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# LONGITUDINAL AMBULATORY BLOOD PRESSURE MONITORING FOR A SEQUENTIAL CHRONOBIOLOGIC ASSESSMENT OF LOSARTAN EFFECTS

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A b s t r a c t

In order to assess the efficacy of losartan for the treatment of hypertension, 13 patients had their blood pressure and heart rate measured around the clock with an ambulatory monitor for one to 15 days before and then during treatment that lasted from one to 14 weeks. Losartan was administered alone or in combination with a diuretic. Parameter tests and a self-starting cumulative sum (CUSUM) control chart, which were used for individual assessment of the patient's response to treatment, showed large inter-individual differences. On the other hand, paired t-tests used for group assessment revealed that treatment with losartan was associated with only a small decrease in diastolic blood pressure. The results indicate the need for monitoring blood pressure over sufficiently long spans so that the patient's response can be reliably assessed on an individual basis.

K e y w o r d s

Blood pressure; Ambulatory monitoring; Losartan; Essential hypertension

## INTRODUCTION

Losartan potassium was the first available orally administered angiotensin II receptor (type $AT_1$) antagonist developed for the treatment of hypertension (*1*). Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the $AT_1$ receptor found in many tissues, such as vascular smooth muscles. It has been suggested that the full anti-hypertensive efficacy of losartan may be delayed for up to 12 weeks (*2*). Losartan administered at 50 mg doses, as compared to 50 mg atenolol, produced comparable blood pressure reductions in patients with isolated systolic hypertension after 16 weeks of treatment and was better tolerated (*3*). Losartan treatment has also been reported to be associated with a remarkable reduction in the left ventricular mass index in patients with left ventricular hypertrophy (*4–7*). An anti-platelet effect of losartan at therapeutic doses has also been reported (*8*), and it was apparently independent of changes in blood pressure, plasma markers of fibrinolytic activity, and

endothelial perturbation. According to *Prasad et al.* (*9*), $AT_1$ receptor antagonism may selectively modulate L-selectin expression on leukocytes and the endogenous stimulation of $AT_1$ receptors by the renin-angiotensin system, thus possibly contributing to the activation of leukocytes and the decreased expression of L-selectin in coronary artery disease. *Dujardin et al.* (*10*) have also reported that losartan can produce a sustained decrease in the degree of mitral regurgitation.

In patients with end-stage renal disease, losartan administration was accompanied by a decline in plasma aldosterone as well as by an increase in plasma renin activity, which resulted in a decline in plasma uric acid concentrations despite the fact that the patients had no residual renal function (*11*). In patients with mild to moderate essential hypertension, losartan treatment was also associated with a lowering of uric acid concentrations (*12, 13*). *Lozano et al.* (*14*) have further reported a reduction in microalbuminuria by losartan in hypertensive patients with non-insulin-dependent diabetes mellitus (NIDDM), whereas *Brenner et al. (15)*, who studied NIDDM patients with nephropathy for an average of 3.4 years, concluded that „losartan conferred significant renal benefits"; primary outcome measures used in their study were the doubling of reference serum creatinine concentrations, end-stage renal disease or death.

## MATERIALS AND METHODS

The blood pressure and heart rate of 13 patients with MESOR-hypertension were measured around the clock by automatic ambulatory monitoring. Blood pressure profiles were obtained from each subject prior to treatment and at the end of treatment (with either 25, 50, 75 or 100 mg of losartan) that lasted from one to 14 weeks. Each monitoring session lasted between 1 and 15 days (usually 7 days). Some of the subjects received 2 mg of trichlormethyazide, a diuretic, in addition to losartan.

Each profile was analysed by the Halberg cosinor analysis (*16, 17*). In order to assess the response to treatment, the rhythm-adjusted mean value (MESOR) before and then during treatment with or without the addition of a diuretic was computed and the difference was calculated for each case. When more than one blood pressure profile was obtained for one patient, the same reference values were used to calculate the response to treatment with different losartan doses (this happened in two subjects out of 13). A self-starting cumulative sum (CUSUM), a control chart procedure (*18*), was applied to determine treatment effects on an individual basis. Circadian rhythm characteristics before and during the treatment were compared using parameter tests (*19*).

