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Relationship between drug dosage and antihypertensive effect in clinical trials.

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It is important to determine the dose adjustment of alternative drugs that patients have taken before hospitalization, therefore the aim of this study was to derive regression equations between drug dosage and pharmacological effect based on clinical trial data in angiotensin II receptor antagonists (ARB). We investigated the characteristics of 3 ARB: candesartan (CND), valsartan (VAL), and azilsartan (AZL). Using data on the daily dose of ARB and the mean blood pressure (BP) before and after ARB administration, we applied Emax model and derived a regression equation between the daily dose and the predicted BP in each ARB. For CND, VAL and AZL, regression equations between drug dosage and predicted BP reduction were derived in systolic BP and diastolic BP. Predicted BP reduction was nearly equivalent between CND 2 mg/day and VAL 20 mg/day, between CND 4 mg/day and VAL 40 mg/day, between CND 4 mg/day and VAL 80 mg/day, between CND 8 mg/day and VAL 160 mg/day, and between CND 12 mg/day and AZL 10 mg/day. These regression equations enable comparison of how BP reduction occurs with these drugs; it is useful for choosing alternative drugs and their appropriate dosage when switching from the drugs the patients have been taken before hospitalization.

Key Words: Medication reconciliation, Alternative drug, Angiotensin II receptor antagonist, Regression equation, Emax model

Introduction

Medication reconciliation by a pharmacist makes it possible to confirm and assess more precisely not only the drug name that patients have taken before hospitalization but also content specification, directions for use and dosage[1,2]. This is an important role for the hospital pharmacist, in addition to dispensation and patient compliance instruction. Moreover, when the drug that the patient was taking before hospitalization is not adopted in the hospital, pharmacists are expected to propose an alternative drug and appropriate dosage as part of the proposal for administration planning. This proposal contributes to the continuation of drug therapy[3].

When the drugs that patients have taken before hospitalization need to be switched to alternative drugs, physicians often prescribe alternative drugs proposed by pharmacists without modification[4]. In some case reports, the patient's values of blood pressure and pulse were varied after the antihypertensive drug was switched from the one the patient had taken before hospitalization to an alternative drug[4]. Therefore, it is critical that pharmacists choose alternative drugs that have clinical effects equivalent to the drugs that the patient was taking before hospitalization in order to maintain the proper drug therapy.

Angiotensin II receptor antagonists (ARBs) are first-line drugs for antihypertensive therapy in the guidelines for the management of hypertension published by the Japanese society of hypertension in 2014 (JSH 2014)[5]. To date, seven ARBs are clinically

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available in Japan. Antihypertensive drugs are compared among the categories, such as ARBs and Ca blockers, in JSH 2014. Comparison of the antihypertensive effects among ARBs have not been described in detail. However, the pharmacological effects, with the exception of antihypertensive effects, have been described, such as the uricosuric action of losartan (LOS)[6] and, the insulin-sensitizing and lipid metabolism-improving effect via the activating action of peroxisome proliferator-activated receptor (PPARγ) of telmisartan (TLM) and irbesartan (IRB)[7]. Little information is available in JSH2014 on the antihypertensive effects to base a decision of an alternative antihypertensive drug with an equivalent clinical effect to that of the drug the patient had taken before hospitalization.

Some reports are available that compare antihypertensive effects among ARBs. LOS 50 mg/day was reported to be equivalent to valsartan (VAL) 80 mg/day[8]. However, it is reported that there are differences in the antihypertensive effects among ARBs at approved moderate doses or high doses in Japan[9-16]. Therefore, the dose of an alternative hypertensive drug should be adjusted based on the power of the antihypertensive effect. Since these reports were mainly carried out in foreign countries, there are few reports which compare the clinical effects of ARBs at low dose, such as LOS 25 mg/day, candesartan (CND) 4 mg/day and VAL 40 mg/day; these are the doses which are approved in Japan.

In combination tablets of CND and hydrochlorothiazide (HCTZ), CND and amlodipine (AML) and TLM and HCTZ, the polynomial expressions of response surface model have been described as a clinical response model for predicting the antihypertensive effect in their summary technical documentation (STED). However, it is not possible to use these model formulae to predict the antihypertensive effects of ARBs expect for CND and TLM, since these model formulae were described only in CND and TLM.

