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Case Report

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Improved Hypertension by Investigating Circadian Rhythm of Blood Pressure

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Abstract

Case: The case is 86-year-old male hypertensive patient with anti-hypertensive drug for 5 years. He has been provided Amlodipine besilate 5mg at 0800h and doxazosin mesylate 2mg at 2300h for long. In June 2020, he noticed unstable fluctuation of Blood Pressure (BP) during morning, afternoon and night. **Results:** Then, he checked the circadian rhythm of BP, which showed higher BP in early morning, decreasing BP 0800-1000h, minimum BP during 1000-1400h, increasing BP during 1400-1800h and stable BP during 1800-2400h. Due to the result, he changed to take amlodipine at 2300h. Consequently, his BP gradually became stable during 24 hours after 2 weeks. **Discussion:** Some factors may exist for contributing improved BP fluctuation. They include a) pathophysiological characteristics of BP circadian rhythm, b) effective time for anti-hypertensive drug, c) accuracy of the obtained BP data and d) the social and psychological reliability of the patient. Regarding d) he was engaged in research and development work as a senior researcher at a chemical company. He has been also a member of New Elderly Association (NEA), which was established by Shigeaki Hinohara. He lives on the philosophy of Hinohara-ism for long, associated with stable mind and body.

Keywords: Hypertension, Circadian Rhythm of Blood Pressure, Antihypertensive drug, Amlodipine besilate, Hinohara-ism.

Abbreviation: BP-Blood Pressure, ISH-International Society of Hypertension, ESC/ESH-European Society of Cardiology/European Society of Hypertension, NEA-New Elderly Association, T2DM-Type 2 Diabetes Mellitus, CHD-Coronary Heart Disease, CKD-Chronic Kidney Disease.

Introduction

Concerning the standard guideline of hypertension, there was practice guidelines for the management of hypertension for adults by the International Society of Hypertension (ISH) in 2020. The 2020 ISH guidelines have been closer to the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines, and they include hypertension prevalence, treatment, and cardio metabolic goals. Historically speaking, hypertension has been one of the most important common diseases, and many hypertensive patients should be dealt with properly in the world. Therefore, several guidelines have been announced in European countries, North America and Japan related with hypertension and heart disease. Furthermore, several guidelines were for older and younger people, patients with obesity and lipids problems. Consequently, treatment of hypertension will require comprehensive and integrative use of each guideline for managements [1-7].

As to physiological parameters such as BP and heart rate, autonomic nervous system has influenced variability signals for cardiovascular system. It has been known that hypertension is a crucial risk factor for cardiovascular disease mortality and its therapeutic management with decreasing cardiovascular complications. Subjects (n=628) with normal and hypertensive patients were analyzed for circadian rhythms of BP. As a result, two groups showed similar tendency [8-10].

Their Systolic BP (SBP), Diastolic BP (DBP) and mean BP decrease during 0930-1500, increase during 1500-1930, have rather deeper reduction during 1930-0200 at night time and morning increase during 0530-0930. From the guideline for ABPM by ESH (European society of Hypertension) position Paper, hypertensive patients with nocturnal rise show poor tendency for cardiovascular prognosis. Similarly, rising pattern at night have higher risk of cardiovascular events. Furthermore, recent review showed that nocturnal rising suggests powerful marker for cardiovascular poor prognosis associated with adjusting for other risk factors [10-13].

Thus, it would be important to examine and deal with the circadian rhythm of blood pressure for the treatment and management of hypertension. Through our medical practice experiences, there was an impressive elderly male patient with hypertension. He showed initially unstable circadian rhythm of BP, but afterwards stable and lower BP after changed time of medication. In this article, general clinical course will be presented associated with some discussion.

Case Report

History of Present Illness

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The case is 86-year-old male patient with hypertension, Type 2 Diabetes Mellitus (T2DM), Coronary Heart Disease (CHD) and hyperuricemia. His general status has been almost stable for more than 5 years. In May 2020, he received general physical examination and laboratory biochemical examination. He has not shown particular complaints such as diabetic symptoms, dyspnea or nocturnal breathing. He has not smoked or drinks alcohol for years.

Social history

He worked as a chemical engineer for long years. His company was Toho Rayon Company and Shikoku Kasei Chemical Corporation. He has made various achievements such as obtaining 20 patents in his daily work. He has been working as a chemical engineer, and did not have any special environmental exposure with some possible toxic agents. He has been also a member of New Elderly Association (NEA), which was established by Shigeaki Hinohara, a supreme physician with active achievements until the age of 105. He has understood and practiced Hinohara-ism every day, enjoying ballroom dancing, karaoke and ground golf, associated with stable mind and body. Such a social and psychological background exists in his regular life [14].

