36)

Parameter	Before treatment	After treatment	P
Hemoglobin (g/dL)	2.91+0.72	2.88±0.72	NS
Leukocytes (/uL)	4315.8±1925.2	4355.6±2247.9	NS
Platelets (10_/uL)	96611.1±60950.2	101444.4±68148.8	NS
Potassium (mmol/L)	4.33±0.63	4.85±0.62	**
Sodium (mmol/L)	138.1±6.3	136.3±6.8	NS
AST *(VfL)*	96.5±127.8	95.9±101.7	NS
ALT *(VfL)*	77±115.9	70+71.2	NS
T. Bilirabin (mg/dL)	2.28±1.8	2.42±3.4	NS
ALP *(VfL)*	213.5±228.7	187.3+113.2	NS
GGT *(VfL)*	80.9+129.8	75.5±84.1	NS
T. Protein (g/dL)	6.7+0.73	6.7±0.88	NS
Albumine (g/dL)	2.91+0.72	2.88±0.72	NS
PTZ (sec)	15.5+2.6	15.4±2.7	NS
Creatinine clearance (ml/min)	57.3+22.7	56.8+25.2	NS
Systolic blood pressure (mmHg)	105.5±14	100.8+13.8	NS
DiastoMc blood pressure (mmHg)	66.9+8.6	64.7+10.5	NS

Note: All values are mean±SD. NS: Nonsignificant (p>0.05).
*: p<0.05 **: p<0.001

preitreatment, miditreatment (fourth day) and post-treatment periods (n=36, p>0.05) also showed no significant difference. These valves, with comparisons, are shown in Table 3.

Valsartan treatment caused a significant decrease in values measured in the pre-mid-and post-treatment period with respect to portal vein diameter, maximal flow velocity and flow volume (n=36, p<0.05). There was also a decrease in portal vein diameter between values measured in the mid-treatment and post-treatment period but it was not significant (p>0.05). There was a significant decrease in portal vein maximal flow velocity and flow volume in the post-treatment period compared to the mid-treatment period (p<0.05).

These values are shown in Table 4.

The decrease in portal vein flow volume values were as follows: 11.7% in mid-treatment values compared to pretreatment values: 14.4% in post-treatment values compared to mid-treatment values: 24.4% in post-treatment values compared to pre-treatment baseline values.

Table 3. Hemodynamic data in hepatic , superior mesenteric and right and left renal arteries at baseline, middle (fourth day) the end of valsartan treatment (eighth day)

Parameter	Before treatment	Fourth day	After treatment	BT MT	BT AT P	MT AT
Hepatic artery						
PSFV (cm/sec)	66.4+23.3	66.4±20.1	68.3+17.3	NS	NS	NS
DFV (cm/sec)	14.9+5.6	13.9+4.4	13.9+3.9	NS	NS	NS
PSFV/DFV	4.48+1.2	4.8+1.3	4.7+1.4	NS	NS	NS
R.I.	0.76+0.09	0.78±0.07	0.79±0.07	NS	NS	NS
P.I.	2.05+0.8	2.06±0.6	2.04+0.5	NS	NS	NS
SMA						
PSFV (cm/sec)	119.9+41.8	120.3+37.7	113.5+37.0	NS	NS	NS
DFV (cm/sec)	18.6+8.5	19.0+6.9	16.8±6.4	NS	NS	NS
PSFV/DFV	6.9±2.2	6.7±2.5	6.9±2.5	NS	NS	NS
R.I.	0.83±0.06	1.05+1.3	0.83±0.06	NS	NS	NS
P.I.	2.43+0.62	2.55+0.67	2.51+0.58	NS	NS	NS
Right renal artery						
PSFV (cm/sec)	29.4+7.4	27.3±7.5	30.6±14.2	NS	NS	NS
DFV (cm/sec)	8.9+2.9	8.3±2.0	8.3±4.0	NS	NS	NS
PSFV/DFV	3.4+1.1	3.5+1.1	3.7±1.1	NS	NS	NS
R.I.	0.68±0.08	0.70±0.09	0.72+0.09	NS	NS	NS
P.I.	1.52±0.4	1.57±0.4	1.66+0.5	NS	NS	NS
Left renal artery						
PSFV (cm/sec)	29.0±9.5	27.1+8.0	31±15.9	NS	NS	NS
DFV (cm/sec)	8.7±2.7	8.3±2.4	8.,6±3.9	NS	NS	NS
PSFV/DFV	3.45+1	3.29±0.8	3.69+1.3	NS	NS	NS
R.I.	0.69+0.09	0.69±0.08	0.71+0.07	NS	NS	NS
P.I.	1.5+0.48	1.5±0.41	1.5+0.38	NS	NS	NS