Currently, there is no criteria for the selection and dose adjustment of alternative ARBs based on the comparison of antihypertensive effects among ARBs. The aim of this study was to derive regression equations between drug dosage and antihypertensive effect based on clinical trials data of ARBs.

Methods

We investigated the characteristics of 3 ARB: CND, VAL, and azilsartan (AZL), that we could derive regression equation between the daily dose and antihypertensive effect using literature of clinical trials from the references of the interview forms and STEDs. Clinical trials of ARB monotherapy on mild to moderate essential hypertension Japanese patients were included. Selection criteria of study design were a fixed-dose study and a forced titration study with a fixed dose for more than 4 weeks. We gathered literature of clinical trials from the references of the interview forms of ARBs and on combination drugs composed of ARB and other antihypertensive drug. In the case of these combination drugs, since the clinical trials were carried out in ARB monotherapy group and combination therapy group, we used data of ARB monotherapy group. For literature not listed as references in interview forms, we collected STEDs from the website of pharmaceuticals and medical devices agency in Japan[17]. We excluded the clinical trials in which participants were non-responders of previous antihypertensive therapy, or had renal or hepatic impairment.

In an international conference on the harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) harmonized tripartite guideline: dose-response information to support drug registration (ICH-E4)[18], it was indicated that titration studies cannot distinguish the response to an increased dose from the response to increased time on drug therapy or a cumulative drug dosage effect. It was also indicated in ICH-E4, however, if most patients completed all doses, and if the study was controlled with a parallel placebo-group, the forced titration study allowed a series of comparisons of an entire randomized group given several doses of drug with a concurrent placebo, just as the parallel fixed dose trial did. Since it is rare for hypertension to be improved spontaneously, prolonged administration of antihypertensive drug could not increase the antihypertensive effect after steady state. Therefore, if there is a sufficient fixed-dose period in which the antihypertensive effect of ARB reaches the steady state, the antihypertensive effect could be estimated by a forced titration study. The antihypertensive effect of ARB nearly reached the steady state in 4

weeks[15,19]. Therefore, both fixed-dose studies and forced titration studies (fixed dose for more than 4 weeks) are included in this research.

Data was extracted on the subject drug, information sources, daily dose of the drug, the number of participants, mean blood pressure (BP) before ARB administration (PreBP), and mean observed BP reduction after 8 weeks of ARB administration (ΔBPo). The observed BP reduction after 8 weeks of ARB administration was used for assessment of BP reduction because the antihypertensive effect was mainly evaluated after 8 weeks of medication.

For each drug, we applied an Emax model[20], following equation 1, and derived a regression equation between the daily dose and the predicted BP reduction (ΔBPp) for systolic BP (SBP) and diastolic BP (DBP), based on daily dose and ΔBPo of each clinical trial. When ΔBPo was not clearly described, ΔBPo was calculated by PreBP minus BP at 8 weeks after of ARB administration. Since the Emax model has two coefficients (Emax and ED50), three or more points of data of daily dose and ΔBPo are required to derive a regression equation. The drugs with less than three points of data of daily dose and ΔBPo were excluded. We calculated prediction error (PE) and absolute prediction error (APE) to validate predictability of a regression equation, following equations 2 and 3. Furthermore, we calculated ΔBPp at the approved dose for each ARB in Japan based on the following regression equations:

$$\Delta BPp = D \times Emax / (D + ED50) \quad \cdots \text{ Equation 1}$$

$$PE = \Delta BPp - \Delta BPo \quad \cdots\cdots\cdots\cdots\cdots \text{ Equation 2}$$

$$APE = |\Delta BPp - \Delta BPo| \quad \cdots\cdots\cdots\cdots \text{ Equation 3}$$

ΔBPp: Predicted BP reduction (mmHg), ΔBPo: Observed BP reduction (mmHg), D: Daily dose (mg), Emax: Maximum drug effect (mmHg), ED50: Median effective daily dose (mg/day).

