

Evaluation for Zero-order Controlled Release Preparations of Nifedipine Tablet on Dissolution Test, Together with Cost Benefit Point of Views

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Many generic drugs have been released to decrease medical expenses, but some problems have been reported with regard to bioavailability and safety. In this study, we compared three once-a-day controlled-release preparations of nifedipine by the dissolution test (one branded and two generic preparations). Although the two generic drugs were equivalent to the branded drug according to the criteria listed in the Japanese "Guideline for Bioequivalence Studies of Generic Products", there was still a possibility of problems arising. For example, side effects could be caused by a rapid increase in the blood level of nifedipine with one generic drug, while bioavailability might be inadequate with the other due to its small area under the concentration vs. time curve. When each drug was prescribed at a dosage of 20 mg once daily for two weeks, the difference in the copayment for the patient was only 10 yen. Accordingly, it is important for doctors and pharmacists to carefully consider whether such a slight difference in price is really a benefit for the patient.

Key words—generic drug; controlled-release preparation; drug evaluation; nifedipine

INTRODUCTION

In Japan, prescription has changed since April 2006, and the use of generic drugs is being promoted to cut medical costs. However, "A Command Investigation Final Report About Generic Drugs"¹⁾ released by the Japan Medical Association in September 2006 revealed various problems with generic drugs in relation to their quality, efficacy, and side effects. In addition, quality evaluation studies have demonstrated that some generic drugs are different from the brand-name drugs.²⁻⁶⁾ Accordingly, the use of generic drugs is being promoted with some anxiety at present and optimal drug choices remain an important problem for pharmacists.

Nifedipine is a calcium antagonist that dilates both coronary arteries and peripheral vessels. It was released in Japan in 1976, and has been used to treat angina pectoris and hypertension for many years. The original nifedipine preparation had a half-life that was comparatively short and the blood level of the drug increased rapidly after administration, which tended to cause side effects.

Accordingly, a controlled-release preparation of

nifedipine was developed to overcome these weak points of the drug. At present, various controlled-release technologies have been developed, and many sustained-release preparations are clinically available. Advanced technical know-how and careful formulation are important for controlled-release preparations because their release characteristics have a large influence on drug safety and bioavailability. In particular, nifedipine preparations need careful evaluation because a slight difference in the release characteristics may lead to side effects or variations in the duration of action.

To ensure the appropriate use of generic drugs, we have previously performed dissolution tests with various generic products. As a result, we found that some twice-a-day controlled-release generic preparations of nifedipine were inferior to the brand-name drug. In comparison with the branded product, the dissolution percentage of some generic drugs was extremely low or extremely high, and our investigation showed that there were also appreciable quality differences between the brand-name drug and the generics.⁷⁾

Once-a-day nifedipine preparations were released in Japan in 2004. In this study, we report on the evaluation of three such drugs by the dissolution test.

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MATERIALS AND METHODS

Test Drugs Adalat CR[®] tablets 20 mg (Adalat CR[®]), the brand-name drug, were obtained from Bayer Yakuhin (Osaka, Japan). Two generic forms of Adalat CR[®] were obtained from Towa Yakuhin (Osaka, Japan) and Zensei Pharmaceutical Industries (Osaka, Japan), respectively (Table 1). Adalat CR[®] is a controlled-release preparation of nifedipine for once-a-day administration and it is designed so that a stable blood concentration of the drug is maintained for 24 hours after oral administration. Adalat CR[®] is a film-coated tablet with two internal components. Its outer layer was designed to dissolve slowly in the moist environment of the upper gastrointestinal (GI) tract, while the inner layer was designed to dissolve rapidly in the less moist lower GI tract⁸⁾ (Fig. 1). Generic A is also a film-coated tablet with two internal components that are similar to those of Adalat CR[®], but its inactive ingredients are different (Table 2). In the case of Generic B, nifedipine is gradually eluted from the controlled-release layer, after which the insoluble layer is exposed. Then the tablet absorbs water through this insoluble layer and swells, after which nifedipine is gradually released from the sides of the tablet⁹⁾ (Fig. 2).

