

Losartan and QT Dispersion in Hypertensive Patients on Maintenance Hemodialysis

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Abstract

QT and corrected QT (QTc) intervals and their increased dispersions (QTd, QTcd) have been linked to the occurrence of arrhythmias in hemodialysis (HD) patients. This study was performed to determine the effects of the angiotensin II receptor blocker losartan on these parameters in HD patients. Our cohort comprised 24 dialysis patients and 14 healthy controls. 15 dialysis patients were treated for 16 weeks with losartan (HD losartan group) but not 9 patients (HD control group). Blood pressures (BP) and electrocardiogram-derived data (Sokolow-Lyon and Cornell voltages, QT, QTd, QTc and QTcd) were measured in all patients. At the beginning of the study, there were no differences in patient characteristics among the 3 groups. Baseline maximum QTc, QTd, QTcd and Sokolow-Lyon and Cornell voltages and BPs of the healthy group were lower than those of HD groups. While these parameters were similar in the dialysis groups, only BPs in losartan group were higher. After 16 weeks, BPs, Sokolow-Lyon and Cornell voltages values in losartan group significantly decreased but not in the HD control group. Whereas maximum QT and QTc, QTd, QTcd, heart rate and QRS interval did not change in the HD groups. Electrocardiographic LVH of 2 patients improved in the losartan group. Losartan reduced BP and electrocardiographic LVH was improved in HD patients without affecting QTd and QTcd during the 16-week study period.

Key words: Hemodialysis, losartan, QT dispersion

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Introduction

Hypertension is an important contributing factor to morbidity and mortality among hemodialysis (HD) patients and it increases the risk for a variety of cardiovascular diseases [1,2]. In HD patients, anti-hypertensive drugs are only indicated after control of dry body weight and adequate blood purification have been achieved [2]. Calcium channel blockers (CCB) are the most frequently prescribed antihypertensive medications [3]. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines also suggest renin-angiotensin system (RAS) inhibitors to be the preferred antihypertensive agents in hemodialysis patients, particularly those with diabetes mellitus or a history of heart failure [4]. The angiotensin receptor blocker (ARB), losartan is a well tolerated antihypertensive by HD patients, with a very low incidence of adverse experiences, and a lower prevalence of anaphylactoid reactions [5-7]. In a study by Suzuki et al [7], the use of an ARBs was shown to be associated with reduced nonfatal cardiovascular events in patients undergoing long-term hemodialysis.

In HD patients, the higher mortality rate of cardiovascular diseases is due to the occurrence of serious complications, such as alterations in cardiac rhythm and sudden death rather than acute myocardial infarction [8,9]. QT dispersion (QTd), which is the difference between maximum and minimum QT intervals across the 12-lead electrocardiogram (ECG), is a reflection of regional variation in ventricular repolarisation and a predictor of arrhythmia and cardiovascular mortality in conditions such as the long QT syndrome, cardiomyopathies and chronic heart failure [10,11]. In HD patients, structural changes in the heart may impair homogen repolarization of ventricle [12]. QTd is longer in patients receiving HD than those who are not, and it tends to be further prolonged after HD treatment[13, 14]. Differences in QTd are observed in a subgroup of patients in the Evaluation of Losartan In The Elderly (ELITE) heart failure study of losartan compared with captopril, and may explain improved survival with losartan[15]. It is possible that losartan may be acting directly or indirectly as an antiarrhythmic agent [16]. Very few studies have investigated effect of ARB on QTd in HD patients [17]. Therefore, we analyzed the effect of losartan on QTd in hypertensive HD patients.

