〔一 般 論 文〕

Comparative Clinical Evaluation of Efficiency and Safety between Original Drug and Generic Products (I)

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Summary：Annual healthcare costs in Japan are currently increasing. Therefore, the Japanese government is recommending the use of generic products. However, some reports have suggested a decrease in drug efficacy and the development of adverse effects when exchanging the original drug with a generic product. The purpose of this study is the comparison of clinical efficiency between original drugs and generic products. Candidate drugs were 2 types of angiotensin-converting enzyme inhibitor, enalapril and lisinopril, as it is important to reduce health expenditure for hypertension. We retrospectively evaluated the efficiency (blood pressure and heart rate), safety (biochemical parameters), medication adherence based on patient data. We set the follow-up period at 6 months before and after substitution. Data were analyzed by Paired-Sample t-tests (statistical significance level of 0.05). A total of 27 patients in the enalapril study and 35 patients in the lisinopril study became candidates for the present study. We found that there were no significant differences before and after substitution. Although there were differences in some biochemical parameters, the range remained within normal levels. With regard to medication adherence, we found no significant differences.

Key words：generic product, efficiency, safety, angiotensin- converting enzyme inhibitor

Background

In recent years, healthcare costs in Japan have steadily increased. In 2008, they exceeded 33 trillion yen, including 6.6 trillion yen (20% of the total healthcare costs) in drug costs. The Japanese government has thus attempted to reduce the costs associated with drugs, and one of the approaches to achieve this has been to recommend generic products. Although the range of generic products on the Japanese National Health Insurance price list has increased, they represent only 16.8% of the market share. This percentage is lower than the United States or Europe, where shares are about 40-60%. To promote genetic products using in Japan, we have to cast aside apprehension among health professions who use them. In fact, there are some report

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suggest it [1-3]. It is therefore essential that accurate information drawing comparisons between original drugs and generic products is available to eliminate this anxiety.

Hypertension is one of the risk factors of cardiac and cerebrovascular diseases [4,5]. The health expenditure for hypertension is 2.2 trillion yen, and accounts for one third of the total health expenditure for cardiovascular disease. Therefore, reducing the health expenditure for hypertension would have far-reaching ramifications for overall health expenditure. It is anticipated that antihypertensive prescriptions will continue to increase in the future. Therefore, we studied original and generic angiotensin-converting enzyme inhibitors in order to evaluate their efficacy and safety.

Methods

Targeted Pharmaceuticals

Our study targeted the widely used angiotensin-converting enzyme inhibitors enalapril and lisinopril. They also have wide variety of generic products. With regard to enalapril, we compared Renivace® (original; BANYU Pharmaceutical Co., Ltd.) with Enalart® (generic; KYOWA Pharmaceutical Industry). With regard to lisinopril, we compared Longes® (original; SHIONOGI & Co., Ltd.) with Longeril® (generic; Nichi-Iko Pharmaceutical Co., Ltd.).

Subjects

Target subjects were ambulatory patients visiting Nakajima Hospital for hypertension treatment. Selected patients included those taking both the original drug and the generic product; i.e., patients who had substituted the original drug Renivace® for the generic product Enalart®, or those who had substituted the original drug Longes® for the generic drug Longeril®.

Exclusion criteria were as follows:

- Patients who took the original drug or the generic product for a period of less than 6 months.
- Patients who had changed their dosage.
- Patients who had taken another drug that is recognized to have drug-drug interactions with the generic product.
- Patients who had been diagnosed with secondary hypertension during the follow-up period.

Data collection

For this retrospective study, we used information from patients' medical records and prescriptions.

Follow-up period

We set the follow-up period at 6 months before and after the substitution, but we excluded the immediate 4-week period after the substitution because we considered this to be a washout period for the original drug, after which steady state levels of the generic product may take effect.

End points

- Blood Pressure and Heart Rate
  Systolic and diastolic blood pressure and heart rate values were obtained when patients were in an ambulatory setting. Mean values and standard deviation were used for analysis.

