TREATMENT OF NON-DIPPER ESSENTIAL HYPERTENSION WITH BEDTIME ADMINISTRATION OF VALSARTAN

Ramon C Hermida, Carlos Calvo, Diana E Ayala, Marta Rodriguez, Manuel Coveló, Artemio Mojon, Jose R Fernandez, Jose E Lopez. Bioengineering and Chronobiology Labs, University of Vigo, Vigo, Spain; Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago, Spain.

Previous results have indicated that valsartan administration at bedtime as opposed to upon awakening improves the day/night ratio of blood pressure (BP) (nocturnal decline of BP relative to the diurnal mean) towards a more dipper pattern without loss in 24-hour efficacy [Hypertension. 2003;42:283-290]. Some studies have found differential effects of antihypertensive drugs according to the dipping status of the patients. Accordingly, we investigated the administration time-dependent antihypertensive efficacy of valsartan in non-dipper patients. We studied 190 non-dipper patients with grade 1-2 essential hypertension (72 men), 53.9±13.2 years of age, randomly assigned to receive single daily valsartan monotherapy (160 mg/day) either upon awakening or at bedtime. BP was measured by ambulatory monitoring at 20-min intervals from 07:00 to 23:00 hours and at 30-min intervals at night for 48 hours before and after 3 months of therapy. Physical activity was simultaneously monitored every minute by wrist actigraphy to accurately calculate the diurnal and nocturnal means of BP on a per subject basis. The highly significant BP reduction after 3 months of treatment with valsartan (P<0.001) was slightly larger after bedtime dosing of valsartan (13.0 and 8.1 mm Hg reduction in the 24-hour mean of systolic and diastolic BP after valsartan on awakening: 15.2 and 10.6 mm Hg when valsartan was administered at bedtime). The day/night ratio was unchanged after valsartan on awakening (0.4 and 0.7 for systolic and diastolic BP; P>0.309). This ratio was significantly increased (7.2 and 7.1 for systolic and diastolic BP, P<0.001) when valsartan was administered at bedtime, which resulted in 75% of the patients reverted to dippers, a significant increase in the percentage of patients with controlled BP after treatment, and a significant reduction in urinary albumin excretion. Independently of dosing time, 160 mg/day valsartan monotherapy efficiently reduces BP for the entire 24 hours of the day. In hypertensive patients who are non-dippers at baseline, dosing time with valsartan should be chosen at bedtime, for increased efficacy during nocturnal resting hours, improved renal function, and the potential associated reduction in cardiovascular risk.

Key Words: Chronotherapy, Non-Dipper, Valsartan

DIFFERING EFFECTS OF AWAKENING VERSUS BEDTIME VALSARTAN ADMINISTRATION ON URINARY ALBUMIN EXCRETION IN HYPERTENSIVE PATIENTS

Ramon C Hermida, Carlos Calvo, Diana E Ayala, Manuel Coveló, Jose E Lopez. Bioengineering and Chronobiology Labs, University of Vigo, Vigo, Spain; Hypertension and Vascular Risk Unit, Hospital Clínico Universitario, Santiago, Spain.

Previous results have indicated that valsartan dosed at bedtime as opposed to upon awakening improves the day/night ratio of blood pressure (BP) towards a more dipper pattern without loss in 24-hour efficacy [Hypertension. 2003;42:283-290]. Urinary albumin excretion (UAEx) in non-dippers has been shown to be significantly greater than in dippers [Am J Hypertens. 1994;7:23-29]. Moreover, the reduction of UAEx provides renal protection and reduces cardiovascular risk [Lancet. 2001;357:1601-1608]. We hypothesized that improving the day/night BP ratio could further reduce UAEx in hypertensive patients. We studied 123 previously untreated non-proteinuric patients with grade 1-2 essential hypertension (50 men and 73 women), 51.0±11.4 years of age, randomly assigned to receive valsartan (160 mg/d) as a monotherapy either upon awakening or at bedtime. BP was measured by ambulatory monitoring at 20-min intervals from 07:00 to 23:00 hours and at 30-min intervals at night for 48 consecutive hours before and after 3 months of therapy. The patients collected their urine during the first 24 hours of ambulatory monitoring. Physical activity was simultaneously monitored every minute by wrist actigraphy to accurately calculate the diurnal and nocturnal means of BP on a per subject basis. The significant BP reduction after 3 months of valsartan was similar for both treatment times (13.9 and 9.1 mm Hg reduction in the 24-hour mean of systolic and diastolic BP after valsartan on awakening; 15.2 and 10.3 mm Hg after valsartan at bedtime). The day/night BP ratio was unchanged after valsartan on awakening, but significantly increased by 5.4% when valsartan was administered before bedtime. UAEx was significantly reduced, mainly after bedtime treatment (31% reduction). This reduction was independent of the 24-hour BP decrease, but highly correlated with the decrease of nocturnal BP (r=0.326, P=0.007) and with the increase in day/night BP ratio, mainly after bedtime treatment (r=0.395, P=0.002). Bedtime valsartan administration improves the day/night BP ratio to a more dipper profile. This results in further decrease of UAEx as compared to morning dosing, and could thus reduce cardiovascular risk, a hypothesis that deserves further prospective investigation.

Key Words: Albumin Excretion, Chronotherapy, Valsartan