Analysis of Recent Papers in Hypertension

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CHRONOTHERAPY IN PATIENTS WITH CHRONIC KIDNEY DISEASE TO REDUCE NIGHTTIME BLOOD PRESSURE—NOT READY FOR PRIME TIME

Ambulatory blood pressure monitoring (ABPM) records blood pressure (BP) outside of the normal office setting. It usually involves taking BP measurements every 15 minutes while awake and 30 minutes while asleep for at least 24 hours. ABPM has established the normal circadian pattern of BP with peak BP levels usually occurring during the midmorning (at about 10 AM) and decreasing progressively throughout the remainder of the day to reach a trough value the following morning at around 3 AM. A slow but steady increase in BP is then observed over the early morning hours before awakening, with an increase at approximately 6 AM, coincident with waking up and arising from an overnight sleep. This normal circadian pattern of BP is maintained among patients with hypertension, although there is an upward shift in the BP curve throughout the entire 24-hour period when compared with normotensive patients. Some patients with hypertension do not exhibit the normal 10% nighttime decrease in BP. These "nondippers" experience increased cardiovascular (CV) morbidity and mortality and heart failure. This pattern is also more common in persons with chronic kidney disease (CKD) and is linked with increasing proteinuria and a more rapid decline in renal function. While no study has tested the benefits of lowering nocturnal BP and restoring the normal diurnal BP pattern for outcome benefit, most experts believe that antihypertensive medications should provide 24-hour BP control and preserve the normal nighttime decrease in BP.

In an uncontrolled, single-arm, pilot study, investigators from Naples, Italy, enrolled dialysis-free and transplant-free patients with CKD from their outpatient nephrology clinic to test whether changing administration of one antihypertensive medication from morning to evening would restore the normal nighttime dip in BP in individuals who were nondippers by ABPM. Patients were eligible if they were being treated with antihypertensive medications and had an estimated glomerular filtration rate (eGFR) determined by the Modification of Diet in Renal Disease Study equation of <90 mL/min/1.73 m^2 and exhibited a nondipper BP profile by ABPM (nighttime-to-daytime mean BP ratio >0.9) with controlled daytime ABPM <135/85 mm Hg.

Thirty-two of a potential 284 screened patients met eligibility criteria and were included in the study. Most excluded patients were considered ineligible based on observed daytime ABPM >135/85 mm Hg. The mean age of the 32 study participants was 67 years; 55% were men. Mean eGFR was 46±12 mL/min/1.73 m^2. The study included 6 patients with stage 2 CKD, 22 patients with stage 3 CKD, 3 patients with stage 4 CKD, and 1 patient with stage 5 CKD. Almost 70% of the patients had hypertensive nephrosclerosis as the etiology of their renal disease, with 27% having diabetic renal disease and the rest interstitial renal disease. Baseline 24-hour protein excretion was 271±284 mg/d.

At baseline, the mean number of antihypertensive medications was 2.4±1.4. Shifts in the timing of antihypertensive medication usage were as follows: patients on antihypertensive monotherapy (11 patients) were asked to take their antihypertensive medication in the evening at the same dose given during the day. Patients on multiple antihypertensive medications (9 patients on 2 drugs and 12 patients on ≥3 drugs were asked to take any

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medications given late in the day in the evening. All classes of antihypertensive drugs could be shifted to the evening except for diuretics, to avoid nocturia. These included angiotensin-converting enzyme inhibitors in 12 patients, angiotensin II receptor blockers in 7 patients, calcium channel blockers in 8 patients, β-blockers in 3 patients, and α-blockers in 2 patients.

At baseline and at study completion after 8 weeks of treatment, patients underwent a clinical evaluation, office BP measurements, and two 24-hour ABPM measurements using a Spacelabs 90207 monitor (Spacelabs Inc, Redmond, WA). The daytime and nighttime periods were based on patient diaries. Monitoring was done on a working day, and patients had no access to their ABPM values. In addition to the BP measurements, a 24-hour urine collection for protein and sodium excretion was performed and routine laboratory tests and weights were recorded. The primary outcome of the study was the effect of changing the timing of antihypertensive therapy on the percentage of patients changing the night to day (N/D) ratio of mean ABPM from >0.9 to ≤0.9.

