Original Article

Dipping Pattern of Nocturnal Blood Pressure in Hypertensive Patients Treated with Azilsartan

P. L. N. Kapardhi, Viraj R. Suvarna[1], Rahul Chavda[2], Reshma Susan Reji[3], Manoj A. Suva[4]

Department of Cardiology, Director Cath Lab, Century Hospitals, Hyderabad, Telangana, [1]Department of Medical, Eris Lifesciences Ltd., [2]Marketing Executive, Eris Lifesciences Ltd., [3]Medical Advisor, Eris Lifesciences Ltd., [4]Medical Services, Eris Lifesciences Ltd., Ahmedabad, Gujarat, India

ORCID:
P. L. N. Kapardhi: https://orcid.org/0000-0003-4158-7023
Viraj R. Suvarna: https://orcid.org/0000-0002-2748-7723
Rahul Chavda: https://orcid.org/0000-0002-1346-0634
Reshma Susan Reji: https://orcid.org/0000-0001-5850-7080
Manoj A. Suva: https://orcid.org/0000-0003-0484-7375

Abstract

Aim: On average, blood pressure (BP) is found to be low during night than during day by approximately 10%–20%. In addition, BP decreases by >20% in some hypertensives or lowered by <10% or few patients may experience rise in BP during night compared to daytime BP. This study was performed to determine the dipping pattern of BP variability of the patients receiving azilsartan with the help of ambulatory BP monitoring (ABPM) system. **Settings:** This was a prospective, observational, open-label, single-center study. **Materials and Methods:** A total of 158 hypertensive patients (systolic BP [SBP] >140 mmHg; diastolic BP [DBP] >90 mmHg) were enrolled to performed ABPM and clinic BP monitoring with ongoing treatment with azilsartan. **Statistical Analysis:** Data are expressed as mean ± standard deviation. Statistical comparisons to test differences between two independent groups were by Student's *t*-test or Mann–Whitney's U-test as appropriate. **Results:** All patients monitored for 24-h BP measurement and reported to had SBP 133.76 ± 15.97 mmHg and DBP 76.16 ± 10.86 mmHg. Pulse rate was found to be 76.18 ± 11.82 bpm. BP variability was found to be high in 23.41% patients. Overall, study showed 34.17% dipper, 3.16% extreme dipper, 51.26% nondippers and 11.39% patients with reverse dipping pattern. In the present study, the dippers are classified to have 18.9% reduction in SBP, whereas 12.5% reduction in DBP. In the dippers group, only 4 patients had normal BP variation (2.53%), whereas high BP variation was found in 50 patients of the group (31.64%). **Conclusions:** ABPM had revealed higher SBP, BP variability (in almost one-fourth patients), dipping pattern and slightly higher pulse rates in hypertensive patients receiving azilsartan treatment. Around one-third of hypertensive patients were found to be dippers and more than half patients were non-dippers. Azilsartan has potent antihypertensive effect over 24 h and can be preferred in high-risk hypertensive patients.

Keywords: Ambulatory blood pressure monitoring, azilsartan, blood pressure variability, dipping, nondipping, reverse dipping

Introduction

Hypertension treatment has evolved over a period of time with a gradual shift from a step care regimen based on BP alone, to total risk-based assessment and management. Blood pressure (BP) is found to be low during night period (sleep) than during day period (waking time) by approximately 10%–20%. In addition, BP decreases by >20% in some hypertensive patients or lowered by <10% in others, and few patients may experience rise in BP during night compared to daytime BP. Recent guidelines on the treatment of hypertension have highlighted the importance of assessing the associated risk factors and the presence and extent of target organ damage along with BP measurements to decide the initiation of treatment and drug selection.[1] As

Received: 16-04-2019 **Revised:** 23-07-2019 **Accepted:** 20-10-2019
Published Online: 11-06-2020

Access this article online

Quick Response Code:

Website: http://www.ijcva.com

DOI: 10.4103/IJCA.IJCA_23_19

Address for correspondence: Dr. P. L. N. Kapardhi, Department of Cardiology, Director Cath Lab, Century Hospitals, Road No.12, Banjara Hills, Hyderabad - 500 044, Telangana, India.
E-mail: dr.kaparthi@gmail.com