- Biochemical Examination
  Biochemical parameters were used as indicators of safety. We observed laboratory data on liver and renal function (alaine aminotrnsferase; ALT, aspartate aminotrnsferase; AST, blood urea nitrogen; BUN, creatinine; Cr), blood cell count (hemoglobin; Hb, hematocrit; Ht, white blood cell; WBC), and other data (potassium; K, sodium; Na) based on accredited drug information. Eosinophil (Eo), amylase (Amy), lipase (Lp) and blood glucose (BG) were added as safety indicators for enalapril. Lactate dehydrogenase (LDH), alkaline phosphatase (ALP), γ - glutamyl transpeptidase (γ-GTP), red blood cell (RBC), platelet (PLT) and uric acid (UA) were also added for lisinopril.

Mean values and standard deviation were used for analysis.

- Medication Adherence

  Medication adherence evaluation used *Daily Medication Adherence* (DMA) [6-10]. DMA is derived from the dosing days and the duration of hospital visits. We compared the duration of drug exposure between the original drug and the generic product. Mean values and standard deviation were used for analysis.

Statistical Analysis

Data were analyzed by Paired-Sample t-tests in order to compare the period before substitution with that after substitution. We used a statistical significance level of 0.05.

Ethical Issues

The study was administered by both the Tohoku Pharmaceutical University Ethics Committee and the Nakajima Hospital Ethics Committee.

Results

I. Enalapril

Subjects

One hundred and seventy-six patients took Enalart®. Among these, 111 did not take the original drug, and 3 patients took the original drug for a duration of less than 6 months. In addition, 3 patients took the generic product for a duration of less than 6 months, 17 patients changed their medication regimen, and 15 patients could not be traced because of a lack of data. Thus, 27 patients were candidates for this study (Fig. 1). There were no cases of drug withdrawal due to adverse effects.

In this study, we excluded patients who took the generic products for a period of less than 6 months. When we traced these patients, there were no problems of efficiency and safety on generic products.

1. Background

The clinical background data for the subjects are shown in Table 1. The mean age of the 27 subjects (21 males and 6 females) was 62.5 ± 10.5 years. Subjects had a past history and/or complications with hyperlipidemia (14 cases), followed by cardiac disease (10 cases) and diabetes mellitus (9 cases). Almost all patients had taken another antihypertensive agent, with calcium antagonists being the most common (22 cases).

2. Efficacy

Systolic and diastolic blood pressure and heart rate values before and after substitution are shown in Fig. 2. No significant differences were seen in blood pressure values before and after substitution. Before substitution, systolic blood pressure was 142.4 ± 10.5 mmHg. After substitution, it was 141.8 ± 10.7 mmHg (P = 0.67, 95% CI = -2.31 – 3.54). Before substitution, diastolic blood pressure was 81.6 ± 8.2 mmHg, and after substitution, it was 80.9 ± 8.3 mmHg (P = 0.36, 95% CI = -0.93 – 2.49). Similarly, heart rate values showed no significant differences before and after

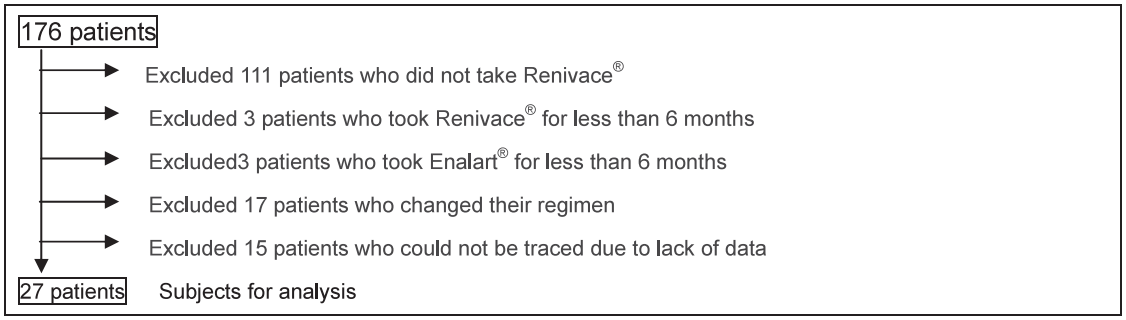

Fig. 1 Determining subjects for enalapril study.