## RESULTS

On the group basis, treatment with losartan was associated with a small decrease of about 4 mm Hg in the MESOR of diastolic blood pressure ($P$=0.049, paired $t$-test; *Table 1*). On the individual basis, there were large inter-individual differences in the response to treatment. They varied from a 14 mm Hg decrease to a 6 mm Hg increase.

The addition of a diuretic to the treatment plan was invariably associated with a decrease in the MESOR of both systolic and diastolic blood pressure, as well as

*Table 1*

The effect of losartan without or with diuretic (trichlormethyazide, 2 mg) on the circadian rhythm of systolic and diastolic blood pressure

| Patient | | | Reference values (no Rx) | | | | Dose | Response to losartan alone | | | | | Response to losartan with diuretic | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | SBP | | DBP | | (mg) | | SBP | | DBP | | | SBP | | DBP | |
| Code | G | Age (years) | M | 2A | M | 2A | | Rx dur• | M | 2A | M | 2A | Rx dur• | M | 2A | M | 2A |
| HM | F | 35 | 150.4 | 30.2 | 104.9 | 18.1 | 100 | 7 | +0.6 | -11.0 | +3.8 | +0.2 | | | | | |
| HS | F | 49 | 142.7 | 46.2 | 82.1 | 23.3 | 50 | 7 | -6.2 | +5.1 | +1.1 | +9.7 | | | | | |
| | | | | | | | 100 | 7 | 0 | -4.7 | -9.9† | -12.2 | | | | | |
| KI | M | 74 | 141.0 | 19.6 | 89.8 | 3.5 | 50 | 2 | -11.4 | +2.3 | -13.7 | +12.6 | | | | | |
| KK | M | 81 | 146.5 | 31.6 | 80.9 | 24.6 | 50 | 7 | -12.2† | +10.7 | -12.7† | -13.3 | | | | | |
| KY | M | 64 | 161.9 | 18.0 | 110.3 | 19.1 | 100 | 8 | -12.6 | -1.1 | -6.9 | -3.1 | 1 | -42.3† | -0.1 | -31.0† | -7.9 |
| MM | F | 54 | 154.0 | 36.9 | 101.7 | 24.3 | | | | | | | 1 | -2.4 | -5.3 | -1.5 | -8.3 |
| MS | M | 48 | 137.0 | 11.0 | 94.3 | 9.9 | 50 | 7 | +2.3 | -0.8 | +6.4† | -0.6 | 7 | -6.3 | -.05 | -3.9† | +0.9 |
| RN | F | 65 | 147.5 | 19.3 | 92.3 | 13.6 | 100 | 8 | +9.8† | +11.8 | +6.3† | +4.2 | | | | | |
| RS | F | 64 | 152.3 | 17.2 | 100.0 | 14.0 | 25 | 8 | -6.9 | -5.0 | -2.9 | -6.4 | | | | | |
| SK | F | 48 | 145.7 | 20.8 | 96.4 | 15.0 | 25 | 3 | -13.6† | +8.1 | -8.7 | +2.8 | | | | | |
| | | | | | | | 50 | 8 | -10.5 | -0.2 | -4.9 | -2.5 | | | | | |
| SM | F | 55 | 165.0 | 32.1 | 102.6 | 21.8 | 100 | 8 | -12.4† | +5.4 | -7.0† | +2.6 | 14 | -25.8† | -9.5 | -16.8† | -5.4 |
| SN | M | 48 | 144.9 | 24.3 | 94.2 | 19.8 | 75 | 1 | -6.9 | -7.4 | -9.7 | -3.2 | | | | | |
| YU | M | 86 | 155.8 | 20.9 | 83.7 | 16.4 | 25 | 1 | +23.0 | -11.4 | +2.6 | +2.6 | | | | | |
| Mean difference | | | | | | | | | -4.1 | 0.1 | -4.0 | -0.5 | | -19.2 | -3.9 | -13.3 | -5.2 |
| ± standard error | | | | | | | | | 2.8 | 2.0 | 1.8 | 1.9 | | 9.2 | 2.2 | 6.8 | 2.1 |
| Paired *t*-test | | | | | | | | | 1.46 | 0.07 | 2.17 | 0.25 | | 2.08 | 1.74 | 1.96 | 2.41 |
| *P*-value | | | | | | | | | 0.17 | 0.95 | 0.05 | 0.81 | | 0.13 | 0.18 | 0.14 | 0.09 |