Statistical analyses were performed by R version 3.0.2[21] and EZR[22]. We derived the Emax model regression equation between the daily dose and ΔBPp by using nonlinear least squares regression.

Results

For CND, VAL and AZL, table 1 summarizes the name of the drug, information sources, trial name, daily dose, number of participants, SBP and DBP of PreBP, and SBP and DBP of ΔBPo. The literature from which data were extracted were all in-house documents of the pharmaceutical companies or STED. Four trials are available on CND, 5 on VAL and 3 on AZL. Mean SBP of PreBP was 148.5 to 159.6 mmHg in CND, 150.5 to 162.7 mmHg in VAL and 158.5 to 160.2 mmHg in AZL. Mean DBP of PreBP was 99.6 to 101.0 mmHg in CND, 99.3 to 102.5 mmHg in VAL and 100.2 to 101.5 mmHg in AZL. Mean of ΔBPo in CND 4mg/day was 8.1 mmHg in DBP, and no data was obtained in SBP. Mean of ΔBPo in CND 8mg/day was 14.8 to 17.3 mmHg in SBP and 7.7 to 12.2 mmHg in DBP, and that in CND 12 mg/day was 17.5 to 19.9 mmHg in SBP and 9.8 to 12.1 mmHg in DBP. Mean of ΔBPo by VAL was 7.6 to 13.9 mmHg for SBP and 6.5 to 9.3 mmHg for DBP in 40 mg/day, and 9.4 to 17.1 mmHg for SBP and 6.0 to 9.7 mmHg for DBP in 80 mg/day. Mean of ΔBPo by AZL was 18.0 mmHg for SBP and 12.4 mmHg for DBP in 5 mg/day, 18.1 mmHg for SBP and 10.7 mmHg for DBP in 10 mg/day, 19.9 to 21.5 mmHg for SBP and 11.0 to 13.9 mmHg for DBP in 20 mg/day, 21.8 to 22.5 mmHg for SBP and 12.4 to 13.7 mmHg for DBP in 40 mg/day, and 22.5 mmHg for SBP and 13.9 mmHg for DBP in 80 mg/day. The number of points of data of daily dose and ΔBPo to derive the regression equation were 4 (daily dose range: 8 mg/day to 12 mg/day) for SBP and 6 (daily dose range: 4 mg/day to 12 mg/day) for DBP in CND. These data for VAL were 9 (daily dose range: 40 mg/day to 80 mg/day) for SBP and 9 (daily dose range: 40 mg/day to 80 mg/day) for DBP; the data for AZL were 8 (daily dose range: 5 mg/day to 80 mg/day) for SBP and 8 (daily dose range: 5 mg/day to 80 mg/day) for DBP.

The values of Emax and ED50 of regression equation between daily dose and ΔBPp in CND, VAL and AZL are shown in Table 2. The largest Emax in SBP, 27.920 mmHg was obtained for CND, followed by AZL of 22.681 mmHg and VAL of 16.625 mmHg. In DBP, Emax for CND and AZL were almost the same, 13.186 mmHg and 13.142 mmHg, respectively. Emax for VAL was the smallest among the 3 drugs, 8.105 mmHg.

Table 1. Characteristics of clinical trials of angiotensin II antagonist monotherapy in mild to moderate Japanese essential hypertension patients.

