ORIGINAL ARTICLE

Evaluation of Losartan in patients with renal transplantation

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Arterial hypertension is a major risk factor for cardiovascular morbidity and mortality in renal transplant recipients. Cyclosporine and FK-506 contribute on the development of hypertension. Losartan, a blocker of angiotensin II receptors (AT1), has been proved to be an effective antihypertensive agent. The present retrospective study evaluated the efficacy and safety of losartan in a group of hypertensive patients with normal graft function. Nineteen patients on therapy with antihypertensive drugs were included in the study because of bad blood pressure control and / or drug side effects. These patients (14 men) received losartan 2.9 years after transplantation at the dose of 25-100 mg/d. All patients of the study had serum creatinine levels ≤ 1.5 mg/dl before treatment with losartan and a twelve month follow up. Systolic (SBP) and diastolic (DBP) blood pressure, serum creatinine (Scr), Ht and Hb were recorded every two months for a period of six months before (BLT) and after initiation of losartan treatment (ALT). Proteinuria and number of antihypertensive agents were recorded BLT (time 0) and six months later. ANOVA for repeated measures, regression analysis for curve estimation and paired t test were used for statistical analysis (SPSS for windows version 9.0).

SBP/DBP were 140.71±13.28/86.42±15.34 mmHg, 140.35±13.93/ 90.00±9.60 mmHg, 137.85 ±13.82/91.42±8.86 mmHg, 139.28±13.98/91.07± 9.84 mmHg 6, 4, 2 and 0 months BLT respectively (p=NS) and 137.10±8.38/ 85.26±6.55 mmHg, 139.73±13.48/88.15±7.49 mmHg and 142.10±14.65/88.68 ±7.60 mmHg 2,4 and 6 months ALT respectively (p=NS). The number of antihypertensive agents per patient was 2.05±0.70/1.68±0.74 (p=0.015), proteinuria was 0.65±0.28/0.52±0.37 g/24h (p=NS) and losartan dose was 50.00±14.43/61.84±24.10 mg/d (p=NS) at time 0 and six months ALT respectively. Scr was 1.14±0.27 mg/dl, 1.17±0.31 mg/dl, 1.20±0.34 mg/dl and 1.12±0.25 mg/dl 6,4,2 and 0 months BLT respectively (p=NS, Scr slope =0.00) and 1.18±0.25 mg/dl, 1.21±0.24 mg/dl and 1.23±0.25 mg/dl 2,4 and 6 months ALT initiation respectively (p=0.038, Scr slope =+0.02). Ht/Hb were 45.94±5.21 %/14.4±2.06 g/dl, 46.15±5.24% /14.99±1.68 g/dl, 46.20±5.91%/14.98±1.90 g/dl, 46.70±5.42%/15.27±1.74 g/dl 6, 4, 2 and 0 months BLT respectively (p=NS) and 44.28±5.30% /14.26±2.01 g/dl, 42.83±6.10%/13.98±1.90 g/dl, 42.24±6.26%/13.81±1.98 g/dl at 2, 4 and 6 months ALT initiation respectively (p=0.02/0.008 respectively). These results show that losartan controls efficiently the blood pressure of hypertensive renal transplant recipients, lowers significantly the need for other antihypertensive agents, causes a significant fall of Ht/Hb and a small but significant rise of serum creatinine level.

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Hypertension occurs in about 75%-80% [1,2] of patients with renal transplantation. Rejection, immunosuppressive agents, recurrent renal disease, renal artery stenosis, native kidney disease are the best known causes of post-transplant arterial hypertension [3,4]. Post transplant arterial hypertension has been associated recently with reduced kidney graft survival [5-8] and its best management is not known yet.

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Losartan, the first of a new class of drugs, binds selectively and competitively to the angiotensin II receptor (AT1). Several trials have shown that losartan can be given in patients with renal failure or under dialysis therapy with a good safety and tolerance profile comparable to placebo [9,10]. The blood pressure lowering effect of losartan has not been connected with hyperkalemia or serum creatinine changes, but is accompanied by a significant reduction of proteinuria, in patients with renal function impairment [11].

The aim of this study was to investigate the safety and efficacy of losartan in the treatment of hypertension of patients with renal transplantation and normal graft function.