substitution; before substitution, heart rate was 81.8 ± 21.8 bpm, and after substitution, it was 78.5 ± 18.4 bpm (P = 0.16, 95% CI = -1.57 – 8.19).

Table 1　Patient background data.

Age (mean±SD)	62.5±10.5	
Male, number (%)	21	(77.8)
Female, number (%)	6	(22.2)
Complications and past history	n	(%)
Cerebrovascular disease	4	(14.8)
Cardiac disease	10	(37.0)
Diabetes mellitus	9	(33.3)
Hyperuricemia	4	(14.8)
Hyperlipidemia	14	(51.9)
Renal dysfunction	1	(3.7)
Liver dysfunction	7	(25.9)
Psychopathic disorder	2	(8.0)
Enalapril dosage / day	n	(%)
2.5 mg	1	(3.7)
5 mg	15	(55.6)
10 mg	11	(40.7)
Number of combined antihypertensive agents	n	(%)
None	2	(7.4)
One	12	(44.4)
Two	13	(48.1)
Types of combined antihypertensive agent	n	(%)
α blocker	8	(29.6)
β blocker	4	(14.8)
Calcium antagonist agent	22	(81.5)
Diuretic agent	1	(3.7)
Angiotensin receptor blocker	3	(11.1)

3. Safety

There was a significant difference in Ht (P=0.02, 95 % CI=-2.25 – -0.27), while other biochemical parameters and comparisons showed no significant differences before and after substitution (Table 2). As there were no suitable subjects available, Amy, Lp and Eo were excluded from this analysis.

4. Medication Adherence

Medication adherence before and after substitution is shown in Fig. 3. A mean value of 97.3 ± 4.4% for adherence before substitution was determined using DMA, while the value after substitution was 98.5 ± 6.6% . No significant differences were noted (P = 0.40, 95% CI = -4.09 – 1.70).

II. Lisinopril

Subjects

One hundred and thirty-five patients took Longeril®. Among these, 84 did not take the original drug, 2 had original drug exposure for less than 6 months, 1 was exposed to the generic product for less than 6 months, and 11 changed their regimen. In addition, a lack of data prevented tracking of