	The name of drug	Information sources	The trial name	Daily dose (mg)	Blood pressure (mmHg) (Mean±SD) PreBP N	SBP	DBP	ΔBPo N	SBP	DBP
CND	CND	IHD	TAK-536/CCT-001	12	82	159.6 ± 7.7	101.0 ± 4.4	73	19.9 ± 13.8	12.1 ± 8.9
	CND	IHD	TAK-536/CCT-005	8	309	159.6 ± 7.3	100.4 ± 4.1	309	17.3 ± 11.8	9.0 ± 7.4
				12	309	159.6 ± 7.3	100.4 ± 4.1	309	17.5 ± 12.7	9.8 ± 8.5
	CND/HCTZ	STED	CCT-001	4	69	155.8 ± 14.7	99.6 ± 3.8	69	ND	8.1 ± 8.1
				8	68	153.7 ± 11.8	100.1 ± 4.3	68	ND	7.7 ± 7.7
	CND/HCTZ	STED	CCT-002	8	148	148.5 ± 12.3	99.7 ± 3.9	148	14.8 (12.8-16.8) *1	12.2 (10.9-13.5) *1
VAL	VAL/HCTZ	STED	1301	40	102	155.7 ± 13.6	101.1 ± 4.9	101	7.6 ± 11.7 *2	6.5 ± 7.9 *2
				80	101	155.0 ± 14.4	100.9 ± 4.9	101	9.4 ± 11.7 *2	6.0 ± 7.9 *2
		STED	1303	40	65	150.5 ± 10.5	99.4 ± 4.4	65	12.4 ± 11.6 *2	9.3 ± 6.5 *2
				80	68	150.9 ± 12.2	99.4 ± 3.8	68	13.0 ± 11.6 *2	9.1 ± 7.1 *2
	VAL/AML	STED	1301	40	169	151.3 ± 10.6	99.3 ± 4.4	169	9.2 ± 10.7 *2	8.4 ± 7.9 *2
				80	163	152.9 ± 11.7	99.5 ± 4.2	163	10.0 ± 12.4 *2	8.7 ± 8.3 *2
	VAL/CLN	STED	AJH801/ET1	40	34	161.5 ± 11.5	101.1 ± 5.4	34	13.9 ± 11.9	7.3 ± 6.4
				80	35	162.7 ± 10.4	102.5 ± 6.1	35	16.0 ± 8.9	6.4 ± 7.4
	VAL/CLN	STED	AJH801/CT1	80	187	160.3 ± 9.0	100.1 ± 4.8	187	17.1 ± 11.5 *2	9.7 ± 7.9 *2
AZL	AZL	IHD	TAK-536/CCT-001	5	89	159.6 ± 7.0	101.1 ± 4.2	85	18.0 ± 11.6	12.4 ± 8.9
				10	83	158.5 ± 7.0	100.2 ± 4.1	74	18.1 ± 14.7	10.7 ± 8.0
				20	85	159.2 ± 6.7	101.5 ± 4.7	81	21.0 ± 12.0	12.6 ± 8.7
				40	82	159.2 ± 7.0	100.4 ± 4.1	81	22.5 ± 14.5	13.7 ± 9.0
				80	84	160.1 ± 7.7	101.0 ± 4.4	77	22.5 ± 12.1	13.9 ± 8.9
	AZL	IHD	TAK-536/CCT-005	20	313	160.0 ± 7.7	100.3 ± 4.3	311	19.9 ± 14.3	11.0 ± 8.9
				40	313	160.0 ± 7.7	100.3 ± 4.3	311	21.8 ± 15.3	12.4 ± 9.9
	AZL/AML	STED	CCT-001	20	151	160.2 ± 8.3	100.4 ± 4.1	151	21.5 ± 12.2	13.9 ± 8.5

PreBP: Blood pressure before angiotensin II antagonist administration, ΔBPo: Observed blood pressure reduction at the time of after 8 weeks angiotensin II antagonist administration, N: Number of participants, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CND: Candesartan, VAL: Valsartan, AZL: Azilsartan, HCTZ: Hydrochlorothiazide, AML: Amlodipine, CLN: Cilnidipine, TCTZ: Trichlormethiazide, STED: Summary technical documentation, IHD: In-house document of the pharmaceutical companies, ND: No data, *1: Mean (95% confidence interval). *2: Calculated by standard error times the square root of number of participants.

Table 2. Estimated the values of Emax and ED50 on regression equation of Emax model.

	Systolic blood pressure		Diastolic blood pressure	
	Emax (mmHg)	ED50 (mg/day)	Emax (mmHg)	ED50 (mg/day)
Candesartan	27.920	5.916	13.186	2.717
Valsartan	16.625	21.688	8.105	1.166
Azilsartan	22.681	1.637	13.142	0.730

Emax: Maximum drug effect, ED50: Median effective daily dose

Based on these values of Emax and ED50 for CND, VAL and AZL, regression equations between drug dosage and ΔBPp were derived in SBP and DBP, following equations 4 to 9. Predicted SBP reduction was described as "ΔSBPp", and predicted DBP reduction was described as "ΔDBPp".