Patients and methods

Nineteen transplanted patients with arterial hypertension were selected to receive losartan in an outpatient basis at Hippokration Hospital of Thessaloniki. They were 45.33±11.77 year old (range 23.95 – 59.11) and had no documented renal artery stenosis. They had received triple [11] or quadruple sequential drug [8] immunosuppression. The demographic data of patients are shown in table 1. No patient had a serum creatinine over 1.5 mg/dl, salt depletion or any active disease at the time of drug initiation. The initial dose of losartan was given according to the needs of each patient. In cases with inadequate control there was a rapid augmentation of the dose at weekly intervals up to the dose of 100 mg/d. The patients that received losartan had a SBP ≥ 140 mmHg and/or a DBP≥ 90 mmHg in two or more readings performed at different days or there was a clinical condition causing considerable discomfort (erythrocytosis, leg oedema, gum hypertrophy). The blood pressure was measured at sitting position always with the same machine.

Blood pressure measurement and blood and urine samples were taken, on an outpatient basis, 6, 4, 2 months before losartan treatment, at starting time and 2, 4 and 6 months after losartan initiation. Serum creatinine, Ht, Hb, uric acid and potassium were measured regularly. Proteinuria (24 hour urine protein in five cases) and cyclosporine levels were measured on losartan initiation and six months later. Also the number of antihypertensive drugs, losartan dose and cyclosporine dose were measured at time 0 and six months later.

Table 1. Demographic data

Male/female	14/5
Mean age (years)	45 (range 24 – 59)
Primary renal disease	
Glomerulonephritis	6
Polycystic kidney disease	5
Interstitial nephritis	4
Diabetic nephropathy	1
Hypertensive glomerulopathy	2
Unknown aetiology	1
Reasons for inclusion	
Uncontrolled BP	11
Erythrocytosis	5
Leg oedema, gum hypertrophy	3

ANOVA for repeated measures was used to examine the value change during time. Student's t-test was used to compare quantitative variables at time 0 and 6 months after treatment initiation. Regression analysis for curve estimation was used to examine the slope of the variables before and after losartan initiation. A value of $P< 0.05$ was considered significant . Quantitative results were expressed as Mean ± SD. The statistical package SPSS for windows, version 9.0, was used.

Results

The SBP and DBP did not show significant changes before and after treatment with losartan (table 2) but the need for antihypertensive drugs decreased significantly (table 3). In four cases the total number of antihypertensive drugs remained stable but there was drug dose reduction that was not taken into account during statistical analysis. In 23 instances SBP was > 140 mmHg and in 18 DBP was > 90 mmHg in the records six months before losartan treatment and in 19 and 11 instances SBP and DBP were > 140 mmHg and > 90 mmHg in the six month period after losartan initiation respectively. The antihypertensive drugs that were substituted by losartan were: calcium channel antagonists, ß-adrenergic blockers, clonidine and minoxidil. Losartan initial mean dose and 24 hour urine protein output did not differ significantly from the values recorded six months later (table 3). No case presented tachycardia or orthostatism.

Side effects such as cough, angioneurotic oedema or dysgeusia were not recorded.

Mean serum creatinine level increased by 0.11 mg/dl during the six month treatment with losartan and this small change was statistically significant (table 4). The slope of mean serum creatinine level was 0.00 the six month period before losartan initiation and +0.02 six months after. Serum creatinine level was found to be > 1.5 mg/dl in 5 instances during the six month period before and in 7 after losartan initiation. In no case there was drug interruption.

Hematocrit and Hb showed 9.63% and 9.56% fall, six months after losartan initiation, which was statistically significant respectively (table 4). Further analysis of Ht and Hb fall did not show any significant difference between patients with Ht > 50% and patients with Ht < 50%. There were 5 patients with erythremia. Three of them at the end of follow up period had Ht < 50%.

Analysis of uric acid and potassium serum levels did not show difference before and after initiation of losartan treatment (table 5). There was no case with hyperkalemia during the six month period before and after losartan initiation. Cyclosporine levels measured at the initiation of losartan treatment and six months later did not show statistically significant difference (table 3, p=0.065). Also there was remission of leg oedema and gum hypertrophy.

Table 2. Levels of systolic and diastolic blood pressure measured at bimonthly intervals before and after initiation of losartan treatment (mmHg)

Months	-6	-4	-2	0	+2	+4	+6
SBP	140.71±13.28	140.35±13.93	137.85±13.82	139.28±13.98	137.10±8.38	139.73±13.48	142.1±14.65
DBP	86.42±15.34	90.00±9.60	91.42±8.86	91.07±9.84	85.26±6.35	88.15±7.49	88.68±7.60

Table 3. Proteinuria, number of antihypertensive drugs and losartan dose at the initiation of treatment and six months later

	initiation of treatment	6 months later
24 hour urine protein (g)	0.652±0.28	0.512±0.36
Number of antihypertensives	2.05±0.70*	1.68±0.74*
Losartan dose (mg/d)	50.00±14.43	61.84±24.10
Cyclosporine levels (μg/l)	128.52±44.94	111.36±34.31