Dissolution Test The dissolution test was car-

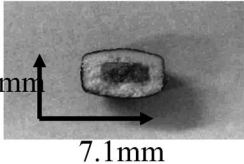
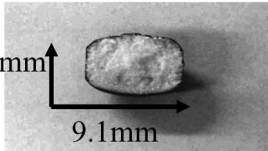
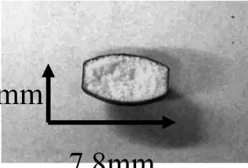
ried out in accordance with the specifications listed in the Japanese Pharmacopeia (14th edition) according to the second revision of the Japan public assay dissolution test method (a paddle method). The paddle speed was set at 100 rpm and the temperature was 37°C. A PJ-3N dissolution test device (Miyamoto Riken Institute of Physical and Chemical Research Industry Co., Ltd. (Osaka, Japan)) was used and the test solution was 0.2M hydrogen phosphate-citric acid buffer (pH 6.8) containing 1% sodium lauryl sulfate.

We did not adopt an official dissolution method. Because of specific dosage forms as once-a-day controlled-release preparations, reproducibility of dissolution percentage of official assay was not good in our pilot study. We verified that the dissolution rate was not affected by the difference of surfactant and we used 1% sodium lauryl sulfate because it worked in a more uniform way than Tween 80 and enough to dissolve nifedipine. The test solution pH 6.8 was the same pH as in bowl.

Six tablets from each lot were tested (Table 1), and the test solution was sampled hourly for eight hours. The amount of nifedipine released into the test solution was determined by dual-wavelength spectrophotometry measured at 342 and 480 nm and the elution rate was calculated.

Judgment of Bioequivalence The equivalence

Table 1. Study medications

Controlled-release Preparation of Nifedipine	NHI price (Yen)	Lot No	structure
Adalat [®] -CR Tablet 20 (Bayer Yakuhin)	43.1	D519 D521 D534	
Generic A Tablet 20	28.6	D407 D408 D410	
Generic B Tablet 20	27.2	BAEFC 110G1 128H1	

