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Full paper

Different chronotherapeutic effects of valsartan and olmesartan in non-dipper hypertensive patients during valsartan treatment at morning

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ABSTRACT

This study was undertaken to evaluate the differences in chronotherapeutic effects of angiotensin-II receptor blockers, valsartan and olmesartan in hypertensive patients with non-dipper blood pressure (BP) pattern during valsartan at morning. Ninety four patients were enrolled, and 40 patients were judged to be non-dippers. In these patients, same dose of valsartan was changed to evening (Val-E, $n = 12$), or olmesartan (equivalent dose of valsartan) was given at morning (Olm-M, $n = 13$) or evening (Olm-E, $n = 15$) for 4 months. BP decreased during sleep and increased during waking hours in Val-E group. In Olm-M and Olm-E groups, BP decreased during sleep and waking hours. Percent reduction in BP at night-time compared to BP at waking hours significantly increased after changing the dose regimen in each group. Serum creatinine decreased and estimated glomerular filtration rate (eGFR) elevated in Olm-M and Olm-E, but not Val-E groups. Positive correlation between systolic BP (SBP) during sleep and serum creatinine, and negative correlation between SBP during sleep and eGFR were detected. These data suggest that dipper BP pattern could be obtained by chronotherapeutic approach using valsartan and olmesartan in non-dipper patients with valsartan at morning. Morning and evening olmesartan, but not evening valsartan improved renal function in these patients.

1. Introduction

Chronotherapy is a pharmacologic approach whereby a drug is given at a time that varies according to physiologic needs. Our previous study using stroke-prone spontaneously hypertensive rats (SHR-SP) showed that blood pressure (BP)-lowering effect of valsartan [an angiotensin-II receptor blocker (ARB)] was longer after dosing at an inactive period than after dosing at an active period and, consequently, the survival period of the animals was longer after dosing at an inactive period (1). However, such effects based on the time of dosing were not observed for another ARB, olmesartan in this animal study. Duration of BP-lowering effect in SHR-SP and prolongation of their survival period after dosing olmesartan at an active period were similar to those after dosing the drug at an inactive period (1). These animal data led us to speculate that the chronotherapeutic effects of valsartan were different from those of olmesartan in hypertensive patients.

There are precedents for chronotherapy in hypertension in clinical practice. For example, Hermida et al. reported that, in untreated hypertensive patients with a non-dipper BP pattern, a dipper BP pattern was obtained in 24% and 75% of patients after dosing of valsartan in the morning and evening, respectively (2).

Recent advances in ambulatory blood pressure monitoring (ABPM) have demonstrated that a higher night-time BP and a non-

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dipper BP pattern are good predictors of cardiovascular events (3,4) and progression of renal disease (5,6). Cardiovascular morbidity and mortality are also reported to elevate in hypertensive patients with a non-dipper BP pattern even under antihypertensive drugs (7). These data suggest that it is important for changing a non-dipper to dipper BP pattern in hypertensive patients. Previous studies showed that switching dosing-time of antihypertensive drugs for morning to evening in patients with a non-dipper BP pattern during morning treatment caused more BP reduction at night-time and increased a number of dipper BP pattern (8–10).

Valsartan is one of ARBs, which are frequently prescribed for the treatment of hypertension and improve the prognosis of patients. However, a non-dipper BP pattern is detected in half (46~58%) of hypertensive patients after dosing of valsartan in the morning (11,12), and therefore, a chronotherapeutic approach might provide a benefit for these patients. To address the issue and potential chronotherapeutic differences between valsartan and olmesartan, this study was performed in hypertensive patients with a non-dipper BP pattern during morning treatment with valsartan as follows; 1) a dosing-time was switched from morning to evening, and 2) ARB was changed to olmesartan, which was given at morning or evening. To evaluate a benefit of chronotherapy, the influences on BP pattern and renal function were determined in each group.

2. Methods

The study protocol was approved by the Ethics Review Board of Jichi Medical University (Tochigi, Japan), and registered with the University Hospital Medical Information Network Clinical Trials Registry, Tokyo, Japan (registration number UMIN000003776). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Hypertension was defined as systolic BP (SBP) $\geq$ 140 mmHg and/or diastolic BP(DBP) $\geq$ 90 mmHg at clinic. The definition of night-time BP dipping was based on SBP; night SBP > day SBP as a "riser", and [1-night SBP/day SBP] $\times$ 100 (%): 0$\leq$ ratio <10 as a "non-dipper"; 10$\leq$ ratio <20 as a "dipper", and 20$\leq$ ratio as an "extreme dipper" (13).