* p=0.015, paired t test

Table 4. Mean values of serum creatinine, Ht and Hb measured at bimonthly intervals before and after initiation of losartan treatment

Months	-6	-4	-2	0	+2	+4	+6
Scr (mg/dl)	1.14±0.27	1.17±0.31	1.20±0.34	1.12±0.25	1.18±0.25*	1.21±0.24*	1.21±0.25*
Ht (%)	45.94±5.21	46.15±5.24	46.20±5.91	46.70±5.42	44.28±5.30**	42.83±6.10**	42.24±6.26**
Hb (g/dl)	14.51±2.06	14.99±1.68	14.98±1.98	15.27±1.74	14.26±2.01***	13.98±1.90***	13.81±1.98***

* p=0.038, ** p=0.02, *** p=0.008 ANOVA for repeated measures

Table 5. Mean values of serum potassium and uric acid levels measured at bimonthly intervals before and after initiation of losartan treatment

Months	-6	-4	-2	0	+2	+4	+6
Uric acid (mg/dl)	7.17±1.62	6.70±1.34	6.97±1.26	7.01±1.21	7.15±1.38	7.22±1.32	7.24±1.38
Serum Potassium (mmol/l)	4.42±0.48	4.47±0.40	4.33±0.32	4.26±0.49	4.42±0.47	4.35±0.47	4.27±0.44

Discussion

Blood pressure control was satisfactory in agreement with other authors [12]. The need for other antihypertensive drugs was reduced significantly (table 3) and the unwanted clinical conditions (erythraemia, leg oedema, gum hypertrophy) improved significantly. There was a decrease in 24 hour proteinuria but was not statistically significant, possibly because of the small number of the sample. Interestingly one of the proteinuric patients remained free of proteinuria. Patients' tolerance to the drug was excellent and no serious side effects were noticed. A slight increase in serum creatinine was noticed, possibly because of changes in the glomerular hemodynamics with a transient decrease in GFR, but no patient was stopped of the drug because of this. Potassium levels six months before and six months after initiation of losartan treatment remained stable. No change in uric acid levels was noticed in spite the report that losartan has uricosuric effect in healthy people and causes a decrease in serum uric acid during chronic treatment [13,14].

A statistically significant fall of Ht and Hb was noticed and this was evenly distributed in our sample (patients with erythrocytosis or not). Stimulation of AT1 receptors of erythroid progenitor cells by AT II is believed to increase red cell mass independently from circulating erythropoietin [15]. Our findings agree with others' [16], that blockade of AT1 receptors results in a decrease of red blood-cell mass independently of erythropoietin and haemoglobin levels. Side effects such as tachycardia (> 100 beats/min), orthostatism, cough, angioneurotic oedema and dysgeusia that have already been repoted [17], were not noticed in our patients.

Optimum management of transplant hypertension remains to be defined. Hypertension treatment requires individualization and this stands for hypertensive renal transplant recipients. Hypertension is an important risk factor for cardiovascular morbidity and mortality. It also affects the progression of renal failure. Thus, long-term control of high blood pressure is required. Calcium antagonists are currently the drugs of choice in this group of patients, able to reverse cyclosporine induced renal vasoconstriction [18]. However, recently it has been reported that these drugs could have deleterious effects in patients with chronic graft nephropathy [19].

The intrarenal renin-angiotensin system is significant for the growth, sclerosis and regulation of hemodynamics of the glomerulus [20]. TGF-β, connected with the Ang II production, is considered to be a significant fibrogenic factor implicated in a number of chronic diseases of the kidney [21]. The proof that AT1 receptor blockers could decrease the synthesis and activation of TGF-β further supports the idea that these drugs are useful in the treatment of hypertension in renal transplant recipients [22]. Having in mind that losartan does not cause changes in the cyclosporine blood levels and does not affect total serum cholesterol, triglycerides, ALAT, ASAT, or bilirubin [12] and based on the six month results of our study, we are justified to continue and examine the possible long term effect of losartan on the chronic allograft nephropathy.

ΠΕΡΙΛΗΨΗ

Γ Βέργουλας, Γρ Μυσερλής, Γ Τρελλόπουλος, Α Αντωνιάδης. **Χορήγηση Λοζαρτάνης σε ασθενείς με νεφρική μεταμόσχευση.** Ιπποκράτεια 2000, 4 (2): 67-72

Σκοπός της μελέτης ήταν να εξακριβωθεί η αποτελεσματικότητα και η ασφάλεια της λοζαρτάνης στην αντιμετώπιση της υπέρτασης των ασθενών με νεφρική μεταμόσχευση.