CND

$$\Delta SBPp = D \times 27.920 / (D + 5.916) \quad \cdots \text{Equation 4}$$

$$\Delta DBPp = D \times 13.186 / (D + 2.717) \quad \cdots \text{Equation 5}$$

VAL

$$\Delta SBPp = D \times 16.625 / (D + 21.688) \quad \cdots \text{Equation 6}$$

$$\Delta DBPp = D \times 8.105 / (D + 1.166) \quad \cdots \text{Equation 7}$$

AZL

$$\Delta SBPp = D \times 22.681 / (D + 1.637) \quad \cdots \text{Equation 8}$$

$$\Delta DBPp = D \times 13.142 / (D + 0.730) \quad \cdots \text{Equation 9}$$

ΔSBPp: Predicted SBP reduction (mmHg), ΔDBPp: Predicted DBP reduction (mmHg), D: Daily dose (mg)

The relationships between the daily dose and ΔSBP or ΔDBP in CND, VAL and AZL are shown in Figs. 1, 2 and 3, respectively. PE (mean ± SD) of regression equations in SBP and DBP were 0.001 ± 1.415 mmHg and −0.006 ± 1.658 mmHg in CND, 0.000 ± 3.017 mmHg and 0.000 ± 1.393 mmHg in VAL, and −0.003 ± 0.825 mmHg and −0.001 ± 1.149 mmHg in AZL, respectively. On the other hand, APE (mean ± SD) of regression equations in SBP and DBP were 1.225 ± 0.029 mmHg and 1.318 ± 0.813 mmHg in CND, 2.593 ± 1.242 mmHg and 1.219 ± 0.519 mmHg in VAL, and 0.617 ± 0.496 mmHg and 0.955 ± 0.527 mmHg in AZL, respectively.

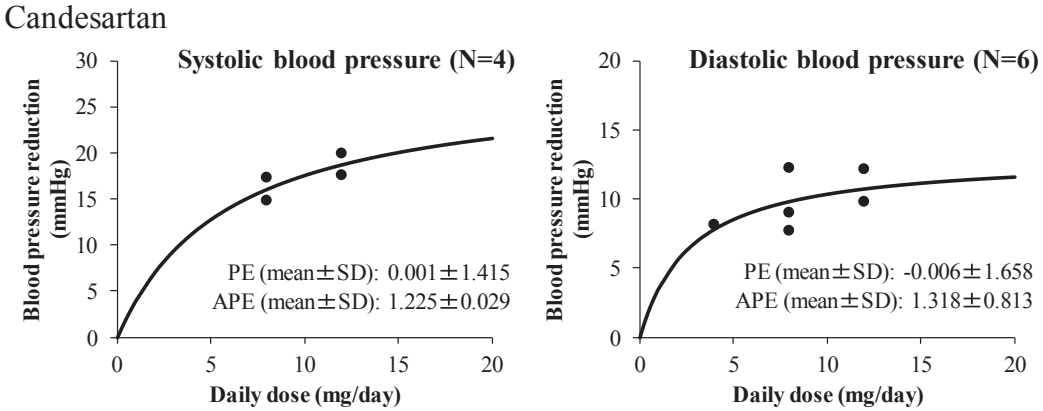

Fig 1. Emax model regression line of relationship between daily dose and blood pressure reduction in candesartan.

PE: Prediction error, APE: Absolute prediction error. Solid circles represent observed reduction of blood pressure. Curved lines represent predicted reduction of blood pressure.