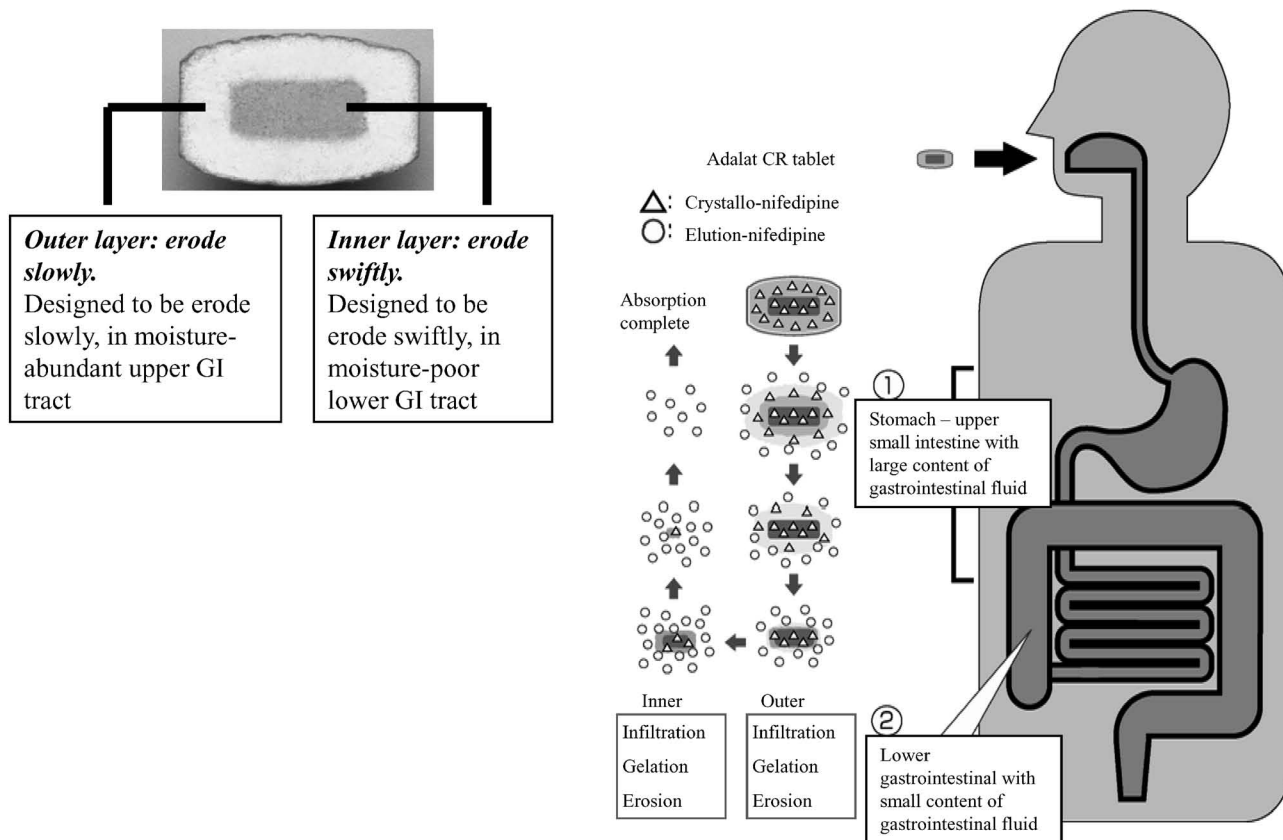


Fig. 1. Release Process of Adalat®-CR

Table 2. Inactive ingredients of the medications

Adalat®-CR	Generic A	Generic B
hydroxypropylcellulose		
magnesium stearate	magnesium stearate	magnesium stearate
diiron trioxide	diiron trioxide	diiron trioxide
aminoalkyl methacrylate copolymer RS		
hydroxypropylmethylcellulose 2910	hypromellose (hydroxypropylmethylcellulose)	hydroxypropylmethylcellulose
macrogol 4000	macrogol	macrogol
titanium oxide	titanium oxide	titanium oxide
	talc	talc
	ethylcellulose	ethylcellulose
	cellulose	low substituted hydroxypropylcellulose
other 2 ingredients	lactic acid	
		povidone
	other 2 ingredients	light anhydrous silicic acid
		other 2 ingredients

of each preparation in the dissolution test was assessed according to the Japanese “Guideline for Bioequivalence Studies of Generic Products”.^{10,11)} The

dissolution profiles of the preparations were judged to be similar if the average dissolution percentage of the generic drugs did not deviate by more than 15% from

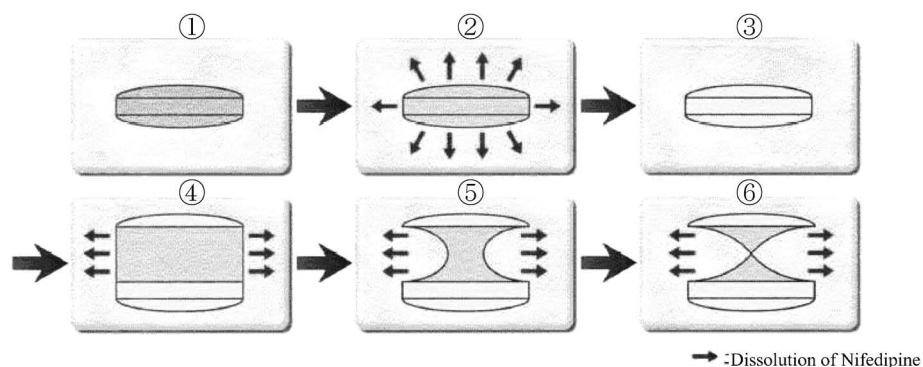


Fig. 2. Release Process of Generic B

① Colored coat layer dissolves. ② Nifedipine in the controlled drug release layer gradually dissolves. ③ The insoluble coat layer is exposed. ④ The tablet absorbs water through the insoluble coat layer and swells. ⑤⑥ Nifedipine is gradually released from the sides of the tablet.