Physical examination

He showed no remarkable condition in physical examination and also no remarkable specific abnormalities on symptoms or signs related to hypertension, diabetes and other diseased states. His vital signs were within normal limits and he showed unremarkable physical symptoms concerning hypertension, diabetes, CHD and hyperuricemia. He showed no particular diabetic complications such as retinopathy, neuropathy or nephropathy. His Body Mass Index (BMI) was 20.4 kg/m². He has shown no particular symptoms or signs about Chronic Kidney Disease (CKD).

Laboratory Exam

The results of laboratory exams were revealed in the following. General standard biochemical data were AST 28 U/mL (5-40), ALT 19 U/mL (5-42), r-GT 12 U/mL (7-74), BUN 28 mg/dL (8-20), Cre 1.1 mg/dL (0.5-1.0), Uric Acid 6.6 mg/dL (3.8-7.0), HDL 60 mg/dL (40-99), LDL 110 mg/dL (70-139), TG 56 mg/dL (30-149), WBC 6900 / μ L (4000-8000), RBC 3.82 x 10⁶/ μ L (4.2-5.4), Hb 11.3 g/dL (12.4-17.6), Plt 13.9 x 10⁴/ μ L (14-34). Data related diabetes were HbA1c 6.2%, post-prandial glucose (2 hours) 180 mg/dL.

Medication

He has been given some kinds of medicine for hypertension, T2DM, coronary heart disease and hyperuricemia. The prescription includes 1) Amlodipine besilate 5mg, 2) doxazosin mesylate 2 mg, 3) Bisoprolol tape 4 mg (β 1 blockade, C07AB07-ATC, D02342-Kegg), 4) Sitagliptin phosphate hydrate 50mg, 5) Febusostat 20mg. Until May 2020, these medicines (1,4,5) were provided at 0800h after breakfast, and medicine (2,3) was provided 2300h before sleep.

Clinical progress

In June 2020, he has noticed unstable fluctuation of Blood Pressure (BP) during morning, afternoon and night. Then, he has tried to check his circadian rhythm of BP during June 1-5. After that, he measured the detail fluctuation of BP during June 16-21 and July 3-7, 2020.

Results

The result of 24-hours measurement of BP during June 1-6 was shown in **Figure 1a**. There was a tendency of large difference of daily BP, associated with higher BP (150-170 mmHg) in early morning, decreasing BP (130-150 mmHg) during 0800-1000h, minimum BP (110-130 mmHg) during 1000-1400h, increasing BP tendency (120-140 mmHg) during 1400-1800h and rather stable BP (120-130 mmHg) during 1800-2400h. Due to the result of BP, he was advised to take amlodipine besilate at 2300h instead of 0800h. This changed method was started from June 16. The BP profile during June 16-21 was shown

in **Figure 1b**. There was some changed tendency, associated with around 140 mmHg during 0400-0800h, 130-140mmHg during 0800-1400h, 120-130 mmHg during 1400-1800h and a little wider distribution during 1800-2400h. After 2 weeks, he showed stable measurements of BP profile during 24 hours (**Figure 1c**). They revealed about 120-130 mmHg during 0100-1000h, 110-120 mmHg during 1000-1600h, 120-130 mmHg during 1600-2300h. The data seemed to be ideal status, associated stable and flat level.

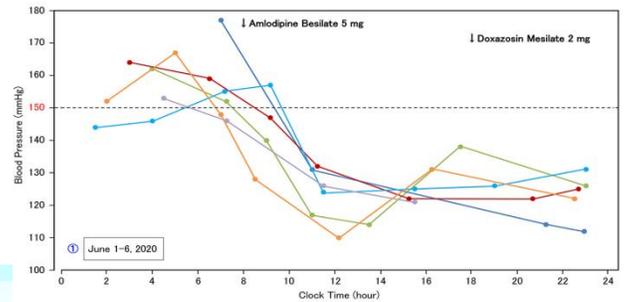


Figure 1a: BP profile during June 1-4 with large BP fluctuation.

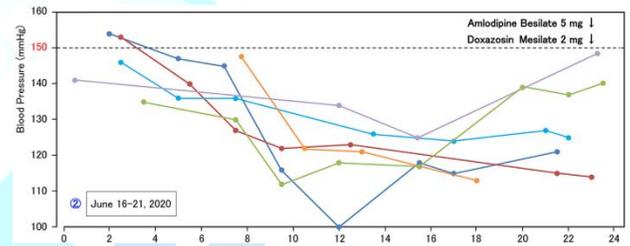


Figure 1b: Rather fluctuation after changed timing of amlodipine from 0800h to 2300h.

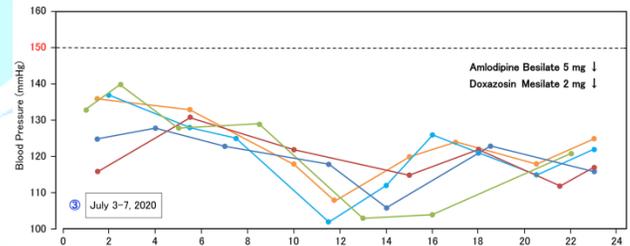


Figure 1c: Stable BP with smaller BP difference.
Figure 1: Results of circadian rhythm of blood pressure with changed timing of antihypertensive drug.