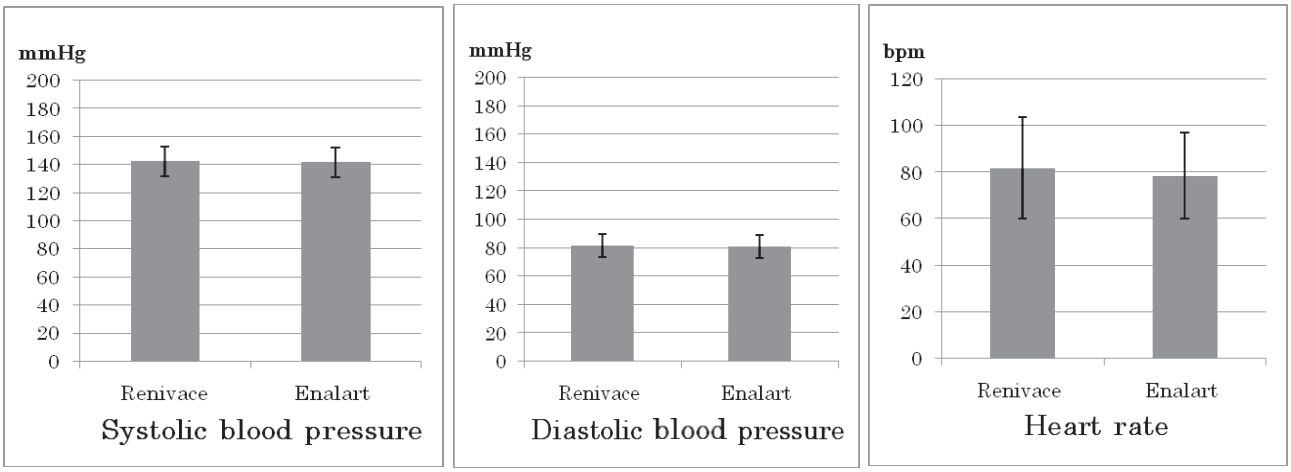

Fig. 2　Blood pressure and Heart rate values before and after substitution (enalapril study). Before substitution, systolic blood pressure was 142.4 ± 10.5 mmHg. After substitution, it was 141.8 ± 10.7 mmHg (P = 0.67, 95% CI = -2.31 – 3.54). Before substitution, diastolic blood pressure was 81.6 ± 8.2 mmHg, and after substitution, it was 80.9 ± 8.3 mmHg (P = 0.36, 95% CI = -1.57 – 8.19). Before substitution, heart rate was 81.8 ± 21.8 bpm, and after substitution, it was 78.5 ± 18.4 bpm (P = 0.16, 95% CI = -1.57 – 8.19).
There were no significant differences in these values were seen.

Table 2　Biochemical parameters before and after substitution of enalapril.

		n	Renivace®	Enalart®	P-value	95%CI
AST	IU/l	16	29.0±16.4	30.5±17.8	0.43	-5.31~2.37
ALT	IU/l	16	29.3±20.0	30.1±19.6	0.63	-4.13~2.56
BUN	mg/dL	14	15.5±3.2	15.0±3.2	0.36	-0.52~1.36
Cr	mg/dL	14	0.7±0.2	0.7±0.2	0.74	-0.06~0.05
Na	mEq/L	10	141.0±1.7	140.6±2.0	0.64	-1.51~2.34
K	mEq/L	10	4.3±0.4	4.3±0.5	0.85	-0.34~0.28
WBC	$\times 10^2/\mu L$	16	58.4±18.6	54.4±12.9	0.12	-1.24~9.23
Hb	g/dL	16	14.0±0.9	14.1±1.0	0.44	-0.32~0.15
Ht	**%**	**16**	**40.8±2.2**	**42.1±3.1**	**0.02**	**-2.25~-0.27**
BS	mg/dL	16	110.0±21.6	109.3±26.3	0.86	-8.01~9.46

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; Na: sodium; K: potassium; WBC: white blood cells; Hb: hemoglobin; Ht: hematocrit; BS: blood sugar.

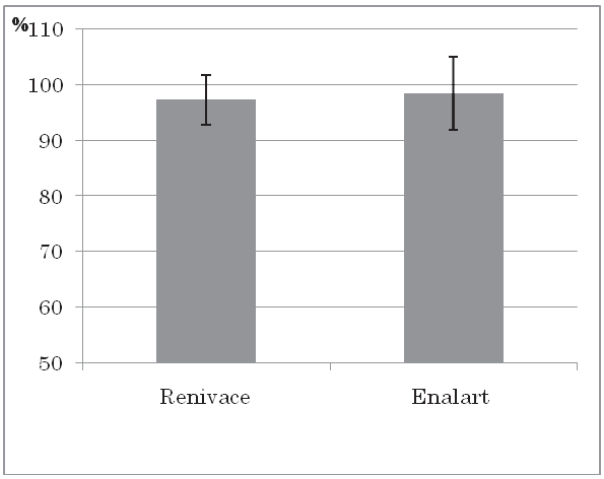

Fig. 3　Medication adherence (enalapril study). A mean value of 97.3 ± 4.4% for adherence before substitution was determined using DMA, while the value after substitution was 98.5 ± 6.6%. No significant differences were noted (P = 0.40, 95% CI = -4.09 – 1.70).

medication in 1 patient. Thus, 35 patients were enrolled (Fig. 4). There were no cases of drug withdrawal or adverse effects.