Material and Method

Patient Selection

Stable subjects older than 18 years receiving routine outpatient HD therapy were recruited for participation in this study. 135 patients were screened for enrollment and patients underwent a complete physical examination including medical history, chest radiograph, ECG and echocardiography, if required for cardiac evaluation. Patients with congestive heart failure, overt ischaemic heart disease, stroke or myocardial infarction, serious hypocalcaemia, hypomagnesaemia or hyperkalemia, hypersensitivity against ACEIs or ARBs, ECG-detected signs of cardiac arrhythmias, bundle branch block, atrial flutter or fibrillation, diabetes mellitus or other systemic disease, concomitant treatment with class I or class III anti-arrhythmic drugs that may lengthen the QT interval were excluded.

28 clinically stable hypertensive patients who had been on HD therapy for at least 6 months were included in the study. They had no hypervolemia and abnormal interdialytic weight changes, and their predialysis mean systolic and diastolic blood pressures (BP) were ≥ 140 and/or 90 mm Hg in six consecutive HD sessions. The study was carried out in accordance with the guidelines of the Helsinki Declaration of Human Studies and with the approval of the local ethics committee. All participating patients gave an informed consent.

The dialyses were carried out in a standard setting (Fresenius 2008 device) with M10 hemophane capillaries (Kawasumi) for 3.5 to 4 hours 2 or 3 times per week. Bicarbonate dialysate containing (in mmol/L) 140 Na⁺, 2.0 K⁺, 1.25 Ca²⁺, and 0.2 Mg²⁺ was used. The blood flow rate was 200 mL/min and the dialysate flow rate was 500 mL/min. The patients' data are summarized in Table 1. Throughout the study, each patient complied with fluid restrictions and diet that consisted of 1.2 g/kg/day protein, 50 mmol sodium, restricted potassium and phosphate, and maintained a constant ultrafiltration volume. Patients were on dialysis for glomerulonephritis (n=3), amyloidosis (n=1), chronic pyelonephritis (n=2), tubular necrosis (n=1), polycystic kidney disease (n=1), hypertension (n=3) or unknown etiology (n=13). Of the cohort, 3 were receiving ACEIs, 2 ACEIs plus β -blockers, 9 CCBs, 4 CCBs plus β -blockers and 1 β -blockers, 14 calcitriol and all of them calcium-containing phosphate binders. None of them had ever been treated with an ARBs. If eligible, all current antihypertensive medications were withdrawn.

Study Design

In 2 weeks of wash-out period, patients received the CCB, nifedipine treatment, if required. 28 patients were divided into two groups regarding age, time on dialysis and BPs: 17 mild to moderate hypertensive patients (median systolic BP: 160 mm Hg and diastolic BP: 100 mm Hg) in the HD losartan group (50 mg/d for 16 weeks) and 11 mild hypertensive patients (median systolic BP: 150 mm Hg and diastolic BP: 80 mm Hg) in the HD control group. Open-label active treatment period in which patients received losartan once daily in the morning administered at a starting dose of 50 mg. HD patients who underwent morning or early afternoon dialysis received losartan after the dialysis session on these days and at approximately the same time on all other days. Daily losartan dose titrated to 100 mg in 6 patients due to a insignificant reduction in BP during the study period. In both groups, nifedipine were added to the treatment in patients who continued to show inadequate BP control. Control subjects were derived from our Internal Medicine outpatient clinics and comprised 14 gender- and age-matched healthy individuals based on previous history and routine clinical examination. All control subjects underwent a detailed examination and they had normal findings.

Measurements

Medical and demographic data was obtained for each subject from the dialysis records. BP measurements were obtained from each patient in the seated position by using a standard mercury sphygmomanometer. Measurements were taken in the morning or noon before dialysis session and daily drug intake (ie, 24 h after dosing, at trough) and after the subject rested for ten minutes in pre-treatment and after 16 weeks. In addition, BPs and body weights were recorded before and after the dialysis sessions. Laboratory evaluations, including hemoglobin (Hb), efficacy of dialysis (Kt/V), normalized protein catabolic rate (nPCR), serum glucose, urea, creatinine, uric acid, electrolytes, ferritin, transferrin saturation, albumin, total cholesterol, triglyceride and intact parathyroid hormone (iPTH) were performed during the baseline period and 16 weeks of active treatment. Tolerability of the study treatment was assessed by monitoring of spontaneous reports of adverse experiences at each visit.