How to cite this article: Kapardhi PL, Suvarna VR, Chavda R, Reji RS, Suva MA. Dipping pattern of nocturnal blood pressure in hypertensive patients treated with azilsartan. Int J Cardiovasc Acad 2020;6:41-5.

compared to conventional clinical BP monitoring, ambulatory BP monitoring (ABPM) more accurately predict cardiovascular morbidity and mortality.[2] Over the last decade, ABPM devices are increasingly used in the diagnosis of hypertension to exclude white coat hypertension, which affects about 15%–30% of the population and also useful in the diagnosis of patients with borderline hypertension, in looking at the efficacy of antihypertensive treatment and identifying nocturnal hypertension.[3] Antihypertensive treatment leads to significant reduction in relative risk of cardiovascular events, although the number of patients needed to be treated (NNT) to prevent one cardiovascular event is substantially high, especially when the disease is mild.[4] In a meta-analysis of 147 trials, the relative risk reduction of coronary artery disease was 21% over a mean of 4.6 years, for a BP reduction of 10/5 mmHg (systolic/diastolic), among patients a pretreatment systolic BP (SBP) of 132–186 mmHg and without any cardiovascular disease (CVD). However, the NNT to prevent one event works out to around 140.[1] This number will be larger if stage one hypertensive is considered. The goal of assessment and risk stratification is to identify high-risk hypertensive patients who would derive the maximum benefit from treatment compared to low-risk hypertensive whose benefit from antihypertensive treatment may not be favorable in terms of risk–benefit ratio, considering the long-term treatment side effects.[5,6] While the presence of target organ damage is a definite indication for initiating treatment, physicians have been looking for simpler clinical tools to identify high-risk individuals. BP that does not dip down to the normal physiological range during the night has been identified as a reliable indicator of increased cardiovascular complications in the future and is emerging as an independent and powerful marker for high-risk hypertensive patients.[7] Azilsartan is a novel angiotensin II receptor blocker (ARB) with potent BP-lowering effects.[8]

The concept of dipper and nondipper

In healthy individuals, BP follows a circadian pattern. BP starts declining from late evening onward, reaches a nadir around midnight, and shoots up just after awakening in the morning. Dips in BP have been described in three windows of sleep: BP starts declining in the visceral window, reaches the plateau level in the basal window, and rises in the preawakening window.[9] This phenomenon of BP dipping has been documented by 24-h ABPM devices. This natural circadian variation may be altered by certain metabolic and cardiovascular changes.[10,11] The present study was conducted with an objective to determine the dipping pattern BP variability of the hypertensive patients receiving azilsartan, with the help of ABPM system.

Materials and Methods

Subjects

The study included 158 hypertensive patients (age 35–60 years) without a history of major CVDs at baseline such as myocardial infarction, stroke, or congestive heart failure were receiving treatment with single-dose azilsartan (20 or 40 mg depending on the patient current status of hypertension) for 6 months. Out of all patients, 62 females (39.24%) and 96 males (60.76%) were included and 22 patients (13.92%) had diabetes. As it was prospective, open-label, observational study, no randomization or blinding or sample size calculation was done and patient selected without any bias. Patients with severe coexisting diseases, debilitating illness, dementia, and impairment of renal function were excluded from the study. The protocol conformed to the clinical guidelines of the local institutions and written informed consent was obtained from each patient. Patients were selected from the electrical chart. All patients were persistently hypertensive (more than 140 mmHg SBP or 90 mmHg diastolic BPs [DBP]) despite treatment with antihypertensive drug azilsartan.

Home blood pressure measurements

Initially, patients were informed how to measure their self BP and then instructed to record their BPs at least twice a week at home in the sitting position, once in the morning before breakfast within 30 min of awakening and again in the evening just before dinner using semi-automatic home BP measurement device that operates on the cuff oscillometric principle and generates a digital display of SBP and DBP and pulse rate. The accuracy of these self-measured BP monitoring readings was checked by well-trained clinic staff. A standard arm cuff was used to obtain the clinic and home BP monitoring readings because the circumference of patients' arm was <14 cm. These BP values were used as a reference for optimization of the dose of azilsartan.[12]