In this study, we excluded patients who took the generic products for a period of less than 6 months. When we traced these patients, there were no problems of efficiency and safety on generic products.

1. Background

The clinical background data of the subjects are shown in Table 3. The mean age of the 35 subjects (12 males and 23 females) was 67.2 ± 9.5 years. Past medical history most commonly included hyperlipidemia (17 cases), followed by cardiac disease (16 cases) and diabetes mellitus (12 cases). Over 90% of the subjects took another antihypertensive agent, and the most common antihypertensive agent was calcium antagonist

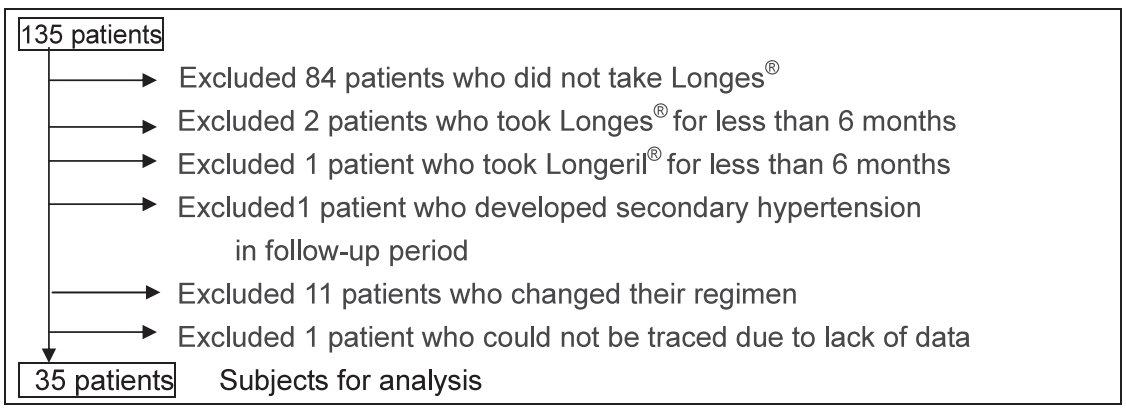

Fig. 4　Determining subjects for lisinopril study.

(88%, 31 cases).

2. Efficacy

Systolic and diastolic blood pressure and heart rate values before and after substitution are shown in Fig. 5. No significant differences in blood pressure were seen before or after substitution. Systolic blood pressure before substitution was 137.3 ± 9.7 mmHg, and after substitution it was 137.6 ± 10.6 mmHg (P = 0.78, 95% CI = -2.84 – 2.15). Diastolic blood pressure before substitution was 77.2 ± 10.9 mmHg, and after substitution, it was 77.7 ± 10.4 mmHg (P = 0.63, 95% CI = -2.37 – 1.46). There were also no significant differences in heart rate before and after substitution; before substitution, heart rate was 80.9 ± 9.5 bpm, and after substitution, it was 81.9 ± 13.5 bpm (P = 0.72, 95% CI = -6.66 – 4.69).

Table 3 Patient background data.

Age (mean±SD)	67.2±9.5
Male (%)	12 (34.3)
Female (%)	23 (65.7)
Complications and past history	n (%)
Cerebrovascular disease	9 (25.7)
Cardiac disease	16 (45.7)
Diabetes mellitus	12 (34.3)
Hyperuricemia	3 (8.6)
Hyperlipidemia	17 (48.6)
Renal dysfunction	2 (8.6)
Liver dysfunction	5 (14.3)
Psychopathic disorder	4 (11.4)
Longeril® dosage/ day	n (%)
5 mg	1 (2.9)
10 mg	26 (74.3)
20 mg	8 (22.9)
Number of combined antihypertensive agents	n (%)
None	4 (11.4)
One	25 (71.4)
Two	3 (14.3)
Three	0 (0)
Four	1 (2.9)
Types of combined antihypertensive agent	n (%)
α blocker	5 (14.3)
β blocker	0 (5.7)
Calcium antagonist agent	31 (88.6)
Angiotensin receptor blocker	1 (2.9)

