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P.M. DOSING OUTCOMES OF ACE INHIBITORS OR ANGIOTENSIN II RECEPTOR BLOCKERS IN HYPERTENSION VERSUS P.M. DOSING IN HYPERTENSION WITH COMORBIDITIES

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Abstract

- Introduction:** The purpose of this research is to compare P.M. dosing outcomes of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in those with hypertension and hypertension plus chronic kidney disease or diabetes.
- Research Methods:** Three databases were searched including PubMed, ClinicalKey, and DynaMed with a time frame of 15 years. Studies chosen for review were peer reviewed, and included randomized control trials, systematic reviews, meta-analyses, and a preclinical animal trial.
- Discussion:** The research shows evidence of reduced blood pressures throughout the night and into the next day, decreased proteinuria, and decreased cardiovascular events when dosing ACE inhibitors or ARBs at night, or dosing at least one antihypertensive medication at night. This research shows beneficial evidence and no documented adverse patient reactions when dosing ACE inhibitors or ARBs at night. However, further research needs to be conducted with larger patient populations to make official recommendations in those with hypertension and hypertension plus diabetes or chronic kidney disease.
- Keywords:** *chronotherapy in hypertension, chronotherapy in hypertension with CKD, chronotherapy in diabetes, chronotherapy of ACE inhibitors, chronotherapy of angiotensin II receptor blockers.*

Introduction

As more discoveries are being made about the intricate details of what occurs during the sleep cycle that is part of our circadian rhythm, chronotherapy research is being done that specifically targets the mechanisms that take place during that time, allowing medications to be more effective and beneficial. In patients with hypertension and hypertension plus other comorbidities, such as diabetes or chronic kidney disease (CKD), dosing angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) at night may prevent blood pressure from spiking during the early morning hours that could initiate myocardial infarctions, strokes, increase kidney damage, and the risk for further diabetic complications. The purpose of this study is to compare P.M. dosing of ACE inhibitors or ARBs in those with hypertension versus those with hypertension plus diabetes or CKD, to determine if there are any beneficial outcomes in that dosing schedule.

Statement of the Problem

- According to the Center of Disease Control and Prevention (2017), nearly half of Americans have hypertension or are taking medication for hypertension, and 1 of 4 adults with hypertension have it under control.
- The American Diabetes Association (2018), statistically states that 2 of 3 Americans with diabetes report having high blood pressure.
- The National Kidney Foundation (2010), reports that high blood pressure is a leading cause of CKD and high blood pressure can also be a complication of CKD.

Research Question

In patients taking ACE inhibitors or angiotensin II receptor blockers, what are the outcomes of P.M. dosing in hypertension versus P.M. dosing in hypertension with comorbidities

Literature Review

Chronotherapy and Circadian Rhythm

- In the early morning hours, heart rate, blood pressure, endothelial cell function, platelet aggregation, and thrombus formation are enhanced in order to prepare for awakening, which may generate myocardial infarctions, arrhythmias, stroke, heart failure, and sudden cardiac death if not managed appropriately (Rabinovich-Nikitin et al., 2019).
- Non-dipping blood pressure pattern is classified as <10% drop in average nocturnal vs. daytime blood pressure. This may result in increased left systolic volume, left ventricular wall thickness, and lower right atrial ejection fraction (Bowles et al., 2018).
- Reverse dipping pattern is when the average nighttime blood pressure is higher than the daytime blood pressure. This may result in severe renal dysfunction, cardiovascular injuries, carotid plaque formation, and lacunar infarctions (Bowles et al., 2018).
- Ambulatory blood pressure readings are more accurate than office blood pressure measurements. Ambulatory blood pressure readings will determine if a patient is a dipper or a non-dipper (Hermida et al., 2017).

Effects of P.M. Dosing of ACE inhibitors or ARBs in Those with Hypertension

- Administering ramipril before bed regulated the asleep blood pressure more effectively when compared to morning administration ($p < 0.001$) and decreased the number of patients that were considered non-dippers when compared to morning administration ($p = 0.026$) (Hermida et al., 2009).
- After treatment of valsartan 160 mg/day in the morning, 57.8% of participants had controlled diurnal blood pressure and 45.1% had controlled nocturnal blood pressure. When valsartan was dosed in the evening, 74.5% of participants had controlled diurnal blood pressure and 61.2% had controlled nocturnal blood pressure (Hermida et al., 2005).
- Urinary albumin excretion reduction correlated with an increase in the diurnal/nocturnal systolic blood pressure ratio ($p < 0.001$) when valsartan was dosed at night (Hermida et al., 2005).
- Plasma fibrinogen levels were decreased in those participants taking valsartan before bed ($p = 0.046$) (Hermida et al., 2005).