The inclusion criteria were as follows; (i) Hypertensive patients took 40–160 mg valsartan once daily in the morning for >2 months; (ii) Dose regimens of valsartan and other antihypertensive drugs were not altered for >2 months, and clinic BP was well controlled (SBP <140 mmHg and DBP <90 mmHg in non-diabetic patients, and SBP <130 mmHg and DBP <80 mmHg in diabetic patients); (iii) Identical dose regimens for hypertension and comorbidities could continue for the following 4 months; (iv) Shift workers were not included; (v) Patients had a non-dipper BP pattern during morning dosing of valsartan.

2.1. Patients

All patients were active during day-time, and took a rest during night-time. Ninety four hypertensive patients were enrolled in the study (Fig. 1). Patients were initially diagnosed as being hypertensive based on clinic BP measurement. The dosing-time of valsartan and other antihypertensive drugs was morning in all patients, except for two patients: one took azelnidipine in the morning and evening, and another took amlodipine at bedtime.

2.2. Study design

The study had a multicenter, open-label, randomized, parallel-group design. The 24-h assessment of BP was done with a portable automatic ABPM device (TM-2431; A&D Co., Ltd., Tokyo, Japan). BP measurements were taken every 30 min from 6 am to 10 pm, and every 60 min from 10 pm to 6 am, to obtain 24-h, day-time, and night-time data. BP data were analyzed using software (TM-2430; A&D Co., Ltd.). "Day-time" and "night-time" were judged based on the diary of each patient.

Two patients withdrew their consent to be included in the study (Fig. 1). The first 24-h BP was assessed in the remaining 92 subjects: 52 patients were judged to be "dippers" and the remaining 40 patients to be "non-dippers". The latter (40/92; 43%) were divided

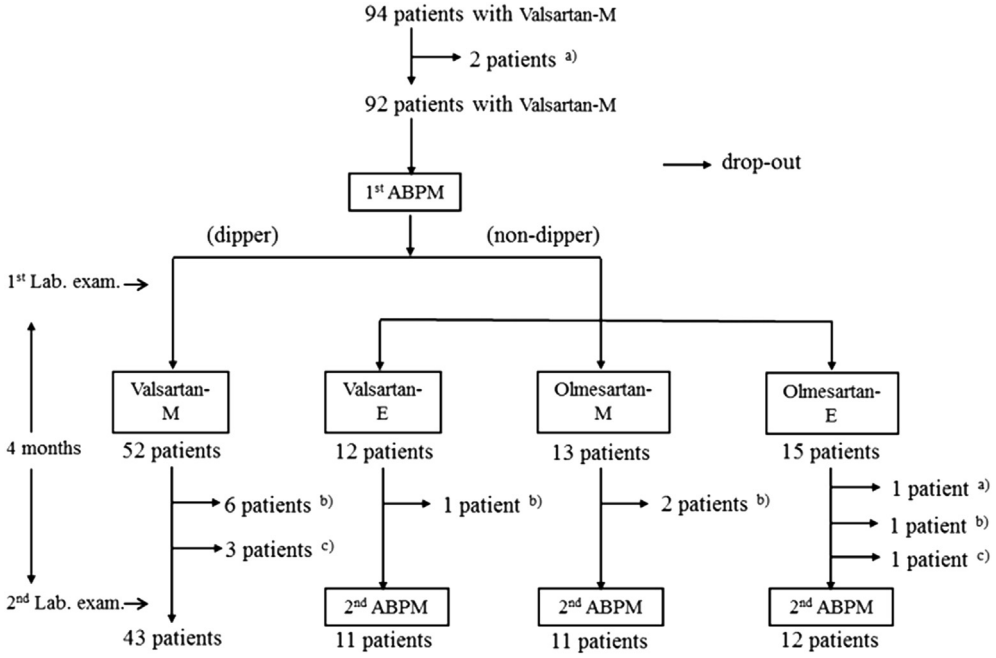

Fig. 1. Study design and number of patients, (a) Patients withdrew their informed consent, (b) Laboratory examinations were not undertaken at 4 months, (c) Antihypertensive drug was changed during the study.