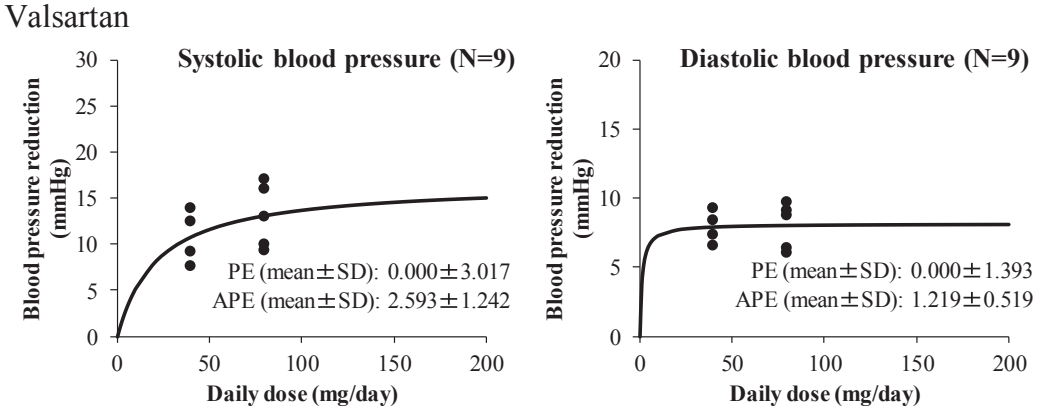

Fig 2. Emax model regression line of relationship between daily dose and blood pressure reduction in valsartan.

PE: Prediction error, APE: Absolute prediction error. Solid circles represent observed reduction of blood pressure. Curved lines represent predicted reduction of blood pressure.

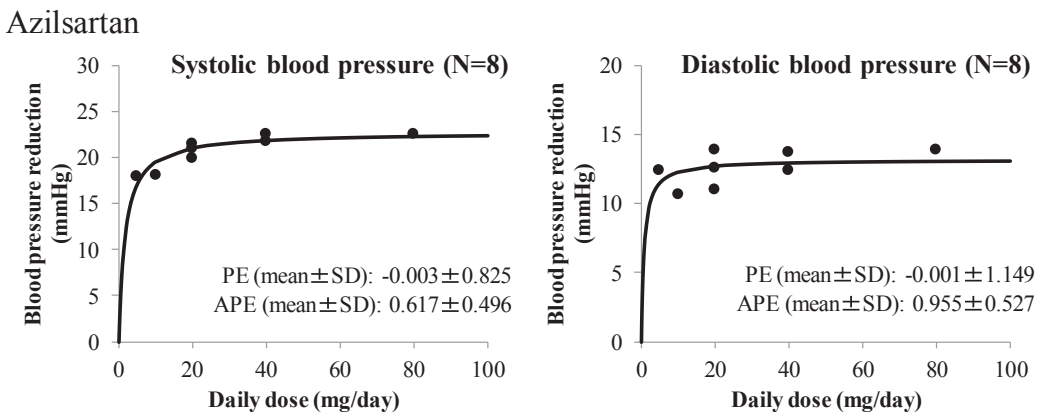

Fig 3. Emax model regression line of relationship between daily dose and blood pressure reduction in azilsartan.

PE: Prediction error, APE: Absolute prediction error. Solid circles represent observed reduction of blood pressure. Curved lines represent predicted reduction of blood pressure.

Based on the derived regression equations, ΔSBPp and ΔDBPp according to the approved daily dose in Japan are shown in Table 3. The predicted BP reduction was almost equivalent between the following: CND 2 mg/day and VAL 20 mg/day, CND 4 mg/day and VAL 40 mg/day, CND 4 mg/day and VAL 80 mg/day, CND 8 mg/day and VAL 160 mg/day, and CND 12 mg/day and AZL 10 mg/day.

Table 3. Daily dose and predicted blood pressure reduction by Emax model regression in candesartan, valsartan and azilsartan.

	Daily dose (mg/day)	Predicted BP reduction (mmHg)	
		ΔSBPp	ΔDBPp
Candesartan	2	7.05	5.59
	4	11.26	7.85
	8	16.05	9.84
	12	18.70	10.75
Valsartan	20	7.98	7.66
	40	10.78	7.88
	80	13.08	7.99
	160	14.64	8.05
Azilsartan	10	19.49	12.25
	20	20.96	12.68
	40	21.79	12.91

BP: Blood pressure, ΔSBPp: predicted systolic blood pressure reduction, ΔDBPp: Predicted diastolic blood pressure reduction

