Editorial Comment

New Insights into the Therapeutic Management of Morning Hypertension with α_1-Adrenergic Receptor Blockers

Hakuo TAKAHASHI[1)]

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For more than 20 years, it has been suggested that the prevalence of cardiovascular (CV) events is higher in the morning, when blood pressure (BP) is also higher than during other periods of the day (*1*). Pickering *et al*. (*2*) tested the effects of bedtime dosing of doxazosin, once daily, while measuring BP for 24 h in a subgroup of the Hypertension and Lipid Trial (HALT) study, and found a selective fall in morning BP. Similar findings have been reported in a Japanese population by Kario *et al*. (*3*).

Several important questions need to be answered in regard to morning hypertension. 1) What are the basic mechanisms of morning hypertension? 2) What are the influences of bedtime medication on nocturnal BP accompanied by morning hypertension? 3) If hypertension is a cause of CV events, do the events decrease by antihypertensive therapy targeted at morning hypertension? 4) Is there any difference in the outcome of treatments with different classes of antihypertensive agents? 5) Are α_1-adrenergic blockers, which are the agents most frequently used for the clinical treatment of morning hypertension, clearly superior to the other antihypertensive agents?

In regard to the first of these questions, the underling mechanism of morning hypertension has been shown to involve an augmentation of the pituitary-adrenocortical axis, which increases the circulating cortisol level, which in turn increases the number of receptors involved in vasopressor mechanisms (*4*); an increase in sympathetic nervous system activity (SNA) leading to increased cardiac output and vascular resistance (*5*); and activation of the renin-angiotensin system (RAS) (*6*). In addition, exaggerated CV responses could be accompanied because of the cardiac hypertrophy and thickened arterial wall during morning hypertension (*7*, *8*). However, these points have not been well explored.

As to the influence of nocturnal BP, the BP level during sleep is known to be extremely low in normal subjects (*9*), but relatively elevated in patients with morning hypertension (*10*). The most important mechanism by which BP decreases during the nighttime is suppression of SNA (*5*), and patients with morning hypertension exhibit relatively elevated SNA (*11*). On the other hand, when BP lowering exceeds the lower limit of the autoregulatory pressure range of cerebral blood flow, cerebrovascular damage may result. Therefore, the ideal antihypertensive agents for use at bedtime may be those which moderately decrease nighttime BP only when it is relatively high.

With respect to the third question, there has been no evidence that antihypertensive therapy targeted at morning hypertension actually reduces the incidence of CV events in the morning. The incidence of cardiac failure was reported to be higher by doxazosin treatment than by treatment with diuretics, angiotensin converting enzyme inhibitors, or calcium antagonists in hypertensive patients with high CV risk (ALLHAT study) (*12*). It is well known that diuretics are superior to vasodilators for the treatment of chronic congestive cardiac failure (*13*). Therefore, doxazosin is usually combined with diuretics to treat cardiac failure (*14*). Since the ALLHAT study does not deal with morning hypertension, and doxazosin was not given at bedtime in this study, this

From the [1)]Department of Clinical Sciences and Laboratory Medicine, Kansai Medical University, Moriguchi, Japan.

Address for Reprints: Hakuo Takahashi, M.D., Ph.D., Department of Clinical Sciences and Laboratory Medicine, Kansai Medical University, 10–15 Fumizonocho, Moriguchi 570–8507, Japan. E-mail: takahash@takii.kmu.ac.jp

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result does not necessarily mean that doxazosin cannot be used for the treatment of morning hypertension.

Regarding the outcomes by different classes of antihypertensive agents, therapies either with sympatho-inhibitory agents or RAS inhibitors are desirable for morning hypertension, because they do not cause excessive fall in nocturnal BP but significantly decrease BP rise in the morning after waking. This is because sympathetic activity is suppressed during the night and activated rapidly after waking up.

There have been several therapeutic trials on the treatment of morning hypertension by bedtime dosing of α_1-adrenergic blockers (*1*, *2*, *15*) and α_2-agonists (*16*). And more recently, studies on the successful treatment of morning hypertension with angiotensin II type 1 receptor blockers (ARBs) (*17*) or calcium channel blockers (*18*) have been reported. Because these agents are potent more than α_1-adrenergic blockers, they may be useful in a clinical setting for patients whose morning hypertension is hard to control. However, evening or bedtime dosing of vasodilators such as potent and short-acting calcium channel blockers, which are independent of the physiological BP control mechanism such as sympathetic nervous system and vasoactive substances, is not recommended because these agents may induce too large a reduction in nighttime BP.

Finally, in regard to the fifth question, the advantages of bedtime dosing of α_1-adrenergic blockers are as follows. α_1-Adrenergic blockers do not cause excessive lowering of BP during either the night or day, but effectively decrease morning hypertension. They improve both lipid metabolism and insulin sensitivity (*19*). Furthermore, because they show sympatholytic activity (*20*), their combination with other sympatho-excitory antihypertensive agents, such as calcium channel blockers, would be reasonable.

In the current issue of *Hypertension Research*, Ikeda *et al*. have provided some interesting, additional findings on the effects of bedtime dosing of α_1-adrenergic blockers (*21*). They found that bedtime dosing of doxazosin added to amlodipine, which is most frequently used once daily in the morning in Japan, caused a significant fall in BP only in the morning and regressed left ventricular hypertrophy. This effect was clearly related to decreases in morning BP and increases in insulin sensitivity. Our ultimate aim of treatment is to decrease the incidence of CV events. Improvement of insulin sensitivity and regression of cardiac hypertrophy, as demonstrated in the study of Ikeda *et al*. (*21*), may predict the possible suppression of future CV complications. These findings may be supported by a previous report in which carotid atherosclerosis was regressed by controlling morning BP (*22*). These findings may open a new clinical avenue for the treatment of morning hypertension and end organ damage.

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