Daytime or Nighttime Administration of Antihypertensive Medications?

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Hypertension is among the most common chronic conditions in the United States and affects nearly 29% of all adults. The prevalence increases to over 63% among those aged more than 60 years.[1] Despite hypertension being a known risk factor for adverse cardiovascular outcomes and the availability of an armamentarium of antihypertensive agents, only over 48% of patients have reasonable blood pressure control—a number that has not changed significantly over the last decade.[1] This prompts a careful consideration into the barriers to controlling hypertension among adults in the United States.

Poor control of hypertension is multifactorial. The barriers to hypertension control could be categorized as (i) disease factors, including underlying genetic factors and comorbidities like sleep apnea contributing to hypertension; (ii) provider influence, specifically in selection of antihypertensive agents and intensification of regimen; and most importantly (iii) patient factors like literacy, perceived benefit of therapy, and adherence to prescribed regimen.[2]

Adherence to therapy is limited by multiple considerations including polypharmacy, complicated nature of the regimen, and adverse drug effects. The timing of antihypertensive therapy administration can impact several of these perceived barriers to improved blood pressure control. The diurnal variability in blood pressure has been well documented. This diurnal variation is mediated by an interplay of multiple neuroendocrine signaling pathways, as demonstrated in Figure 1. This figure also indicates the role of various antihypertensive agents in the diurnal variation in blood pressure.

In most individuals blood pressure tends to be lower while asleep and peaks right after awakening. However, in some individuals this diurnal variation does not exist or is attenuated. These individuals, labeled as "non-dippers," have greater end-organ damage including greater left ventricular hypertrophy, silent cerebrovascular disease, and chronic renal damage as compared with "dippers."[3] Hence, nighttime blood pressure control is an important consideration when deciding the timing of administration of antihypertensives.

Another area of importance that is often neglected in the treatment of hypertension is the impact of chronotherapy on diurnal heart rate variation. Heart rate variability is an important predictor of cardiovascular outcomes, and poor heart rate variability has been suggested to be an independent predictor of all-cause mortality.[4] Thus, after considerations of time to peak effect, nighttime administration of negative chronotropic medications like beta-blockers and calcium channel blockers may offer a clear advantage.

In fact, nighttime administration of all antihypertensive agents has shown to be associated with decreased nocturnal hypertension, reduction in non-dipping pattern of ambulatory blood pressure and overall improved cardiovascular outcomes. Hermida *et al.*[5] in the multicenter prospective Hygia trial showed a significant 45% reduction in cardiovascular outcomes with ingestion of ≥1 blood pressure-lowering medications at bedtime as compared with ingestion of all medications upon waking. This was an open-label trial of around 19,000 patients in a primary care setting in Spain, with a follow-up period of 6.3 years. The large population sample size and long follow-up period are major strengths of this trial which clearly showed the beneficial effects of bedtime intake of antihypertensive medications. This study population, however, lacked racial diversity. Therefore, more studies need to be conducted in diverse populations before the routine bedtime intake of antihypertensive drugs can be recommended widely. Further, this study did not address the effect of bedtime vs. morning intake of antihypertensive drugs in dippers and non-dippers on cardiovascular outcomes separately. It has been widely shown that non-dippers benefit from nighttime administration of antihypertensive medications, but the same effect has yet to be shown in the dipper population. Still, the beneficial effects of this study are hard to ignore. The bedtime administration of all the antihypertensive medications not only can

