Improvement of Blood Pressure Control by Adherence Check in Patients With Apparent Treatment-Resistant Hypertension: A Case Series

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ABSTRACT: Adherence to medications is an important challenge while treating chronic disease such as resistant hypertension, which is defined as uncontrolled blood pressure (BP) despite treatment with more than 3 antihypertensive drugs to achieve targets. It is possible that poor adherence is the most significant contributor to rates of pseudo-resistance among treated hypertensive patients. In this report, we describe 4 patients with apparent treatment-resistant hypertension, who received intervention to promote adherence by pharmacists who set the prescribed medicines in a weekly medication calendar and conducted a weekly pill count. The results showed that the intervention of pharmacists to medication adherence improved systolic BP in patients with apparent treatment-resistant hypertension; however, further controlled trials are required to strengthen supporting evidence.

KEYWORDS: adherence to medication, hypertension, pharmacist

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Introduction

Globally, it is well known that hypertension is one of the most common risk factors for cardiovascular disease, stroke, and death.[1] A large number of patients with hypertension fail to achieve their recommended blood pressure (BP) despite treatment with more than 3 antihypertensive drugs,[2,3] which is called resistant hypertension.[4] Resistant hypertension has prognostic significance because it has been associated with a high risk of cardiovascular events as well as all-cause morbidity and mortality.[5,6] Among resistant hypertensive patients, poor adherence is very common.[7] Durand et al[8] found that 1 in 3 cases of resistant hypertension is due to poor adherence. In addition, Hayes et al[9] reported that the prevalence of true resistant hypertension was only 3% when the white coat phenomenon, dosing, and adherence were taken into account.

According to the World Health Organization (WHO) definition, the term "adherence" is the extent to which a person's behavior of taking medications or following a diet and/or lifestyle changes in response to recommendations from a health care provider.[10] In routine clinical practice, medication adherence plays a major role in the management of resistant hypertension. In many cases, medication adherence is left to patients themselves until the next visit. We conducted a prospective pilot study to improve adherence via weekly checking by pharmacists in patients who were diagnosed with resistant hypertension.

Methods

Prior to patient enrollment, this study was approved by the Osaka University of Pharmaceutical Sciences Ethics Committee Review Board (No. 0033). Consecutive adult hypertensive patients whose BP was poorly controlled, systolic BP ⩾140 and/or diastolic BP ⩾90 mm Hg, even though at least 3 antihypertensive agents had been taken for more than 1 month, were eligible to be enrolled in this study. Patients were excluded if there was a history of cardiovascular events (myocardial infarction, stroke, or heart failure) within 6 months, undergoing treatment with dialysis, or they were unable to provide informed consent. Four patients were recruited in a clinic (Doi Clinic, Kyoto, Japan) between April 2017 and March 2018. All patients provided written informed consent to participate. A statement was also obtained confirming that consent had been secured from all patients to publish the findings of this study.

As for BP measurements, the values were measured twice consecutively in a sitting position after a rest of at least 2 min at each visit. Physicians or nurses used the auscultation method with a mercury or aneroid sphygmomanometer, or the cuff-oscillometric method with electronic arm-cuff devices that had been validated and approved by the Ministry of Health, Labour, and Welfare, Japan.

As for the determination of adherence to treatment, pharmacists set the prescribed medicines into a weekly medication calendar with 21 compartments for the timing of doses (3 times/d for 7 days), allowing patients to easily pick up multiple tablets from each compartment and visualize whether they had taken medicines. After taking the medicines, patients returned their emptied press-through-packaging (PTP) sheets into the same compartment of the calendar. If patients did not take medicines, the medicines were left in the compartments. If