Discussion

In this report, hypertensive patient with large BP difference has improved by measuring the diurnal BP fluctuations and changing the time of taking antihypertensive drugs. Several factors seem to be involved in this situation. They are the physiological and pathological characteristics of BP circadian rhythm, the length of effective time for anti-hypertensive drug, accuracy of the obtained BP data and the social and psychological reliability from the background of the patient. Some discussions are described in the following. There are three patterns for BP profiles during night time. They are dippers, non-dippers and risers or reverse dippers. These three groups were also found in several studies using home BP, ABPM and in hospitalized older patients. Elderly patients show riser pattern and reverse dipping patterns in common. According to the lots of data (1.7 million) of BP in England, the results of systolic and diastolic BP were shown as the same as the from outpatient populations by Ambulatory BP Monitoring (ABPM). For late middle age in-patients, nocturnal dipping BP changes were not clear. Instead of that, they showed rather late nocturnal BP rise, associated with



higher nighttime systolic BP than the peak systolic daytime BP. This tendency was observed for the patients with and without hypertension. This circadian tendency for in-patients were not been observed so far. However, these patterns seem to be compatible with the results of ABPM in the community studies. By a systematic review, dipping at night was evaluated as a lower risk of cardiovascular events, whereas rising BP during night time seems to be associated with elevated risk [12,15-21].

Recent investigations have revealed that non-dipper patients tend to show more damage of target organs and their related complications. In the case of normal physiological states, there are several functional characteristics such as increased heart rate, blood pressure and vasospastic tone, excessive platelet aggregation and activity. Some proteins with regulatory missions or activator for platelet activity including SCUBE1 (containing the protein-1 domain containing the signal peptide-cub-egf domain) and soluble CD40 Ligand (sCD40L). Both were reported to be significantly higher in the non-dipper patients than normal subjects. After the current case changed the time to taking the antihypertensive drug, the circadian rhythm of BP was improved to stable situation. This change seemed to be involved in amlodipine administration. There was a report of pharmacokinetics and comparative bioavailability of amlodipine [22-25].

The protocol was administration of amlodipine 2.5, 5 and 10mg to 12 healthy male volunteers. The results were summarized as follows: a) diastolic BP was decreased by 1.1, 4.8 and 8 mmHg six hours in 3 doses, b) the time until the peak level was 5.6-6.4 hours, respectively, c) each half-life was 31.2, 33 and 36.8 hours, respectively. The author suggested that amlodipine would be effective once daily because of its gradual absorption and long half-life.

Considering both of the pharmacokinetics of amlodipine and actual progress of current case (Figure 1a,b,c) together, the peak time seems to be related to unstable fluctuation of BP. In our usual medical practice, many patients with hypertension have often taken anti-hypertensive drug once in the morning. In some cases, measuring diurnal BP fluctuation may contribute the screening for detecting unstable BP. Hypertension is one of life style-related disease. Concerning the standard management for hypertension, there was High Blood Pressure Clinical Practice Guideline by American College of Cardiology/American Heart Association Task Force. It includes six items of I-A level for recommendations for non-pharmacological interventions. They include weight control, healthy diet including DASH (Dietary Approaches to Stop Hypertension) diet, sodium reduction, supplementation of potassium, encouraging physical activity and decrease of alcohol consumption. Various factors are involved in the fluctuation of blood pressure. In this case, there is no smoking or no risk factors for dyslipidemia. Then, it would be necessary to consider the possibility of influence, such as hypertension, cardiovascular disease, smoking and sleep-respiratory disease. In particular, no obvious abnormal findings were found in this case. The patient has been originally a scientist, and his lifestyle has persisted regular and ideal situation. In addition, he has been enlightening by Hinohara-ism, and recently living along with the philosophy [4,14,26-32]. In this way, it is considered that BP has been evaluated and controlled this time due to the excellent social and psychological conditions.

In summary, an 86-year-old patient with hypertension showed unstable BP fluctuations. After measuring daily BP profile and changing taking time for anti-hypertensive drug, BP became stabilized. This course was discussed from some aspects including BP circadian rhythm, antihypertensive drugs, obtained data and the background of the patient. This report will be hopefully useful for future research and treatment of hypertension.

Ethical Considerations

This research has been conducted in compliance with the ethical principles presented on the Declaration of Helsinki. Moreover, there was

comment for the Ethical Guidelines against the Research in the medical field for Human beings and also against the conduction of the Good Clinical Practice (GCP). We have applied adequately "Ethical Guidelines for Epidemiology Research" for the related guideline. These principles were originated from Japan by the Ministry of Health, Labor and Welfare and also by the Ministry of Education, Culture, Sports, Science and Technology. For the current subject, the written informed consents from the patient.

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