Standard Drug: Adalat®-CR 20mg (D521)

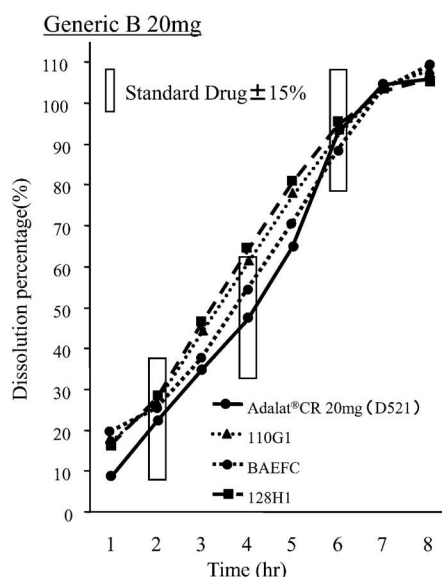
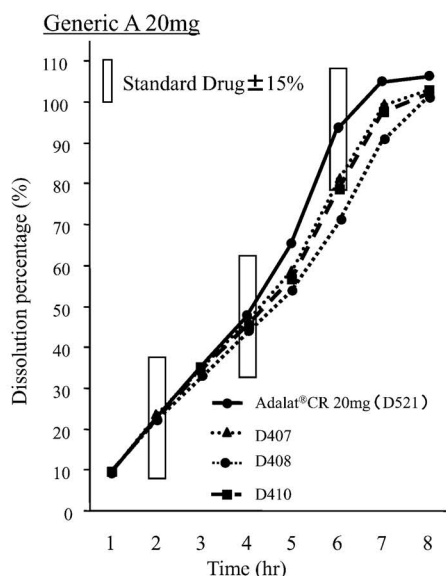


Fig. 3 Dissolution Profile of Nifedipine from Adalat® CR and the Generic Preparations
Rectangles indicate the dissolution percentage of Adalat® CR 20 mg (D521) $\pm 15\%$.

that of the branded drug after 2, 4 and 6 h (when the average dissolution percentage of the branded drug was approximately 30%, 50%, and 80% respectively).

We used actual measurements without dilution correction in this study and the percentage of the dissolution was over 100% (Fig. 3). We thought that there was not a problem in evaluation of these drugs because the initial dissolution profile was most important for controlled-release-preparations of nifedipine.

RESULTS

Equivalence of Drug Release The dissolution

percentage of nifedipine from Generic A and Generic B is shown in Fig. 4. For Generic A, the dissolution percentage of the tablets from all lots tested was in the appropriate range at 2 and 4 h after the start of the test. However, the tablets from two lots deviated from this range at 6 h. For Generic B, the dissolution percentage of tablets from all the lots was in the appropriate range at 2 and 6 h after starting the test. However, tablets from one lot deviated from this range at 4 h.