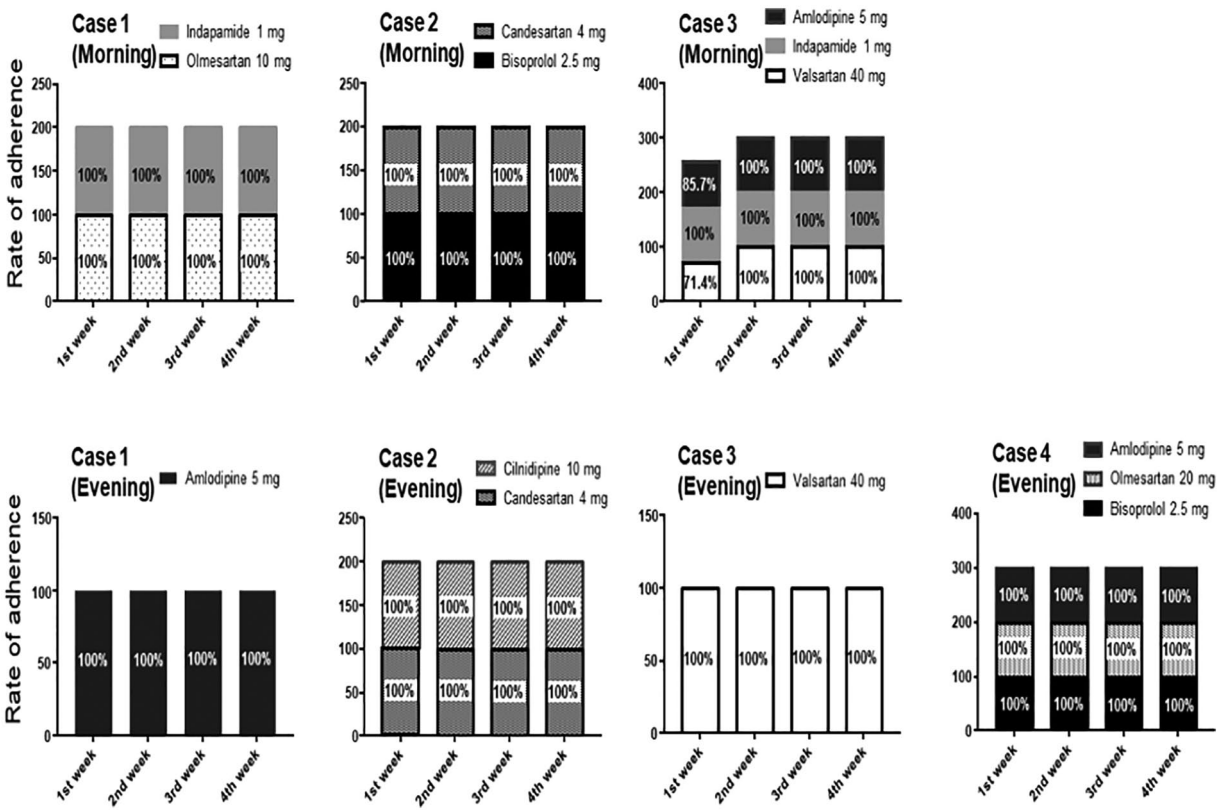

Figure 1. Rate of adherence to treatment in adult hypertensive patients. Pharmacists set prescribed medicines in a weekly medication calendar and conducted a weekly pill count.

patients took medicines appropriately, emptied PTP sheets were contained in the compartments. After 1 week, patients revisited the clinic with this calendar and received another calendar for the next week. In cases where patients forgot to revisit the clinic, pharmacists visited the patients. Pharmacists performed pill counts and estimated the adherence rate for individual patients.

During consultation with pharmacists, they told participants that nonadherence to medications was based on low-level awareness of hypertensive complications, and efforts for behavioral modification are important, especially for those with a longer duration of hypertension even if they had no obvious symptoms. This intervention was standardized across all 4 cases.

Results

Case 1

The first case was a 78-year-old man with a diagnosis of hypertension made 14 years ago, with no previous cardiovascular disease nor history of smoking or drinking. This participant was prescribed indapamide 1 mg once a day, olmesartan 10 mg once daily, and combination tablet of amlodipine 5 mg and atorvastatin 10 mg once daily. Pharmacists set the prescribed medicines in the weekly medication calendar for 4 weeks and instructed him to put emptied PTP into the relevant compartment after taking the medicine. After 1 week, this participant brought the calendar to the clinic, and pharmacists counted the emptied PTP and interviewed him about adherence. During the intervention, he took all prescribed medicines (Figure 1) and showed decreases in systolic and diastolic BPs (Table 1).

Case 2

The second case was a 68-year-old man diagnosed with hypertension 9 years ago with no previous cardiovascular disease, who had no history of smoking or drinking. This participant was prescribed bisoprolol 2.5 mg once a day, candesartan 4 mg bid, and cilnidipine 10 mg once daily. Similar to the previous case, pharmacists conducted adherence intervention. This participant visited the clinic with the calendar every week. This participant took all the prescribed medicine (Figure 1). As shown in Table 1, the post BP level was markedly decreased.

Case 3

The third case was an 80-year-old man diagnosed with hypertension 14 years ago, who had no previous cardiovascular disease or history of smoking, but had a drinking habit (2 drinks/d of liquor for everyday). This participant was prescribed valsartan 40 mg bid, indapamide 1 mg once daily, and amlodipine 5 mg once daily. The participant did not take amlodipine on day 2 or valsartan in the morning of days 6 and 7. After the pharmacist conducted the interview, the participant took all prescribed medicines in the second week (Figure 1). There was a slight decrease in the systolic and diastolic BPs (Table 1);

Table 1. Patient characteristics and blood pressure before and after the intervention of adherence check by pharmacists.

CASE NUMBER	SEX	AGE, Y	DURATION OF HYPERTENSION, Y	CLINIC SYSTOLIC BLOOD PRESSURE, mm Hg			CLINIC DIASTOLIC BLOOD PRESSURE, mm Hg		
				PRE	POST	CHANGE	PRE	POST	CHANGE
Case 1	M	78	14	145	118	–27	76	60	–16
Case 2	M	68	9	181	151	–30	104	100	–4.0
Case 3	M	80	14	168	160	–8	85	87	+2
Case 4	F	77	13	145	129	–16	83	78	–5

however, after 1 month of the intervention, he was admitted due to cerebral infarction.