All values are mean±SD, BT: Before treatment, AT: After treatment (eighth day), DFV: Diastolic flow velocity, P.I: Pulsatility index.
NS: Nonsignificant, MT: Mid period of treatment (fourth day), PSFV: Peak systolic flow velocity, R.I.: Resistivite index, SMA: Superior mesenteric artery

Table 4. Hemodynamic data in portal vein at baseline, middle (fourth day) and end of valsartan treatment (n=36)

Parameter	Before treatment	Fourth day	After treatment	BT MT	BT AT P	MT AT
Diameter(mm)	12.9*2.7	12.6*2.8	12.3*2.5	*	*	NS
MFV (cm/sec)	17.9*3.8	16.6*2.8	15.4*2.9	*	*	*
PVFV (nü/min)	855.2*443.8	755.3*402.3	646.7*268.6	*	*	*

All values are mean±SD, *: p<0.05
BT: Before treatment, AT: After treatment (eighth day), PVFV: Portal vein flow volume.
NS: Nonsignificant. MT: Mid period of treatment (fourth day), MFV: Maximum flow velocity.

In Child A, B and C patients, there was a significant decrease among values measured in the pre-mid-and post-treatment periods with respect to portal vein diameter and maximal flow velocity (p<0.05 for each group). There was a significant decrease in portal vein flow volume values obtained in the pre-mid-and post-treatment periods (p was <0.001 in Child A and C groups and <0.05 in Child B group). These values and comparisons are shown in Table 4.

Decreases in flow volume of the portal vein in Child A group patients were as follows; mid-treatment (fourth day) compared to baseline values was 8.2%, post-treatment compared to mid-treatment was 24.4%, and post-treatment compared to mid-treatment was 32.4%.

Decreases in flow volume of the portal vein in Child B group patients were as follows; in mid-treatment compared to beseline was 12.3%; post-treatment compared to mid-treatment was 7.1%; and post-treatment compared to pre-treatment was 18.5%.