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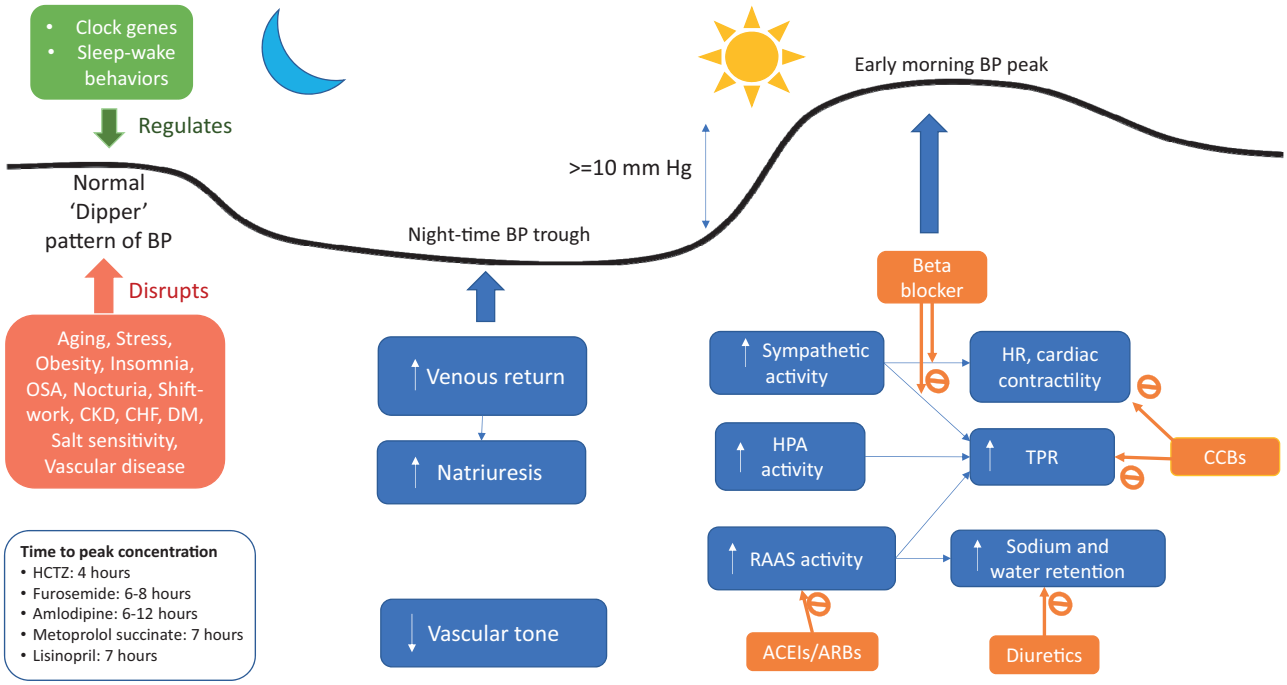

Figure 1. Normal diurnal variation in blood pressure (BP) and role of chronotherapy in management of hypertension. In majority of healthy population, BP is the lowest during nighttime and peaks right after awakening, otherwise known as the "dipper" pattern of diurnal BP variation. This accounts for approximately 10 mm Hg of BP variation in dippers. In contrast, "non-dippers" do not exhibit this variation or exhibit it to a lower degree, often due to a disruption in the normal sleep–wake cycle or through effects of pathological processes on neuroendocrine pathways. The normal variation is controlled by clock genes which further regulate neuroendocrine signaling through the hypothalamus. The physiological processes that coincide with sleeping include increased venous return on assuming a supine position leading to greater circulating volume and increased natriuresis. This, along with decreased vascular tone leads to a nighttime fall in BP. The time of awakening corresponds to a natural surge in neurohormones including increase in catecholamines, glucocorticoids, and maximal activity of the renin–angiotensin–aldosterone (RAAS) pathway. The times of peak activity of common antihypertensive agents including diuretics, beta-blockers, calcium channel blockers (CCBs), and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and their inhibitory effects on various steps of the neurohumeral control of BP are indicated. Taking antihypertensives around bedtime would theoretically lead to the timing of maximal activity of antihypertensive agents to correspond with the surge of prohypertensive enzymes/hormones. Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; HCTZ, hydrochlorothiazide; HPA, hypothalamic–pituitary axis; HR, heart rate; OSA, obstructive sleep apnea; TPR, total peripheral resistance.

improve the cardiovascular outcomes but also can substantially improve patient compliance and adherence to medication regimen.

Bedtime administration of antihypertensive medications has been found to be particularly useful in patients with comorbid conditions such as chronic kidney disease, diabetes, and obstructive sleep apnea.[6] Essentially for improving antihypertensive medication adherence and cardiovascular outcomes, a comprehensive holistic approach is needed. This includes steps such as chronotherapy for antihypertensive medications along with a team-based collaborative approach to improve patient education and compliance. Here, we need to mention the results of Barbershop study by Victor *et al.*[7] In a cluster-randomized trial, the authors found that health promotion by barbers combined with pharmacists-driven antihypertensive medications management resulted in a large reduction in blood pressure in African-American patients. Their simple approach emphasized the value of health promotion, education, regular follow-up, and blood pressure measurement in a setting comfortable and convenient to the patient population. This study also showed a considerable reduction in both systolic and diastolic blood pressures, with cohort retention of 95%, few adverse effects and improvement in patient satisfaction.

Lastly, the impact of lifestyle changes on cardiovascular outcomes in hypertension management is often not given due importance. Simple things like following a low salt, plant protein-based diet, decreased animal fat intake, optimal sleep hygiene, adequate physical activity, avoiding a sedentary lifestyle, smoking cessation, and using relaxation techniques such as yoga/meditation can help not only in improving blood pressure control but improvement in patient's sense of well-being. Importantly, patients feel more connected with physicians who are not just concerned about their test results/medications but the overall health and well-being of patients.

DISCLOSURE

The authors declared no conflict of interest.

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