Blood pressure monitoring with ambulatory blood pressure monitoring-05

ABPM was performed using ABPM-05 device (Meditech Ltd., Hungary) which tracks BP and pulse rate, and it provides information on BP variability, overnight dipping, and morning surge for managing and controlling hypertension. ABPM-05 is a silent, compact, and very reliable ABPM. A large LCD screen ensures easy readability, and its lightweight design provides for maximum patient comfort. Using 2 AA rechargeable batteries ABPM-05 can make measurements up to a period of 48 h. The device can store more than 600 readings in its solid-state memory for an unlimited length of time. Extra measurements can be triggered, and events can be marked manually. The device can be adjusted to the patient's lifestyle with a push of the day/night button. The study participants were instructed to hold the hand at heart level during the BP measurements. Central BP was assessed by applying the n-point moving average method, a mathematical low-pass filter, to the radial pulse waves. This method was validated against invasive measurements as well as against validated noninvasive methods for taking central pressure measurements. Nighttime was defined as from 9:00 PM to 6:00 AM.[13]

Statistics

Data are expressed as mean ± standard deviation. Statistical comparisons to test differences between two independent

groups were by Student's *t*-test or Mann–Whitney's U-test, as appropriate.

Results and Discussion

Absolute rate systolic and diastolic pressure

Defining normal ABPM BP values is difficult, and normal values are different in adults, children, and pregnant women. However, according to the most widely accepted criteria, normal daytime values are below 135/85 mmHg, while normal nighttime values are <120/70 mmHg and values are below 130/80 mmHg for the whole 24-h period in adults. A total of 158 patients were monitored for their 24-h SBP and DBP was calculated. 24-h mean variable of ABPM on azilsartan-treated patients is mentioned in Table 1. The number of patients with dipping status is shown in Figure 1.

The difference of values of mean systolic blood pressure and diastolic blood pressure between active and passive time

All the data of 158 patients were observed and the difference between the mean value of BP variable in the day (active time) and night time (passive time). There was a markable reduction in the SBP and DBP reported in the dipping pattern, and there is a significant difference observed in the mean value of the same. Whereas, 18 patients reported to have higher mean passive time (night) BP with value 143/75.22 mmHg when compared to with that of the mean value of day (active) BP with value 136.56/73.11 mmHg. The number of patients with dipping status and BP variability is shown in Figure 2.

Table 1: 24-h mean variable of ambulatory blood pressure monitoring on azilsartan-treated patients

Parameters	Value of 24 h (mean±SD)
SBP	133.76±15.97
DBP	76.16±10.86
Pulse	76.18±11.82
BP variability, number of patients (*n*=158)	
High	37
Normal	121
Dipping status, number of patients (*n*=158)	
Dipper	54
Extreme dipper	5
Nondipper	81
Reverse dipping	18

P<0.05, not significant. SD: Standard deviation, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP

Hypertensive subjects with dipping pattern (dippers)

A total of 54 patients were reported to have the dipping pattern of BP of about 10%–20% decrease from the daytime BP values. In the present study, the dippers are classified to have 18.9% reduction in SBP and 12.5% reduction in DBP. In the dippers group, only four patients had normal BP variation, whereas high BP variation was found in 50 patients of the group. Mean BP variability on 24-h BP observation of dippers is shown in Table 2.

Hypertensive subjects without dipping pattern (nondippers)

Total 81 patients were reported to have the dipping pattern of <10% decrease in BP from daytime values. In the present study, the dippers are classified to have 7.1% reduction in SBP, whereas 6.7% reduction in DBP. In the dippers group, only four patients (2.53%) had normal BP variation, whereas high BP variation was found in 50 patients (29.64%) of the group. Dippers fail to follow the circadian rhythm which accounts to fall of BP by ≤10% and have the higher risk of cardiac-related damage. Mean BP variability on 24-h BP observation of nondippers is shown in Table 3.

Hypertensive subjects with dipping pattern (extreme dippers)

On the basis of the percentage of dipping status, patients were classified into different categories. In the present study, only five patients (3.17%) were found to have higher BP dipping when compared to daytime BP. The mean SBP and DBP of the passive time were found to be reduced by 31.60% and 18.60%, respectively. All of the patients had high BP variability and 60% patients had high morning surge.