Μελετήθηκαν αναδρομικά 19 ασθενείς οι οποίοι έλαβαν λοζαρτάνη διότι η αρτηριακή τους πίεση (ΑΠ) δεν ρυθμίζονταν επαρκώς ή υπήρχαν ανεπιθύμητες δράσεις άλλων αντιυπερτασικών φαρμάκων. Οι ασθενείς (14 άνδρες) με μέση ηλικία 45 έτη (διακύμανση 23 – 59 έτη), είχαν πάρει τριπλή ή τετραπλή διαδοχική ανοσοκαταστολή και έλαβαν το φάρμακο 2,9 έτη μετά τη μεταμόσχευση. Η κρεατινίνη ορού ήταν ≤ 1,5 mg/dl κατά την έναρξη χορήγησης του φαρμάκου και είχαν συμπληρωθεί 6 μήνες θεραπείας με αυτό. Καταγράφηκαν, ανά δίμηνο, 6 μήνες πριν και 6 μήνες μετά τη χορήγηση του φαρμάκου, η Συστολική ΑΠ (ΣΑΠ) και Διαστολική ΑΠ (ΔΑΠ), η κρεατινίνη ορού, ο Ht και η Hb. Επίσης καταγράφηκε η λευκωματουρία, τα επίπεδα της κυκλοσπορίνης και ο αριθμός των αντιυπερτασικών φαρμάκων πριν και 6 μήνες μετά τη χορήγηση

του φαρμάκου. Για τη στατιστική ανάλυση χρησιμοποιήθηκε ANOVA για πολλαπλές μετρήσεις και t test για ζεύγη τιμών.

Η ΣΑΠ/ΔΑΠ ήταν 140,71±13,28/86,42±15,34 mmHg, 140,35±13,93/ 90,00± 9,60 mmHg, 137,85±13,82/91,42±8,86 mmHg 6, 4 και 2 μήνες αντίστοιχα πριν από τη χορήγηση Losartan, 139,28±13,98/91,07±9,84 mmHg κατά την έναρξη του φαρμάκου και 137,10±8,38/85,26±6,55 mmHg, 139,73±13,48/88,15 ±7,49 mmHg και 142,10±14,65/88,68±7,60 mmHg 2, 4 και 6 μήνες αντίστοιχα μετά τη χορήγηση του φαρμάκου (p=NS). Ο αριθμός των αντιυπερτασικών φαρμάκων ανά ασθενή ήταν 2,05±0,70 πριν και 1,68±0,74 μετά(p=0,015), η λευκωματουρία (4 ασθενείς) ήταν 0,652±0,28 g/24h πριν και 0,512± 0,366 g / 24h μετά(p=NS) και η δόση του Losartan ήταν 50,00±14,43 mg/d κατά την έναρξη και 61,84±24,10 mg/d μετά από 6 μήνες(p=NS). Η κρεατινίνη ορού ήταν 1,14±0,27 mg/dl, 1,17±0,31 mg/dl, 1,20±0,34 mg/dl 6, 4 και 2 μήνες πριν τη χορήγηση Losartan αντίστοιχα, 1,12±0,25 mg/dl κατά την έναρξη χορήγησης του φαρμάκου(p=NS) και 1,18±0,25 mg/dl, 1,21±0,24 mg/dl και 1,23±0,25 mg/dl 2, 4 και 6 μήνες μετά τη χορήγηση του φαρμάκου αντίστοιχα (p=0,038). Ο Ht/Hb ήταν 45,94±5,21%/14,4±2,06 g/dl, 46,15±5,24%/14,99± 1,68 g/dl, 46,20±5,91%/ 14,98±1,90 g/dl, 46,7±5,42%/15,27±1,74 g/dl, 44,28 ± 5,30%/ 14,26±2,01 g/dl, 42,83± 6,10%/13,98±1,90 g/dl, 42,24±6,26% /13,81 ± 1,98 g/dl τις αντίστοιχες χρονικές περιόδους (p=0,02/0,008 αντίστοιχα μετά χορήγηση Losartan).

Συμπερασματικά το αντιυπερτασικό φάρμακο λοζαρτάνη ελέγχει ικανοποιητικά την ΑΠ των μεταμοσχευμένων ασθενών, μειώνει σημαντικά την ανάγκη χορήγησης άλλων αντιυπερτασικών φαρμάκων, ελαττώνει τη λευκωματουρία και χαρακτηρίζεται από στατιστικά σημαντική αύξηση της κρεατινίνης του ορού (< 0,5 mg/dl) με παράλληλη πτώση του Ht/Hb.

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