ECG examination procedure and assessment

ECG was recorded on the day after HD in order to exclude the HD-related instantaneous electrolyte, total body fluid, and BP changes. Simultaneous 12-lead ECG was performed

(Hewlett-Packard Pagewriter 100i or 200i with a 25 mm/s paper speed, gain 10 mm/mV) in identical conditions for all patients. All ECGs were obtained after a 5-min resting period in the supine position. All patients were in sinus rhythm. All ECG were analysed blindly for QT intervals by a single observer who was unaware of the patient's clinical condition. In case of interfering premature complexes, the lead concerned was not included in subsequent analysis.

The QT intervals were measured manually with callipers from the onset of the depolarization of the QRS complex to the end of the T wave, defined as a return to the isoelectric T-P baseline. In case of prominent U wave, the T wave end was taken as the nadir between the T and U waves. If the end of T wave could not be reliably determined, the lead was excluded from analyses. A minimum of 10 leads were studied in each patient. For each lead, three consecutive cardiac cycles were measured and averaged. Heart rate was determined from the Q-Q interval in the measured consecutive complexes. Each QT interval was corrected for heart rate by calculating corrected QT interval (QTc) according to the equation of Bazett [$QTc = QT/RR^{1/2}$] [18]. QTd and QTc dispersion (QTcd) were determined as differences between the minimal and maximal QT and QTc values in different leads on the same recording. For electrocardiographic diagnosis of left ventricular hypertrophy (LVH), Sokolow-Lyon voltage (>3.5 mV) was calculated as $SV1 + RV5$ or $RV6$ (whichever is taller)[19] and Cornell voltage (>2.8 mV in men and 2.0 mV in women) as $RaVL + SV3$ with 0.6 mV added to female subjects[20].

Reproducibility

To determine the intraobserver variability of QTc and QTcd measurements, all ECG strips were evaluated by one investigator on two different occasions. There were no significant differences between the pretreatment first and second readings in all groups: 1.5 ± 0.8 ms for QTd and 0.07 ± 1.7 ms for QTcd (intra-class correlation coefficients: $r=0.987$ and $r=0.966$, respectively; $p<0.001$). After 16 weeks, differences between the posttreatment first and second readings in dialysis groups were similar: -1.2 ± 1.0 ms for QTd and -0.8 ± 1.3 ms for QTcd (intra-class correlation coefficients: $r=0.974$ and $r=0.968$, respectively; $p<0.001$).

Statistical analysis

Clinical and laboratory data were expressed as mean $\pm$ SEM. In three groups comparisons, Kruskal-Wallis nonparametric ANOVA were used in case of variances of groups were not homogeneous. If significant, two group comparisons were performed with Mann Whitney U test.

In HD groups the numerical variables were compared with Wilcoxon signed rank test in intragroup comparisons and with Mann-Whitney U test in intergroup comparisons. Comparisons of ratios in both groups were performed with Fischer exact test. All statistical analysis was done with statistical programme of SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). P values ≤ 0.05 were considered significant.

Results

All HD patients completed the trial except 4 patients –two from each group- who were transferred to other dialysis centers. The age, sex distribution, BMIs, baseline heart rates and QRS intervals in ECG between all groups were similar at the beginning of the study ($p > 0.05$). In HD groups, primary diagnosis, dialysis durations, number of sessions, Kt/V, nPCR, hematological parameters, serum albumin and iPTH levels did not differ. Baseline maximum QTc, QTd, QTcd and Socolow-Lyon and Cornell voltages, BPs and serum creatinine levels in the healthy group were lower than those of HD groups while hemoglobin levels were higher ($p < 0.001$). In HD losartan group systolic and diastolic BPs were higher than that of HD control group. Socolow-Lyon and Cornell voltages, maximum QT and QTc, QTd and QTcd in dialysis groups were comparable ($p > 0.05$).