Case 4

The fourth case was a 77-year-old woman diagnosed with hypertension 13 years ago, who had no experience of previous cardiovascular disease and no history of smoking or drinking. This participant was prescribed bisoprolol 2.5 mg once daily, olmesartan 20 mg once daily, and amlodipine 5 mg once daily. It was difficult for this participant to visit pharmacists weekly to check adherence, so pharmacists visited her home and conducted the pill-check. The participant stated that the adherence check helped her to take medicine, and her adherence was good for 4 weeks (Figure 1). After 4 weeks, there was a reduction in the systolic and diastolic BPs, as shown in Table 1. This suggests that the adherence check by pharmacists leads to medical improvement.

Discussion

This study demonstrated that improved adherence resulted in a reduction of BP, and 2 in 4 patients were below the 140/90 mm Hg cut-off for hypertension after weekly intervention to promote adherence by medical staff, that is, they were not true cases of resistant hypertension in the first place, but were pseudo-resistant due to poor adherence. These findings are consistent with a cross-sectional study[9] showing a lower prevalence of true resistant hypertension. We found that good adherence leads to decrease in BP, and uncontrolled BP was due to poor adherence.

Nonadherence is common among patients with resistant hypertension. A retrospective study revealed that a quarter of patients were nonadherent to treatment with antihypertensive drugs.[11] In addition, meta-analysis of antihypertensive adherence in patients in general[12] and in resistant hypertension[8] showed that treatment adherence was poor. One study reported that the high level of nonadherence was partly due to the long duration of disease.[13] Indeed, in our study, the median duration of hypertension was approximately 13 years.

Our results revealed that the rate of adherence while undergoing intervention was high (99.3%) and a marked decrease in BP was observed. In Japan, antihypertensive drugs are prescribed every 4 weeks in many cases, and general advice is given by doctors at the time of prescription, but few patients and their families revisit while taking medications. Therefore, it is important that medical staff check and promote medication adherence regularly. If a regular check of adherence is conducted regardless of the method, it is possible that patients might make a more conscious effort to take medicine.

Several methods to evaluate adherence have been reported: direct and indirect methods. Among direct methods, there is an analysis of drug concentrations in urine or serum. The determination of antihypertensive drugs concentrations is a precise method for assessment of nonadherence in patients with resistant hypertension by means of liquid chromatography-mass spectrometry (LC-MS). Recently, Hayes et al[14] reported that it is possible to examine nonadherence to medications using a LC-MS technique. As for indirect methods, prescription refill records and pill-counting of returned untaken medications, and automatic electronic time-stamping of package opening are well known.[13,15] In this study, pharmacists set prescribed medicines into the weekly medication calendar and pill-counted weekly, and we noted a marked decrease in systolic BP. Of course, setting medicines by pharmacists and checking refills is a burden on health care staffs. However, our study suggests that it is important to not only hand prescribed medicines to patients but also promote their adherence.

The results of this study suggest that apparent treatment-resistant hypertension in community health care is partly due to poor adherence, and weekly adherence checks by health care staffs is helpful for achieving BP control. Patient awareness may influence the outcome of self-management. Further studies are needed to investigate whether our findings are replicable in large clinical studies.

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Author Contributions

Study design: KH, TD, and HM. Data collection: KH, AI, SO, TD, IN, TW, MU, KI, and HM. Data analysis: KH, AI, SO, TD, and HM. Drafting manuscript: KH, AI, SO, and HM.

Revising manuscript content: KH, AI, SO, TD, IN, TW, MU, KI, and HM. Approving final version of manuscript: KH, AI, SO, TD, IN, TW, MU, KI, and HM.

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REFERENCES

1. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA*. 1996;275:1571-1576.
2. Daugherty SL, Powers JD, Magid DJ, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation*. 2012;125:1635-1642.
3. Hayek SS, Abdou MH, Demoss BD, et al. Prevalence of resistant hypertension and eligibility for catheter-based renal denervation in hypertensive outpatients. *Am J Hypertens*. 2013;26:1452-1458.
4. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72:e53-e90.
5. De La Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension*. 2011;57:898-902.
6. Muntner P, Davis BR, Cushman WC, et al. Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2014;64:1012-1021.
7. Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. *J Hum Hypertens*. 2016;30:83-89.
8. Durand H, Hayes P, Morrissey EC, et al. Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. *J Hypertens*. 2017;35:2346-2357.
9. Hayes P, Casey M, Glynn LG, et al. Prevalence of treatment-resistant hypertension after considering pseudo-resistance and morbidity: a cross-sectional study in Irish primary care. *Br J Gen Pract*. 2018;68:e394-e400.
10. Osterberg L, Blaschke T. Adherence to medication. *N Eng J Med*. 2005;353:487-497.
11. Tomaszewski M, White C, Patel P, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. *Heart*. 2014;100:855-861.
12. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med*. 2012;125:882-887.
13. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. *Hypertension*. 2013;62:218-225.
14. Hayes P, Casey M, Glynn LG, et al. Measuring adherence to therapy in apparent treatment-resistant hypertension: a feasibility study in Irish primary care. *Br J Gen Pract*. 2019;69:e621-e628.
15. Burnier M, Schneider MP, Chiolero A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *J Hypertens*. 2001;19:335-341.