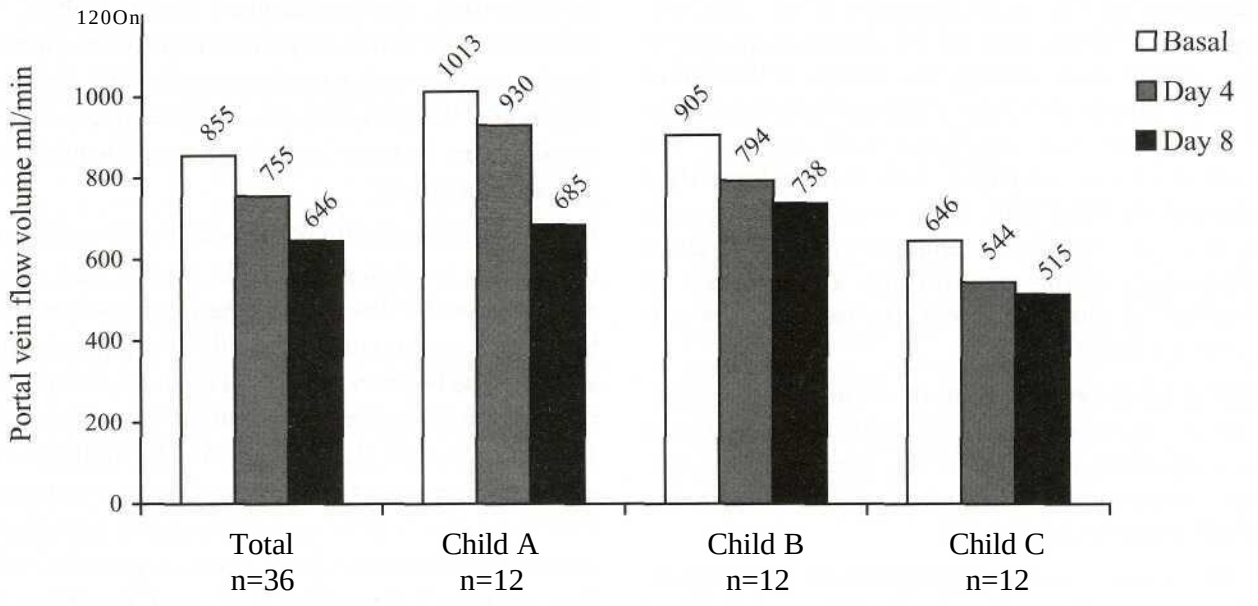
Decreases in flow volume of the portal vein in Child C group patients were as follows: mid-treatment compared to pre-treatment was 16.3% post-treatment compared to mid-treatment 4.8%; post-treatment compared to pre-treatment was 20.3%.

Decreases encountered in portal vein flow volume in the whole group (n=36) and in Child A, B and C groups are shown in Figure 1.

Table 5. Hemodynamic data in portal vein at baseline, middle (fourth day) and end of valsartan treatment in Child A, B and C patients.

Parameter	Before treatment	Fourth day	After treatment	P
Child A				
Diameter (mm)	13.5±3.3	13.5±3.4	12.5*2.6	*
MFV(cm/sec)	19±4.4	17.1±3.3	15.2*2.7	*
PVFV (ml/min)	1013.8*540.1	930±499.9	685.4*218.9	**
Child B				
Diameter (mm)	13.5±2.8	12.9+2.8	13.0*2.8	*
MFV(cm/sec)	17.8+3.3	17.0±2.3	15.7+2.3	*
PVFV(mVmin)	905.0±385.1	794.7±353.3	738.9*318.8	*
Child C				
Diameter (mm)	11.6±2,2	11.0±2.2	10.9*2.1	*
MFV(cm/sec)	16.8±3.9	15.5*2.8	15.5*3.9	*
PVFV (ml/min)	646.6±285.9	541.1*234.6	515.6*224.3	**

All values are mean±SD., *: p<0.05, **: p<0.01
BT: Before treatment, AT: After treatment (eighth day), PVFV: Portal vein flow volume.
MT: Middle of treatment (fourth day), MFV: Maximum flow velocity.



Note: p was <0.05 between basal-day 4, basal-day 8, day4-day 8 in total patients and in Child A, B and C groups.

Figure 1. Decrease encountered in portal vein flow volume in total patients (n=36) and in Child A, B and C groups.

DISCUSSION

Previous suggestions that A-II may play a role in the pathogenesis of PH in cirrhosis (11-16,30-31) prompted the present authors to evaluate the effects of valsartan, a non-peptid A-II receptor antagonist, on portal and splanchnic hemodynamics in cirrhotic patients.

The AT II antagonists were initially administered intravenously with saralasine to decrease the raised portal pressure (32), but long-term use of saralasine was not appropriate due to its short duration of action and poor oral bioavailability (19,33).