After 16 weeks, maximum QT and QTc, QTd, QTcd, heart rate and QRS interval did not change in both dialysis groups. In HD losartan group systolic and diastolic BPs, Socolow-Lyon and Cornell voltages values significantly decreased although these parameters did not change in the HD control group. In the baseline period there was ECG evidence of LVH in 11 patients (73%) in the HD losartan and 7 patients (77%) in HD control groups. These ratios were higher than that of healthy control (0%, $p < 0.01$). After 16 weeks LVH of 2 patients improved in the losartan group. No significant changes in BMI were observed in HD losartan ($23.2 \pm 1.0 \text{ kg/m}^2$) and control ($23.4 \pm 1.9 \text{ kg/m}^2$) groups during the 16-week study period ($p > 0.05$). After 16 weeks, there was no significant difference in the mean Hb (8.9 ± 0.4 and $9.0 \pm 0.7 \text{ g/dl}$), serum ferritin (387 ± 151 and $225 \pm 104 \text{ ng/ml}$), transferrin saturation (20.9 ± 3.3 and $21.9 \pm 5.0 \%$) values and erythropoietin doses (140 ± 30.9 and $119.1 \pm 18.4 \text{ U/kg/wk}$) among the HD losartan and HD control groups, respectively and no significant change in each group was observed ($p < 0.05$).

Discussion

The results of this study demonstrated that an ARB losartan, administered once daily at doses of 50 or 100 mg, was effective in lowering BP and reducing electrocardiographic LVH in hypertensive patients requiring HD throughout the 16-week treatment period with no important side effects but did not affect QTd and QTcd.

Cardiovascular death in dialysis patients usually is sudden or due to progressive heart failure. Determinants of sudden cardiac death like arrhythmia, LVH and increased QTd are therefore of great importance [21]. Cardiac arrhythmias are frequent among HD population, particularly during and immediately after a dialysis session [22]. HD increases QTc interval in ESRD patients, mainly related to myocardial fibrosis, vascular calcification, autonomic neuropathy and rapid changes in electrolyte plasma concentrations[9,12,23]. These changes may lead to inhomogeneity of both myocardial depolarization and repolarization that reflect at ECG record as increased QTcd [23]. Moreover, QTcd was found to be independent predictors of total and cardiovascular mortality in uraemic populations [24]. In a recent study, HD patients with LVH had the longest QTcd and a statistically higher mortality rate [25]. However, the impact on QTcd can be less important in the absence of significant coexisting cardiac disease [23]. Among 48 HD patients who were suffering from cardiac symptoms such as congestive heart failure, ventricular arrhythmia or chest pain, prolongation of QTcd after HD had cardiovascular deaths with higher incidence than those did not show the prolongation [26]. Normal values of QTd have never been established and have been reported to vary widely between 10 and 71 ms [27]. QTd and QTcd in our hypertensive dialysis patients were markedly higher than those of healthy controls.

Targeting the RAS has been shown to exert antiarrhythmic effects and to reduce mortality rates in HD patients. ACEIs, independently of their antihypertensive effect, may dramatically reduce mortality among chronic HD patients 65 years or younger [28]. In a different study, it have shown that regression of left ventricular mass induced by the ARB irbesartan rather than by the β 1-selective adrenoceptor blocker atenolol is accompanied by improved repolarization in hypertensive patients with LVH, irrespective of their systemic blood pressure [29]. It has been shown that a wide QTd can narrow when congestive cardiac failure was treated with enalapril [30]. However, a substudy of the former ELITE heart failure study showed that captopril, but not losartan, increased QTd[15]. Then, a QTd substudy was prospectively included in the protocol of the ELITE II trial [31]. Losartan and captopril treatments both reduced heart rate significantly,