Discussion

We derived regression equations based on Emax model between daily dose and BP reduction using clinical trials data of 3 ARB (CND, VAL and AZL) monotherapy in Japanese mild to moderate essential hypertension patients. We derived regression equations between daily dose and BP reduction for CND, VAL and AZL. Then, we showed values of ΔBPp were estimated in these 3 ARB by the approved daily dose in Japan. These regression equations enable comparison of the mechanism by which BP reduction occurs for the drugs, and they are useful for choosing alternative drugs and the appropriate dosage when switching from the drugs the patients have been taken before hospitalization. When switching from CND, successive BP control will become possible with equivalent BP reduction by switching from CND 2 mg/day to VAL 20 mg/day, or from CND 4 mg/day to VAL 40 mg/day or CND 8 mg/day to VAL 160 mg/day. On the other hand, ΔSBPp and ΔDBPp in CND 12 mg/day were estimated to be 18.70 mmHg and 10.75 mmHg, respectively. Because these estimated values of BP reduction were larger than the estimated Emax of VAL (16.625 mmHg in SBP and 8.105 mmHg in DBP), it would be difficult for VAL to be substituted for CND 12 mg/day. AZL 10 mg/day could be used as an alternative to CND 12 mg/day.

When switching from VAL, we could switch from VAL 20 mg/day to CND 2 mg/day or 4 mg/day, or from VAL 40 mg/day or VAL 80 mg/day to CND 4 mg/day or from VAL 160 mg/day to CND 4 mg/day or CND 8 mg/day for successive BP control.

When switching from AZL, AZL 10 mg/day could be switched to CND 12 mg/day. The previous study[23] has shown that the differences of BP reduction between AZL 40 mg/day and CND 12 mg/day are 4.4 mmHg (95% confidence interval (CI): 2.20 to 6.53 mmHg) in SBP and 2.6 mmHg (95% CI: 1.22 to 4.08 mmHg) in DBP, and suggested BP reduction by AZL 40 mg/day was larger than that by CND 12 mg/day. In this study, ΔSBPp and ΔDBPp in AZL 40 mg/day were estimated to be 21.79 mmHg and 12.71 mmHg, respectively. Since the differences of BP reduction between AZL 40 mg/day and CND 12mg/day were also estimated to be 3.09 mmHg for ΔSBPp and 1.96 mmHg for ΔDBPp in this study, these differences were consistent with the difference of BP reduction between AZL 40 mg/day and CND 12 mg/day in the previous study. Furthermore, the difference of BP reduction between AZL 20 mg/day and CND 12 mg/day were estimated to be 2.26 mmHg for Δ

SBPp. When AZL 20mg/day or AZL 40mg/day was switched to CND 12mg/day, patients value of BP might increase due to the weakened antihypertensive effect. It would be difficult for CND 12 mg/day to be substituted for AZL 20mg/day or AZL 40 mg/day.

Previous in vitro study indicated that AZL had a higher affinity to angiotensin II receptor type 1 and it bound this receptor more tightly than VAL[24]. Clinical BP reduction by VAL might be weaker than that by AZL, and it would be difficult to use VAL as an alternative drug for AZL, because estimated the values of Emax in VAL, 16.225 mmHg in SBP and 8.105 mmHg in DBP, were smaller than ΔSBPp (19.49 mmHg) and ΔDBPp (12.25 mmHg) in AZL 10mg/day in this study.

It was reported that PreBP was correlated with BP reduction after antihypertensive drug administration when the range of PreBP was approximately 100 mmHg[25,26]. This correlation indicated that the greater BP reduction was observed by antihypertensive drug when the patient's PreBP was higher. Although we did not take into account PreBP in derived regression equations, the range of PreBP in the trials that we used to derive regression equations was narrow, 150 to 160 mmHg for SBP and 99 to 100 mmHg for DBP, and means of APE were also small. This range of PreBP might little affect prediction of antihypertensive effect by regression equations.

We could derive regression equations only in CND, VAL and AZL, though 7 ARB were available in Japan. Further study is needed to explore the clinical data and regression equations for other drugs in order to help choose appropriate alternative drugs.

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