3. Safety

There were significant differences in Cr (P = 0.01, 95% CI = -0.11 – -0.02), ALT (P = 0.02, 95% CI = -5.71 – -0.45) and Ht (P = 0.03, 95% CI = -1.63 – -0.08). Other biochemical examination comparisons showed no significant differences before and after substitution (Table 4).

4. Medication Adherence

Medication adherence before and after substitution is shown in Fig. 6. The mean adherence value before substitution, as determined by DMA, was 96.2 ± 6.8%, while that after substitution was

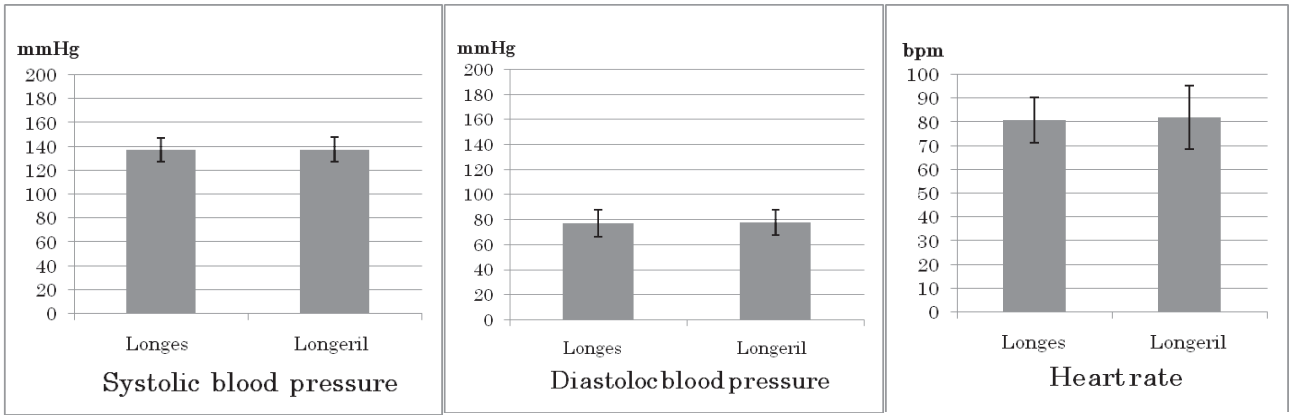

Fig. 5 Blood pressure and Heart rate values before and after substitution (lisinpril study). Systolic blood pressure before substitution was 137.3 ± 9.7 mmHg, and after substitution it was 137.6 ± 10.6 mmHg (P = 0.78, 95% CI = -2.84 – 2.15). Diastolic blood pressure before substitution was 77.2 ± 10.9 mmHg, and after substitution it was 77.7 ± 10.4 mmHg (P = 0.63, 95% CI = -2.37 – 1.46). Before substitution, heart rate was 80.9 ± 9.5 bpm, and after substitution it was 81.9 ± 13.5 bpm (P = 0.72, 95% CI = -6.66 – 4.69).There were no significant differences in these values were seen before or after substitution.