Schneider et al (19) evaluated the orally active A-II receptor antagonist losartan in cirrhotics using, hepatic venous pressure measurement, which is an invasive method, and they reported that a 46.8% and 44.1% decrease in portal pressure gradient was obtained. It should be noted that the number of patients in the different Child groups were not equal (25 Child A, 17 Child B and only three in Child C group). A further study published in abstract form by Debernadi-et al. (20) supported the beneficial effects of A-II receptor antagonists in reducing portal pressure.

In contrast, Tangül et al. studied cirrhotic patients with doppler US and reported that losartan had no effects on portal vein diameter, flow rate or flow volume (34).

Valsartan, a non-peptid A-II receptor antagonist is usually prescribed at a dose of 80 mg/day in the treatment of arterial hypertension (37,39). Pharmacodynamic studies of valsartan have shown that it is mainly excreted via the biliary route and its clearance is decreased in patients with mild to moderate hepatic disorders (40-41). Although it was recommended that valsartan should be used with care in such patients, it was not considered necessary to modify initial dosage (36), thus it was prescribed at a dosage of 80 mg per day in this study.

Non-selective beta blockers have long been accepted as the first therapeutic approach in the prophylaxis of variceal hemorrhage in cirrhosis (42-43). Gaiani et al. (44) and Piscaglia et al. (45) found that the decrease in portal blood flow during acute administration of propranolol was 32.9% and 23.2% respectively and in these studies, those showing a 20% decrease in portal blood flow volume were considered to be responsive to the treatment (22-25).

In this study, there were significant decreases in portal vein diameter, flow rate and flow volume. In all patients, a 24.4% decrease in portal flow volume was observed at the end of the treatment period, day eight ($p<0.05$). The results of this study showed that valsartan treatment was as effective as beta blockers used in the studies of

Gaiani et al. (44) and Piscaglia et al. (45),who reported a 32.9% and 23.2% decrease in portal flow volume respectively. The results of Tangül et al. (35), who used doppler USG and losartan in cirrhotics, were not consistent with those of our study in terms of portal vein flow volume(they reported no effect) but, there were similar results in that no significant change in hemodynamic parameters in the renal artery, as measured by doppler US was found with the use of either valsartan or losartan.

Unlike hemodynamic data from the hepatic, superior mesenteric and renal arteries, significant hemodynamic changes in the portal venous system suggested that the effect of the drug in the portal system was greater.

In the present study, a symptomatic hypotension reaction was observed in two patients on the first day of treatment, but after a short period of bed rest, it returned to normal and did not recur in, spite of continuing treatment. In one study comparing valsartan with placebo in essential hypertension patients, it was reported that valsartan led to orthostatic hypotension in 0.3% of patients (36). Schneider et al. (19), who used losartan in cirrhotic patients reported similar results and also a slight but significant decrease in blood pressure occurred after one week of treatment. In this study, apart from the temporary hypotension episode observed in two patients, there was no significant change in blood pressure during treatment.

In this study, no significant change in creatinine clearance was found, any these results are similar to others using valsartan in non-cirrhotic patients (13,36,46). We also found no significant change in renal artery Doppler investigations following valsartan treatment.

Serum potassium values increased after valsartan treatment in patients overall (n=36) and when divided into the three Child-Pugh groups ($p<0.05$), but it was above normal in only two patients and even so was below 6 mmol/L. This increase did not necessitate cessation of treatment in any patient. In a comparative study using A.C.E. inhibitors in essential hypertension patients, it was reported that valsartan lead to a more than 20% increase in serum potassium levels in 4.4% of patients (36). The studies of Schneider et al. and Tangül et al. (19,35), using losartan, another AT II antagonist, in cirrhotic patients, reported no change in serum potassium values,unlike the results of this study.

In conclusion, a significant decrease in portal vein diameter, flow velocity and flow volume occurred in cirrhotic patients during short term valsartan treatment, which suggests that this drug can be used safely in portal hypertension treatment. It is neccessary to show the prophylactic application of the valsartan in variceal bleeding by long term studies. Further studies should be undertaken to evaluate the long term prophylactic effects of valsartan on variceal bleeding.

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