Effects of P.M. Dosing of ACE inhibitors or ARBs in Those with Hypertension and Chronic Kidney Disease

- eGFR was unchanged in those with bedtime dosing of one antihypertensive ($p = 0.551$) (Hermida et al., 2011).
- Patients who took one antihypertensive upon bedtime showed lower amounts of cardiovascular events when compared to awakening administration ($p < 0.001$) (Hermida et al., 2011).
- Proteinuria was significantly decreased with dosing at least one antihypertensive at night ($p < 0.001$) (Minutolo et al., 2007).
- There was no decrease in nocturnal blood pressure in those taking medications at night inhibiting the RAAS system (systolic $p = 0.5$ and diastolic $p = 0.2$) (Minutolo et al., 2007).
- Bedtime dose of valsartan decreased changes in the left ventricular mass index in those with a non-dipping pattern when compared with morning administration ($p < 0.05$) (Wang et al., 2013).

Effects of P.M. Dosing of ACE inhibitors or ARBs in Those with Hypertension and Diabetes

- Overall blood pressure was decreased with bedtime administration in those taking at least one antihypertensive medication (Hermida et al., 2011).
- Participants taking one antihypertensive medication at night had an overall decreased in cardiovascular disease events ($p = 0.038$) (Hermida et al., 2011).
- C-Reactive protein was reduced upon administration of one antihypertensive medication at night ($p = 0.017$) (Rossen et al., 2014).
- Fibrinogen levels were unaffected with bedtime administration of at least one antihypertensive medication ($p = 0.153$) (Rossen et al., 2014).
- Urinary creatinine was decreased with bedtime administration of at least one antihypertensive medication ($p < 0.001$) (Rossen et al., 2014).
- Nocturnal blood pressure was significantly reduced with bedtime administration of olmesartan ($p = 0.007$) (Tofe Povedano et al., 2009).
- Olmesartan dosed in the morning increased the dipper population to 74% and nocturnal administration increased the dipper population to 82% ($p = 0.012$) (Tofe Povedano et al., 2009).
- No significant difference in the amount of albumin excreted between the morning and nocturnal administration of olmesartan ($p = 0.669$) (Tofe Povedano et al., 2009).

Discussion

Chronotherapy and Circadian Rhythm

- Results revealed taking at least one antihypertensive at night would improve regulation of nocturnal blood pressure to prevent increased cardiovascular related complications (Bowles et al., 2018).
- Ambulatory blood pressure readings are beneficial to providers in order to determine if a patient is at increased risk for cardiovascular disease, myocardial infarctions, stroke, kidney damage, or diabetes by classifying their dipping status while sleeping. Thus, evening administration of antihypertensives could be warranted for a patient to prevent the above listed diseases (Hermida et al., 2017).
- Plasma aldosterone is at its highest level in the middle to late night hours during the sleep cycle (Smolensky et al., 2017).

Effects of P.M. Dosing of ACE inhibitors or ARBs in Those with Hypertension and Hypertension plus CKD or Diabetes

- Many studies revealed that dosing ACE inhibitors or ARBs at night decreased nocturnal blood pressure, overall blood pressure, and participants with a non-dipping pattern to a dipping pattern that have hypertension and hypertension with diabetes. Cardiovascular events may be prevented when patients are converted to a dipping pattern to minimize the early morning physiologic processes that occur to prepare for waking. Dipping and non-dipping blood pressure patterns were not studied in the trials cited for CKD.
- Decreased protein excretion into the urine was demonstrated when dosing valsartan at night and using at least one antihypertensive medication at night in those with hypertension and hypertension with CKD. This dosing regimen may prevent further kidney damage and sequelae of low serum protein levels. Olmesartan did not show any difference in the amount of albumin excreted between morning or evening administration.
- Fibrinogen levels were decreased in hypertension participants taking valsartan at bedtime, which may prevent future myocardial infarctions or stroke. Fibrinogen levels were not analyzed in the studies used for CKD, and fibrinogen levels were not affected in those with hypertension and diabetes.
- eGFR was unchanged in participants taking antihypertensives at night with chronic kidney disease. Based on this study, dosing antihypertensives at night for the sole purpose of altering eGFR would not be recommended since there was no significant benefit.
- Because there are benefits of dosing ACE inhibitors, ARBs, or at least one antihypertensive medication at night, with no reported adverse patient events, it would be worth trialing evening doses of these medications to determine if the above listed comorbidities improve.