Table 4　Biochemical parameters before and after substitution of lisinopril.

		n	Longes®	Longeril®	P-value	95%CI
AST	IU/l	24	24.2±7.9	25.6±10.0	0.19	-3.44~0.73
ALT	**IU/l**	**24**	**21.4±8.5**	**24.5±12.0**	**0.02**	**-5.71~-0.45**
γ-GTP	IU/l	24	39.3±31.7	42.6±37.0	0.08	-7.04~0.49
LDH	IU/l	24	195.2±37.8	203.4±32.8	0.13	-18.73~2.58
BUN	mg/dL	20	15.5±4.0	14.7±4.2	0.27	-0.62~2.09
Cr	**mg/dL**	**20**	**0.66±0.2**	**0.72±0.24**	**0.01**	**-0.11~-0.02**
ALP	IU/l	24	233.2±55.1	231.0±55.7	0.67	-8.44~12.85
UA	mg/dL	4	5.4±0.6	5.3±0.6	0.49	-0.49~0.82
K	mEq/L	10	4.4±0.3	4.4±0.4	0.98	-0.13~0.13
Na	mEq/L	10	140.6±1.5	141.4±1.5	0.17	-1.86~0.39
Hb	g/dL	24	13.1±1.1	13.2±1.1	0.46	-0.27~0.13
Ht	**%**	**24**	**39.4±3.4**	**40.2±3.1**	**0.03**	**-1.63~-0.08**
RBC	$\times10^2$/μL	24	422.0±38.1	428.7±35.8	0.08	-14.29~0.91
PLT	$\times10^4$/μL	24	19.8±3.4	20.2±3.5	0.24	-1.09~0.29
WBC	$\times10^2$/μL	24	53.2±14.0	56.1±14.0	0.17	-7.13~1.37

AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: γ-glutamyl transpeptidase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; Cr: creatinine; ALP: alkaline phosphatase; UA: uric acid; K: potassium; Na: sodium; Hb: hemoglobin; Ht: hematocrit; RBC: red blood cells; PLT: platelets; WBC: white blood cells.

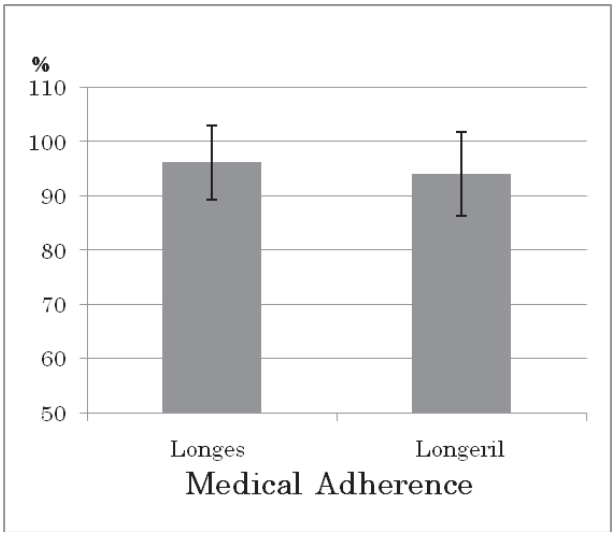

Fig. 6　Medication adherence (lisinopril study). The mean adherence value before substitution, as determined by DMA, was 96.2 ± 6.8%, while that after substitution was 94.1 ± 7.7%. There were no significant differences (P = 0.17, 95% CI = -0.96 – 5.12).

94.1 ± 7.7%. There were no significant differences (P = 0.17, 95% CI = -0.96 – 5.12).

Discussion

In this study, we found no significant differences before and after substituting medications with generic drugs (Renivace® to Enalart®, and Longes® to Longeril®). Additionally we found no subjective symptom changes after substitution. Although, there were differences in some biochemical parameters (elevated hematocrit levels in the enalapril study, and elevated creatinine and alanine aminotransferase levels in the lisinopril study), all ranges remained within normal levels, but we should trace these changes. Additionally, sample size is small. Therefore there is a possibility that laboratory data which showed no significant differences are not equivalent in before and after substitution. We need quintuple to decuple sample size to evaluate equivalence.

Angiotensin-converting enzyme inhibitors also have cardioprotective effects, renal protective effects and cerebroprotective effects [9,10]. In other reports, preventative effects against migraine headaches were noted [11,12]. In our study, we used only systolic blood pressure, diastolic blood pressure and heart rate values as indicators of efficacy, and so other effects of generic angiotensin-converting enzyme inhibitors remain to be evaluated.