Evaluation of Dissolution Profiles The dissolution profiles of nifedipine from Adalat CR® and the generic drugs are shown in Fig. 3. Although dissolution of nifedipine from all preparations occurred at

Standard Drug: Adalat®-CR 20mg (D521)

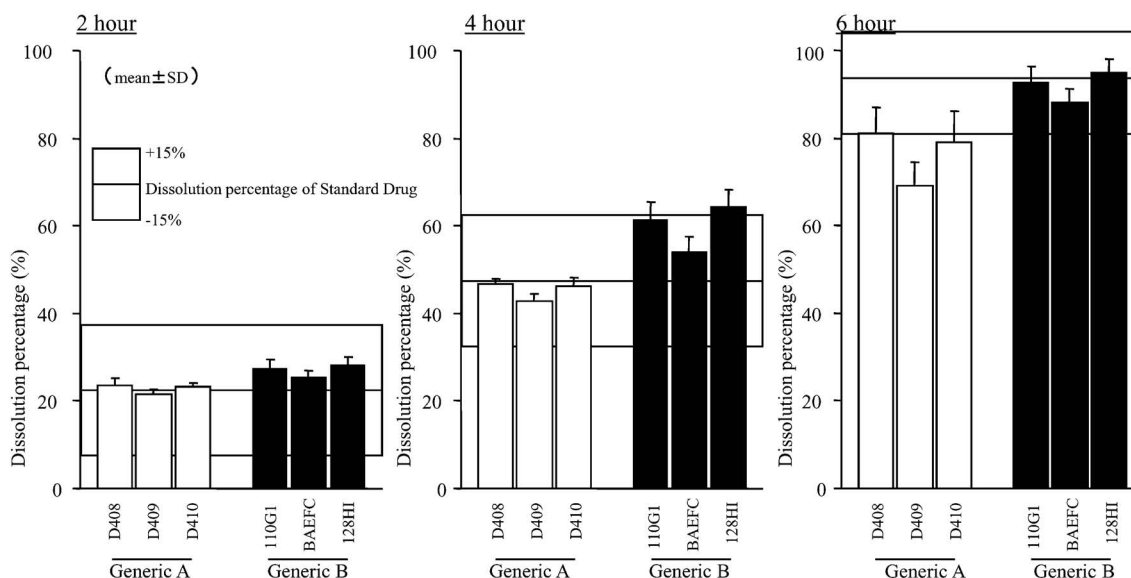


Fig. 4 Dissolution Percentage of Nifedipine from Generic Preparations Compared with the Brand Name Product

an approximately constant rate, some differences were found between the brand-name drug and the generics. With Generic A, the dissolution percentage of nifedipine after 4 h tended to be low for tablets from all lots tested and after 6 h it was extremely low for one lot. On the other hand, the dissolution percentage of nifedipine from Generic B was much higher during the early part of the test (at 1 h in particular), and this trend persisted throughout the examination. After Generic B tablets had dissolved, insoluble matter remained in the test vessel. This seemed to be Ethylcellulose from the dissolution control film.

DISCUSSION

Modern pharmaceutical technology has recently made dramatic progress in the case of drug delivery systems which are developed to obtain a stronger therapeutic effect from agents that have already been marketed as well as for use with novel compounds. Oral controlled-release preparations are a representative type of drug delivery system. Advanced pharmaceutical technology is necessary for controlled-release preparations because their dosage form design is based on a large amount of information about the physicochemical characteristics and pharmacokinetics of the active ingredient. If the dissolution percentage of the active ingredient from a preparation is

variable, there is the risk of side effects occurring or insufficient therapeutic efficacy.

In this quality evaluation study, we performed dissolution tests on two generic forms of Adalat CR®, a once-a-day controlled-release nifedipine preparation, based on the Japanese “Guideline for Bioequivalence Studies of Generic Products”. As a result, both generic preparations were found to be within an adequate range of the branded drug, except for tablets from one lot. In the “Guideline”, it is stated that bioequivalence can be confirmed by a dissolution test of oral controlled-release preparations if the dissolution profiles are judged to be similar because the average dissolution percentage of the test product does not deviate by more than 15% from that of the reference product under any of the test conditions at three times when the average dissolution percentage of the reference product is about 30%, 50%, and 80%, respectively. Both Generic A and Generic B almost satisfied these criteria.