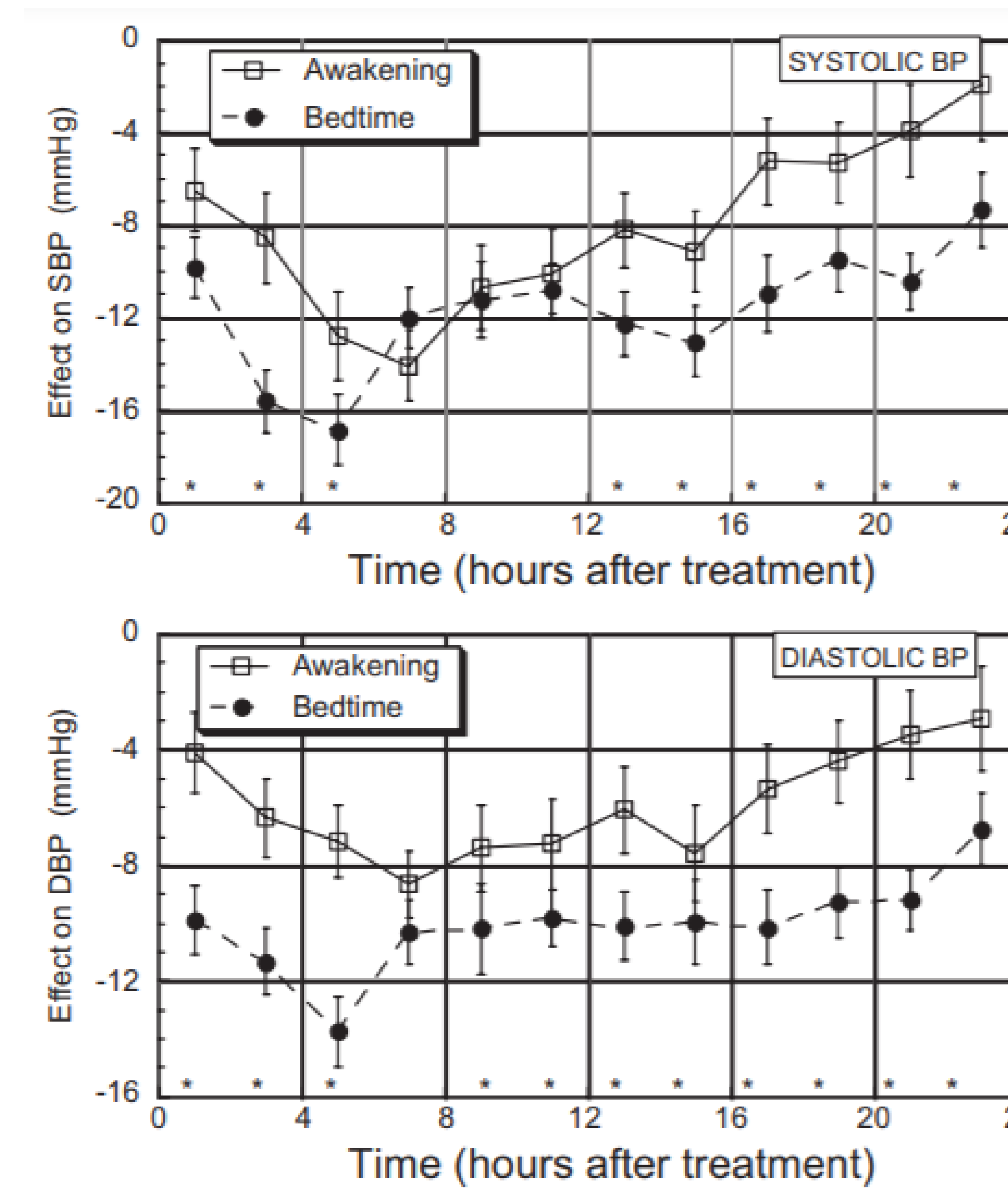


Figure 3. Changes (in units of mm Hg) from baseline along the 24-hour after treatment in SBP (top) and DBP (bottom) with ramipril (5 mg/d) ingested on awakening or at bedtime in patients with grade 1 or 2 uncomplicated essential hypertension studied by 48-hour ABPM before and after 6 weeks of timed treatment. * $P < 0.05$ in BP reduction between the 2 groups.

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Applicability to Clinical Practice

- Research has shown benefits of dosing ACE inhibitors or ARBs at night in order to decrease blood pressure throughout the night and into the next day to avoid constant elevation and early morning spikes in blood pressure that may initiate cardiac events, cerebrovascular events, or further kidney damage.
- The advantages of utilizing chronotherapy when dosing ACE inhibitors or ARBs is the potential of not adding another medication to a patient's already long list of prescriptions, not increasing the financial burden to those having to take another medication, and slowing the progression of chronic disease states. One disadvantage to the theory of dosing ACE inhibitors or ARBs at night is the potential for non-compliance with the evening dose if patients are already taking medications in the morning.
- Further research needs to be done with larger patient populations to make official recommendations on dosing ACE inhibitors or ARBs at night before bed in those with hypertension and hypertension with diabetes or chronic kidney disease. However, because there were no documented patient adverse events or complications that arose from these trials, it would be worth trying this type of intervention on patients who are willing to be compliant with the dosing regimen.

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