In order to accurately evaluate efficacy, we compared medication adherence before and after substitution. We found no significant differences for either enalapril or lisinopril. According to reports on medication adherence, an 80% adherence rate is needed to be considered successful pharmacotherapy, and our study had a rate of over

90％. Numerous medication adherence surveys have been taken, and it has been confirmed that there is a close relationship between adherence and drug efficacy. Therefore, it is important to evaluate changes in medication adherence before and after substitutions.

In order to evaluate the economic effectiveness, we calculated copayments that assumed each drug was administered individually (data not shown). We set the duration of drug exposure at 6 months. According to the price listings, we set Renivace® (5 mg) at 83.7 yen, Enalart® (5 mg) at 14.7 yen, Longes® at 78.9 yen, and Longeril® at 18.9 yen. All prices are per tablet. Copayments decrease after changing to generic products from original drugs. In cases where prescribing include generic products, special fees (fees for information about generic products and fees for dispensing for generic products) are added to the basic compounding fee under the national medical insurance system in Japan. However, the total copayment costs, including the additional fees, of generic drugs remain lower than the price of the original drug. When antihypertensive drugs are taken for a long period, patients clearly benefit from the diminished economic burden, as does the government.

In a survey taken in 2006 by the JMA Research Institute, Inc., 452 hypertensive patients aged 40 to 80 years acted as subjects. A total of 60% of patients felt that the costs of their medical care were too high and 90% said that if the effectiveness and safety were the same, they would switch to a more inexpensive drug. Thus, almost all patients wanted to diminish their out-of-pocket medical costs. According to that report, copayments may increase in the future, leading to greater dissatisfaction with high costs.

In order to reduce costs, patients reported a range of behaviors: 36.5% had decreased the number of hospital visits; 24.6％ had decreased the number of other medical care facility visits; 15.3％ had decreased the amount of drugs taken; and 14.2% had decreased the dosage. In fact, according to a report on medication adherence, only 53％ [13] of patients showed more than 80% adherence. Another report suggested that 50-70％ patients who take antihypertensive drugs adhere to the specified regimens [14]. This is because hypertension is rarely noticed as a subjective symptom. Therefore, patients stop taking the drug or forget to use it regularly. However, we believe that copayment costs are one of the reasons for non-adherence. In fact, some reports have suggested that economic issues are responsible for some cases of non-adherence [15,16]. Thus, substituting original drugs for generic products not only reduces copayments, but may improve medication adherence and continuation of therapy.

In this study, we were unable to determine the number of patients who felt that copayments were too high, as we did not carry out such a questionnaire. However, we inferred the subjects who feel defrayment copayment is lower rate, because medication adherence that both original drug and generic products keep over 90% .

In this study, adherence was calculated by DMA, but that method does not reflect reduced amounts of drug taking or reduced dosages. In the future, we need to conduct a survey by questionnaire and/or estimate blood levels of drugs in order to obtain accurate information regarding medication adherence.

This study was retrospective, and thus had some limitations. In cases where there was a lack of data, analysis could not be performed. In addition, as the number of cases was low, the applicability of the findings is limited. A prospective study with a greater number of cases is thus required.

And we should mention that our data are limited to Enalart® and Longeril®, it does not accommodate another kind of generic products.

In this report, we could not remove value of background other than efficiency of drugs.

We also used blood pressure values obtained at the doctor's office, and these are susceptible to effects such as white coat hypertension. In recent

years, home blood pressure testing has been found to be beneficial in eliminating these effects. Several reports have made recommendations for estimating effectiveness of medication therapy [17,18], including the use of home blood pressure values.

By substituting original drugs with generic products, individual economic burden is reduced. However, not all generic products are useful, since there are differences in the availability of information, variations in quality and the ability to maintain a stable supply [19]. Therefore, to develop clinical information on generic products and to store such information, it is important that pharmaceutical products are used appropriately.

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