However, some problems were noted on reviewing the results of the dissolution test in detail. First, there were differences of the dissolution profiles. Nifedipine has a short half-life and high lipid solubility, so rapid elevation of the blood level of this drug can easily cause adverse reactions. Thus, the dissolution profile is very important for a controlled-release preparation of nifedipine and we must evaluate the initial dissolu-

tion profile most carefully for the risk of adverse reactions. However, the current guideline only states that two dissolution profiles can be judged to be similar when the average dissolution percentage of the generic drug does not deviate by more than 15% from that of the branded drug at three times during the test, and there is no specification regarding serial changes of the dissolution profile. Under such circumstances, can we say that generic drugs are really equivalent to brand-name drugs?

In this study, the average dissolution curves of each generic drug actually showed differences from that of the branded drug. For Generic B, the difference was particularly marked in the early part of the test. Breimer reported that a sudden increase of nifedipine in the blood, even if the actual concentration is low, causes the heart rate to increase by activation of the sympathetic nervous system, so that the efficacy and safety of nifedipine preparations depend on the rate of change of drug blood levels rather than the absolute values.¹²⁾ Generic B had a very high initial dissolution rate of dissolved nifedipine in comparison with the branded drug. Accordingly, the development of side effects as a result the rapidly rising blood concentration of nifedipine is a concern. On the other hand, Generic A had an initial dissolution profile (until three hours) resembling that of the branded drug, but the dissolution percentage became slower from four hours on. Therefore, this preparation may have a weaker therapeutic effect.

As a controlled-release tablet of nifedipine shrinks during dissolution in the GI tract, its surface area becomes smaller. There is also less digestive juice in the lower GI tract, so release of nifedipine from the tablet decreases and the area under the concentration vs. time curve (AUC) deteriorates. Adalat CR[®] was designed to increase the dissolution of nifedipine in the lower GI tract. It has two different components that dissolve at different speeds to maintain the AUC of nifedipine.⁸⁾ In contrast, delayed dissolution of Generic A tablets could influence their therapeutic effect because the AUC will become smaller than that for Adalat CR[®].

Such results suggest that these two generic controlled-release preparations of nifedipine are not equivalent to the branded drug, even though the current guideline regards these preparations as similar. Thus, Adalat CR[®] is difficult to evaluate for bioequivalence using the criteria in the current guideline.

Generic drugs are the same as the brand-name drug in distribution, metabolism, excretion after absorption, but different in dissolution profiles.

For specific dosage forms such as controlled-release preparations, we may need to establish new evaluation criteria and test methods. These should consider the dissolution rate and dissolution profile in detail based on the characteristics of each individual preparation and the background of its development.

The other problem that arises is differences of the manufacturing process and additives. According to the current guideline, if the active ingredient and the dose are the same as those of a branded drug, the manufacturing process and additives of the generic drug do not have to be the same. Therefore, the stability, solubility, and absorption of two preparations may not be the same, and such differences could have an influence on safety. Although solubility and absorption are examined by the dissolution test and assessment of bioequivalence, there is not enough evaluation of differences in safety related to use of differing additives. In this study, insoluble matter remained after Generic B tablets had dissolved, and this was not found in the case of the branded drug. Further examination may be necessary to determine the long-term influence of such residue. To assess stability, worst-case tests in open containers are demanded for branded drugs, but only an accelerated test is required for generic drugs at the time of application.

Recently, single-dose packing of tablets and capsules has become a trend, particularly to improve the compliance of elderly patients and prevent incorrect drug ingestion. Furthermore, the duration of prescription has increased in Japan since the Ministry of Health, Labour and Welfare abolished the limit on long-term prescriptions in 2002. In this situation, it could be a problem if the stability of generic drugs is not as good as that of branded drugs. For example, nifedipine has a problem with stability to light and it is readily degraded by exposure to light. However, the information provided by some generic companies is only the results of an accelerated test for their preparation. We think that generic drugs with active ingredients that are easily degraded, such as an ester or an amide with a secondary amine, should be evaluated by criteria similar to those for branded drugs.