The underlined values were found to be statistically significant by the zero hypothesis; †, statistically significant differences evaluated by the self-starting cumulative sum; G, gender; M, MESOR; 2A, double circadian amplitude (mm Hg); •Rx dur, duration of treatment in weeks; SBP, systolic blood pressure; DBP, diastolic blood pressure.

with a decrease in their circadian amplitude. Because profiles during the combined losartan-diuretic treatment were obtained only from four subjects, statistical significance could not be evaluated, although the decrease was large, being 42 and 31 mm Hg for the MESOR of systolic and diastolic blood pressure, respectively (*Table 1*).

## DISCUSSION

Similarly to our results, other studies have also shown a benefit of combining losartan with a diuretic (*13, 20, 21*). *Owens et al. (22)* found evidence to suggest that the uricosuric effects of losartan might ameliorate the uric acid retention effects of therapy with hydrochlorothiazide.

Although several studies of losartan efficacy have used ambulatory blood pressure monitoring, results of many large trials still remain based on single measurements in the clinic. Moreover, when ambulatory monitoring is used, it is usually done for 24 or 48 hours only. Interestingly, *Vetter et al. (23)* noticed an improvement in compliance of therapy with home blood pressure monitoring. The recommended use of ambulatory monitoring for 7 days as a minimum (*24*) stems from several objectives. First, improvement in both the precision and the accuracy of daily mean values of blood pressure is needed in order to assess the extent of day-to-day variability in circadian characteristics of blood pressure and heart rate. This should be completed by a diary to determine which, if any, activities or life events adversely affect the blood pressure pattern. Second, availability of a longitudinal record that will enable us to assess the patient's response to treatment on an individual basis. Third, possibility to make a chronodiagnosis, which is the first step in administration of chronotherapy, i.e., timed treatment.

Only chronobiologic methods of assessing results, but not the timing of losartan, were tested herein. It remains to be answered whether modest or no results obtained with the drug in some subjects were due to the absence of timing or to an insufficient dose. The positive effect of adding treatment with a diuretic drug to that with losartan is impressive, since a decrease in blood pressure was invariably recorded (except for a small increase in the circadian amplitude of diastolic blood pressure in one subject). The tabulated individual results further show that short, i.e., 24-hour profiles are not reliable and that long-term systematic monitoring is necessary to assess the effects of timing and dosage and to optimise treatment to become most effective.

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## LONGITUDINÁLNÍ AMBULANTNÍ MONITOROVÁNÍ KREVNÍHO TLAKU PRO CHRONOBIOLOGICKOU ANALÝZU PŮSOBENÍ LOSARTÁNU

S o u h r n

Účinnost losartanu pro léčení vysokého krevního tlaku byla zjišťována u 13 pacientů, kteří si ambulantně, 24 hod denně monitorovali krevní tlak a srdeční frekvenci po dobu jednoho až 15 dní před začátkem léčby trvající jeden až osm týdnů. Losartan byl podáván samostatně nebo v kombinaci s diuretikem. Parametericke testy a test kumulativní sumy (CUSUM), které byly použity pro individuální zhodnocení účinnosti léčby, ukázaly velké inter-individuální rozdíly. Na druhé straně párový t-test byl použit pro skupinové zhodnocení léčby losartanem a ukázal, že terapie losartanem vedla pouze k malému poklesu diastolického krevního tlaku. Výsledky ukázaly potřebu monitorování krevního tlaku dostatečně dlouhou dobu tak, aby bylo možno správně nastavit antihypertenzivní léčbu pro každého pacienta individuálně.

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