Hypertensive subjects with dipping pattern (reverse dippers)

Unlike another dipping pattern, the patients of reverse dipping group had higher nighttime BP when compared

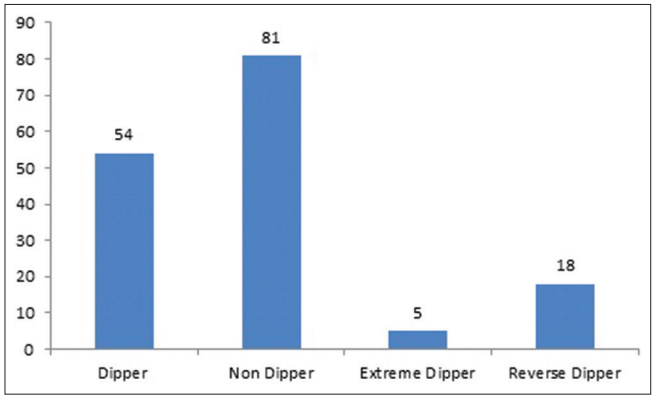

Figure 1: Patients with dipping status

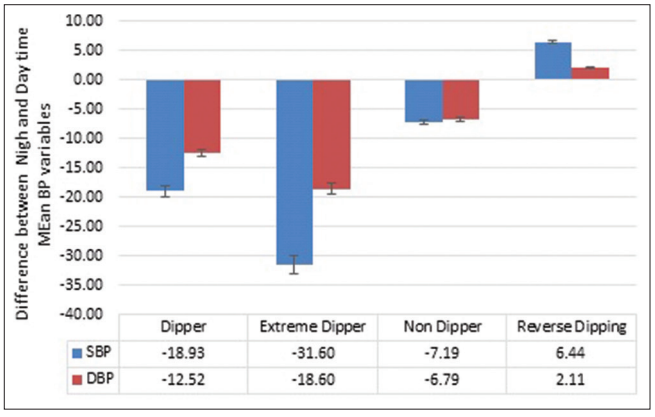

Figure 2: Patients with dipping status and blood pressure variability

to that of active time. This may prognosis into a higher risk of organ failure and stroke. In the present study, 18 patients (11.39%) were found to have reversed dipping pattern. Data are represented as mean BP variability on 24-h BP observation of reverse dippers in Table 4.

Discussion

Hypertensive patients were undergone 24-h ABPM, and differences between the mean value of BP variable in the day (Active time) and night (Passive time) were reported. Azilsartan at a dose of 20–40 mg has shown significant reduction in the SBP and DB*P* value in hypertensive patients and also reduced the dipping pattern. In accordance with a study conducted by Alfonso Mention Perez and Cao (2017) demonstrated that azilsartan once daily at dose up to 40 mg (with exception of 2.5 mg for clinic DBP) lead to significant reduction in SBP and DBP (based on both clinic trough and 24-h ABPM measurements) relative to placebo in patients with mild to moderate uncomplicated essential hypertension. Reductions in SBP and DBP with azilsartan 20 and 40 mg were statistically superior to those observed with olmesartan 20 mg.[14] Azilsartan medoxomil is effective and safe ARB with a unique pharmacologic profile versus other antihypertensive agents including slowed angiotensin II type 1 receptor dissociation rates and improved receptor specificity. Studies have shown that azilsartan medoxomil 80 mg once daily reduced BP by a greater extent than olmesartan and valsartan with similar safety and tolerability profile.[8] This ABPM study revealed that hypertensive patients had higher SBP, BP variability (in almost one-fourth patients), dipping pattern, and slightly higher pulse rates. A study by Duggal *et al*. reported normal dipping pattern in 45% patients, nondipping in 46% patients, extreme dipping in 6% patients, and reverse dipping in 3% of patients with diabetes and hypertension.[2] Similar to this study findings, the present study also revealed the normal dipping pattern in 34.17% patients, nondipping in 51.26% patients, extreme dipping in 3.16% patients, and reverse dipping in 11.19% of patients in hypertensive patients. Around one-third of the hypertensive patients (34.17% patients) were found to be dippers and more than half patients were nondippers. Azilsartan is a novel ARB which has a potent antihypertensive effect over 24 h can be preferred as antihypertensive drug as either monotherapy or in combination with other drugs in high-risk hypertensive effect.[15]

Table 2: Mean blood pressure variability on 24 h

Variable	Value (mean±SD)
24 mean SBP	130.89±12.83
24 mean DBP	75.43±10.42
Mean pulse	77.89±12.54
BP variation, number of patients	
High	50
Normal	4
Morning surge, number of patients	
High	14
Normal	40

BP observation of dippers. SD: Standard deviation, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP

Table 3: Mean blood pressure variability on 24 h

Variable	Value (mean±SD)
24 mean SBP	134.68±16.79
24 mean DBP	77.57±10.27
Mean pulse	75.91±11.15
BP variation, number of patients	
High	54
Normal	27
Morning surge, number of patients	
High	9
Normal	72

BP observation of nondippers. SD: Standard deviation, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP

Table 4: Mean blood pressure variability on 24 h

Variable	Value (mean±SD)
24 mean SBP	138.83±17.76
24 mean DBP	73.94±13.51
Mean pulse	74.61±11.96
BP variation, number of patients	
High	12
Normal	6
Morning surge, number of patients	
High	2
Normal	16

BP observation of reverse dippers. SD: Standard deviation, BP: Blood pressure, SBP: Systolic BP, DBP: Diastolic BP

Conclusions

ABPM had revealed higher SBP, BP variability (in almost one-fourth patients), dipping pattern and slightly higher pulse rates in hypertensive patients receiving azilsartan treatment. Around one-third of hypertensive patients were found to be dippers and more than half patients were non-dippers. Azilsartan has potent antihypertensive effect over 24 h and can be preferred in high-risk hypertensive patients.

Acknowledgment

We are thankful to all the patients for providing their participation in the observational study and providing approval for sharing the results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mahabala C, Kamath P, Bhaskaran U, Pai ND, Pai AU. Antihypertensive therapy: Nocturnal dippers and nondippers. Do we treat them differently?

Vasc Health Risk Manag 2013;9:125-33.
2. Duggal A, Bal BS, Singh N. Study of dipping and non-dipping patterns in patients of type 2 diabetes mellitus with hypertension and its association with microalbuminuria. Ann Int Med Dent Res 2017;2:20-4.
3. Mohamed AL, Katiman E, Hassan JA. Ambulatory blood pressure monitoring profile as a useful prognostic tool in patients with primary hypertension. Malays J Med Sci 2003;10:76-83.
4. Wallis EJ, Ramsay LE, Jackson PR. Cardiovascular and coronary risk estimation in hypertension management. Heart 2002;88:306-12.
5. Tocci G, Valenti V, Sciarretta S, Volpe M. Multivariate risk assessment and risk score cards in hypertension. Vasc Health Risk Manag 2007;3:313-20.
6. Phillips RA, Xu J, Peterson LE, Arnold RM, Diamond JA, Schussheim AE, *et al.* Impact of cardiovascular risk on the relative benefit and harm of intensive treatment of Hypertension. J Am Coll Cardiol 2018;71:1601-10.
7. Hamrahian SM. Pathophysiology of Hypertension. Available from: https://emedicine.medscape.com/article/1937383-overview. [Last updated on 2017 May 18; Last accessed on 2019 Aug 13].
8. Baker WL, White WB. Azilsartan medoxomil: A new angiotensin II receptor antagonist for treatment of hypertension. Ann Pharmacother 2011;45:1506-15.
9. O'Brien E. The circadian nuances of hypertension: A reappraisal of 24-h ambulatory blood pressure measurement in clinical practice. Ir J Med Sci 2007;176:55-63.
10. Bloomfield D, Park A. Night time blood pressure dip. World J Cardiol 2015;7:373-6.
11. Grossman E. Ambulatory blood pressure monitoring in the diagnosis and management of hypertension. Diabetes Care 2013;36 Suppl 2:S307-11.
12. Suzuki H, Seki M. Effects of azilsartan in ambulatory patients on maintenance hemodialysis: Monitoring at night and at home. J Nephrol Ther 2014;S1 (007):1-4.
13. Jankowski P, Bednarek A, Olszanecka A, Windak A, Kawecka-Jaszcz K, Czarnecka D, *et al.* Twenty-four-hour profile of central blood pressure and central-to-peripheral systolic pressure amplification. Am J Hypertens 2013;26:27-33.
14. Perez A, Cao C. Azilsartan in patients with mild to moderate hypertension using clinic and ambulatory blood pressure measurements. J Clin Hypertens (Greenwich) 2017;19:82-9.
15. Kario K, Hoshide S. Rationale, study design, and implementation of the ACS1 study: Effect of azilsartan on circadian and sleep blood pressure as compared with amlodipine. Blood Press Monit 2014;19:123-8.