but QTd remained practically unchanged. In previous smaller studies, regression of LVH with various antihypertensive regimens has been associated with a decrease in QTd [32,33]. But, their mean left ventricular mass index at study baseline was much higher and there was a greater reduction in their left ventricular mass [32,33] when compared with those of patients in the ELITE II trial [31]. The Losartan Intervention For Endpoint Reduction (LIFE) study in hypertensive patients with LVH assessed the relation of regression of LVH to changes in electrocardiographic measures of ventricular repolarization [34]. Reductions in echocardiographically determined left ventricular mass and electrocardiographic LVH indexes were both associated with a decrease in QT interval duration and QTd independent of the study medication used, namely atenolol and losartan. The possibility that the reduction in QT, QTc, and their dispersions with ACEIs may be related to the reversal of hypertension-induced structural and functional alterations of coronary microcirculation and left ventricle or their some direct antiarrhythmic effects [30,32]. ACEIs had no significant effect on plasma levels of AII, it is possible that tissue concentrations of renin-angiotensin hormones were altered favorably by ACE inhibition over the course of 1 year [30]. Because AII and aldosterone are thought to initiate patchy myocardial fibrosis, enalapril-induced changes in the tissue RAS could reduce fibrosis and hence QTcd [30].

ARBs differ from the ACEIs by achieving a more complete blockade of AII's actions and by not affecting bradykinin metabolism. Losartan and its active metabolite, E3174, may directly affect the membrane currents controlling action potential duration [35]. They have been shown experimentally to prevent sustained ventricular dysrhythmias [16,36]. The antiarrhythmic efficacy of E3174 may be due to an attenuation of deleterious effects of local cardiac AII formed during acute myocardial ischemia or, alternatively, a non-AII-related activity specific to E3174 [36]. Losartan (50 mg/d for 4 weeks) has beneficial short-term ECG repolarization effects in hypertensive men [37]. The ARB telmisartan significantly improves the sympathovagal balance increasing parasympathetic activity, and cardiac electrical stability reducing the heterogeneity of ventricular repolarization in hypertensive patients with LVH [38]. Miyajima et al [39] showed that QTcd and high lipoperoxidation levels in hypertensive patients decreased significantly 6 months after treatment with the ARB valsartan when compared to the baseline values, but not left ventricular mass. The changes in QTcd were positively correlated with changes in the serum levels of lipoperoxidation and with changes in diastolic BP. Moreover, RAS inhibitors by the way that change cell membrane electrolyte gradient may decrease QTd [17]. Averbukh et al [17]

demonstrated a significant reduction of QTd in 24 patients on chronic HD following a prolonged treatment with ACEI cilazapril (2.5 mg, 3 times a week) or with ARB valsartan (80 mg, 3 times a week) for 8 consecutive weeks. After both treatments, the total intracellular Ca/Mg ratio was increased, inversely correlating with reduced QTd. The lack of a reduced effect of losartan on QTd and QTcd in our small dialysis cohort could be due to differences in the study population and methodology or the shorter study duration for structural changes in the heart. Therefore, a direct comparison of other studies with our preliminary investigation was difficult. Our study used a manual method to measure OTd. Our method is in agreement with some previous studies. The mechanism responsible for the irregular response of QTcd in patients receiving HD is unclear. It may be assumed that ischaemic damage of the heart leads to a prolongation of QTcd not only at baseline, but after HD as a response [26]. HD population also has several uraemic conditions such as hyperkalemia, volume overload, metabolic acidosis and secondary hyperparathyroidism.

Despite our negative findings ACEIs and ARBs can have some theoretical clinical advantages beyond BP lowering in the antihypertensive treatment of dialysis patients at greater risk for sudden death due to cardiovascular complications. Whether these effects might protect subjects requires further long-term investigation in a selected dialysis population.

Major limitation of our study was number of patients, It was was relatively small.

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