After the 8-week study period, 28 (88%) of the 32 patients had converted from a nighttime nondipper to a dipper profile, reducing nighttime BP an average of 7 mm Hg without an increase in daytime BP. In addition, 94% of patients showed a decrease in N/D ABPM ratio, from 0.95±0.04 to 0.87±0.04 (P<.001) after the change in time of drug administration. Office BP was also reduced at the end of the study, with the average systolic BP decreasing from 136±16 mm Hg to 131±13 mm Hg while average diastolic BP decreased from 77±10 mm Hg to 75±8 mm Hg (P=.02 for both). These changes occurred regardless of the class of antihypertensive medication used. Significant decreases in urinary protein excretion were also seen by study end from 271±284 mg/d to 182±225 mg/d. No change in eGFR, body weight, or urinary sodium excretion was observed.

In nondipping hypertensive patients with stage 2 through 5 CKD and well-controlled daytime ambulatory BP, the normal circadian rhythm of BP can be restored (nondipping status corrected) by shifting 1 antihypertensive drug from morning to evening. This chronotropic effect is independent of the number of antihypertensive drugs required and the class of antihypertensive drug shifted. The authors conclude that, pending the results of larger studies, this pilot study provides a simple intervention for improving 24-hour ambulatory BP control, potentially reducing proteinuria and further reducing the risk of CV disease and renal disease progression.—*Minutolo R, Gabbai FB, Borrelli S, et al. Changing the timing of antihypertensive therapy to reduce nocturnal blood pressure in CKD: an 8-week uncontrolled trial.* Am J Kidney Dis. *2007;50(6):908–917.*

COMMENT

Elevated nocturnal BP and an abnormal dipping status are common in patients with CKD. The pathophysiologic mechanism(s) behind this abnormal nocturnal elevation of BP remains uncertain. Altered sodium excretion has been implicated most often, although activation of the sympathetic nervous system, elevations in angiotensin II and aldosterone levels, and insulin resistance have also been postulated as explanations. Regardless of the pathophysiologic mechanism(s) responsible, the presence of elevated nocturnal BP and the failure to reduce BP at night (nondipping) have been associated with a greater risk of cardiovascular morbidity and mortality as well as end-stage renal disease. Whether chronotherapy, or the timing of drug intake and BP response, would favorably alter the abnormal circadian rhythm in patients with CKD was investigated in this pilot study.

The present study found that by shifting the timing of one antihypertensive medication after 8 weeks of treatment, patients' BP profile converted from nighttime nondipper to normal dipper. Mean nighttime BP was reduced 7 mm Hg without an increase in daytime ambulatory BP. In addition, 94% of patients showed a decrease in N/D ABPM ratio, from 0.95±0.04 to 0.87±0.04 (P<.001) after the change in time of drug administration. Office BP levels were also reduced, with average systolic BP decreased from 136±16 to 131±13 mm Hg, while average diastolic BP decreased from 77±10 to 75±8 mm Hg (P=0.02 for both). These changes occurred regardless of the class of antihypertensive medication used. Significant decreases in urinary protein excretion were also seen by study's end.

Although this was the first study to investigate the role of ABPM, dipper status, and chronotherapy in patients with well-controlled BP and CKD, caution must be exercised in generalizing from these data. First, this was only an 8-week trial without a control arm, there was no randomization, and the patient population involved only 32 patients who were selected based on ABPM. Second, the patients studied all had controlled ambulatory BP, which prevented confounding through BP changes caused by treatment intensification. Third, this was a study from Italy that enrolled no ethnic minorities;

since only 17% of participants had diabetes, the study population may not be reflective of the CKD population in the United States.

This pilot study, however, provides preliminary data to guide the design of a larger clinical outcome trial to investigate whether changing the time of antihypertensive medication administration from earlier in the day to the evening will improve CV and renal outcomes. Until the role of ABPM becomes more established in clinical practice, utilizing combinations of antihypertensive medications, each of which provides adequate 24-hour BP control, should be recommended. While it remains an interesting subject for future clinical investigations, the role of chronotherapy for outcome improvement still remains unproven.