Generic drugs are produced at a low cost and their development process and approval examinations are

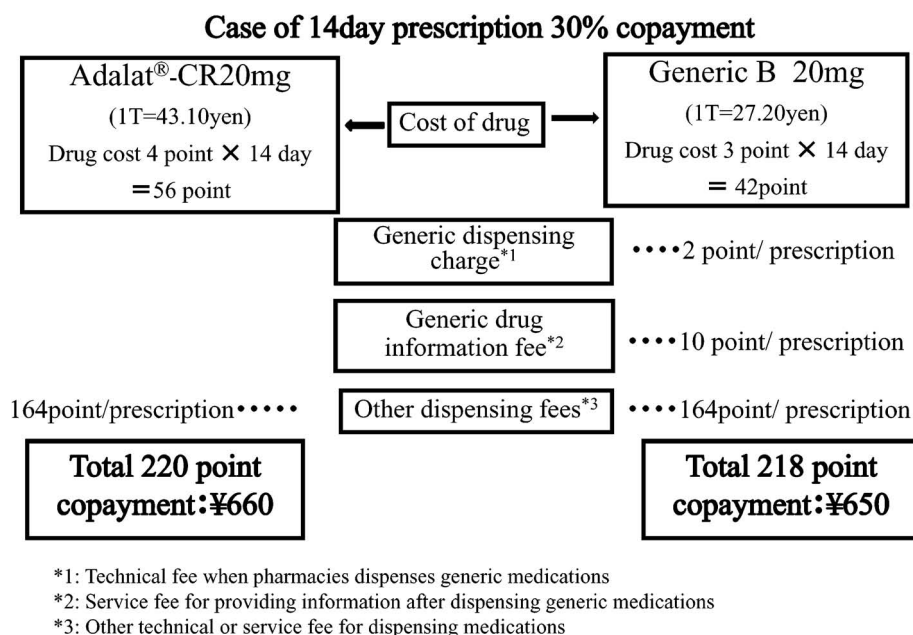


Fig. 5 Comparison of Drug Costs for the Patient

*1: Technical fee when pharmacies dispense generic medications. *2: Service fee for providing information after dispensing generic medications. *3: Other technical or service fees for dispensing medications.

simplified. A merit of generic drugs is expected to be that medical costs will be reduced. Recently, advertising has claimed that generic drugs can reduce the individual patient copayment for medical expenses, but this sometimes makes the patient awaken excessive expectations. If the copayment is not reduced by as much as expected at hospitals and pharmacies, patients often make complaints.

Figure 5 shows the individual patient copayment required at a health insurance pharmacy when different once-a-day controlled release preparations of nifedipine are prescribed for two weeks. Actually, the difference of the individual copayment for the patient is only 10 yen when the generic drug reporting charge (ten points) and generic drug prescribing charge (two points) are added. Patients do not understand such dispensing fees and can be dissatisfied because they have large expectations about the decrease of their individual copayment. The copayment may decrease by several thousand yen for a generic drug if the National Health Insurance price of a brand-name drug is high, but there are also cases where there is little difference when the National Health Insurance price is already reduced. Accordingly, we think that it may be necessary to calculate the individual copayment when we use generic drugs in the future, and that it is important for doctors and pharmacists to make a

careful decision about whether a slight difference such as that in the present case (10 yen) is really of benefit to the patient.

We do not deny that promoting generic drugs may help to slow the increase of medical expenses and we think that such drugs will be used more widely in the future. However, it is essential to contribute to medical economics without reducing the quality of medications (safety/bioavailability) provided to the patient.

To promote the uptake of generic drugs, establishment of more appropriate evaluation criteria and test methods is necessary, and we must overcome current anxiety about the quality of generics. Because such methods have not been established, pharmacists should evaluate each drug appropriately and make a careful selection.

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