—Regular Articles—

Evaluation of the Method for Nifedipine Administration for a Rapid Onset of Clinical Effect: A Clinical Study in Normal Volunteers

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Nifedipine is frequently used for patients who require an immediate reduction of blood pressure elevated temporarily by various administration techniques including sublingual route without administrating intravenous infusion of vasodilator. A cross-over clinical study was conducted to investigate the optimal administration metho of nifedipine for rapid management of hypertension. Four method of administering 10 mg nifedipine (the capsule was bitten and swallowed, sublingually with a hole in it or the contents administered orally or intranasally with a syringe) were evaluated with regarded efficacy, safety, and usefulness in 6 normal volunteers. Systolic and diastolic blood pressures were correlated with the nifedipine serum concentration in each method. Nifedipine pharmacokinetic parameters differed among the 4 administration methods. Nifedipine was absorbed rapidly by not only intestinal mucosa but also the nasal or oral mucosa. The pharmacological effect of intranasal or sublingual administration was superior. However, mint oil which is present in nifedipine capsules stimulates nasal mucosa when administered intranasally. For clinical usage, nifedipine capsules in which a hole is made with a needle, administered sublingually, can be effectively and safely used for rapid management of systemic hypertension.

Key words——nifedipine; hypertension; sublingually; pharmacokinetics

INTRODUCTION

Nifedipine, a calcium channel blocking agent, is frequently used for the treatment of angina pectoris and hypertension. It is administered by various methods especially for pseudoemergency control of sudden and temporal increases in the blood pressure in Japan and European countries[1] although Grossman et al.[2] reported that sublingual administration of nifedipine might produce serious adverse effects. Although a method for administration of nifedipine for pseudoemergency antihypertensive treatment is described in the package insert of nifedipine products in Japan or some countries, it is actually administered by various techniques according to the custom of the ward or the judgment of the nurses while their effectiveness or safety remains unclear. A questionnaire survey of major medical institutions in Japan that we conducted revealed that the contents of capsule preparations have been administered sublingually or intranasally and that there are a number of problems with these administration methods; e.g., the dose is unsteady as the contents of a capsule are aspirated with a syringe, and the maneuver of puncturing the capsule using an injection needle is dangerous.[3]

We carried out a clinical study of 4 methods of administration of the contents of nifedipine capsules frequently employed clinically to obtain a rapid reduction of elevated blood pressure in healthy adults. By evaluating the antihypertensive effect, pharmacokinetics, safety, and convenience of administration, we recommend an optimal method for nifedipine administration for pseudoemergency treatment.

METHODS

1. Preparation Lemar® (Kyorin Pharmaceutical Co., Ltd.) 10 mg soft capsules were used as a nifedipine preparation.

2. Subjects The subjects were 6 healthy adult volunteers (4 males and 2 females) with a mean age of 25.3 years. Following approval of institutional ethical committee, the purpose of the study, nature of the test drug, testing methods, and expected side effects were explained to the subjects in advance orally and in writing, and their written consent was obtained. The subjects were selected according to the following criteria. (1) The subjects could participate in all 4 clinical studies. However, the subjects could at any time drop out from the study by their will. (2)

They are healthy individuals who had no disease, or past history of disease, of major organs including the heart, kidney, and liver.

3. Administration Methods Four methods of nifedipine administration commonly employed clinically in expectation of a rapid antihypertensive effect were selected.

A: The contents of a capsule aspirated with a syringe is orally swallowed.

B: A hole is made in a capsule, and the capsule is placed sublingually until it dissolves spontaneously.

C: A capsule is broken by biting before it is swallowed (the method indicated in the package insert as a method that produces a rapid onset of action).

D: The contents of a capsule aspirated in a syringe are administered intranasally.

4. Dose Ten milligrams of nifedipine contained in 1 capsule was administered. However, 8.12 $\pm$0.32 mg (Mean$\pm$SD, $n=6$) was administered actually in administration A and D because it was unable to withdraw 100% of the liquid contents from a capsule with a needle and syringe.

5. Testing Methods A four-way cross-over study was performed with washout intervals of 2—3 weeks. The subjects were prohibited from taking any medication within 1 week before the test and administered the test drug after a 10-hour fast including abstention from alcoholic beverages. Clinical laboratory tests were performed before and after each test, and the absence of abnormalities in the blood profile, renal function, or hepatic function was confirmed. On the day of the test, all subjects were given the same meal (lunch).

6. Blood Sampling Blood samples were obtained at 13 points before and after (5, 10, 15, 20, 30, 45, 60, 90, 120, 240, 360, and 480 min) the nifedipine administration, and the nifedipine concentration was measured. A heparin-locked indwelling needle was used until 120 min after the administration, and 5 ml of venous blood was collected at each point from the brachial vein. The samples obtained were placed in brown test tubes with aluminum foil covers, and were centrifuged (3,000 rpm, 20 min) promptly. The serum obtained was stored by freezing at -20℃ until analysis.

7. Observation Items The blood pressure (systolic, diastolic) and heart rate were measured before and every 5 min until 180 min after the administration and every 30 min thereafter until after 480 min. A household-use automatic sphygmomanometer (Omron HEM-703CP®, oscillometric method) was used for the measurements.

Subjective symptoms and side effects were examined by the interviews of physician with the subjects and observation of changes in their condition (blush, perspiration, etc.).

8. Method for the Measurement of Serum Nifedipine Concentration The external standard method of high-performance liquid chromatography published by Miyazaki et al.[4,5] was evaluated, and analytical conditions were adjusted.

One milliliter of serum was mixed with 100 μl of methanol and 3 ml of acetonitrile, agitated with a vortex mixer, and centrifuged (3,000 rpm, 10 min), and serum was collected. Three milliliters of the serum was poured into a brown test tube containing 1 ml of distilled water, and 4.5 ml of a mixture of acetone and chloroform (1 : 1) was added. After the contents of the test tube were shaken and centrifuged for 10 min (3,000 rpm), the aqueous layer was removed, 5 ml of the organic layer was transferred to another brown test tube, and condensed to dryness in a centrifugal evaporator (VC-36, Taiyo Kagaku; heated to 45℃) over about 1 hour. The residue was dissolved with 100 μl of an external standard solution (**Butanben** 2 μg/ml), the solution was filtered, and 20 μl of the filtrate was injected into the HPLC system. All these methods were performed under subdued light.

A LC-6A HPLC system (Shimadzu) and a SPD-6A UV detector (Shimadzu) were used. The analysis and assay of nifedipine were performed by warming the ODS reversed phase column (5C-18C, BENSIL; ϕ4.6$\times$150 mm) to 47℃ in a column oven (CTO-6A, Shimadzu).

The mobile phase was a mixture of 0.01 M disodium hydrogen phosphate buffer (pH 6.1) and methanol (52 : 48). The flow rate was 0.8 ml/min, the detection wavelength was 238 nm, and the detection sensitivity was adjusted to 0.0025 a.u.f.s.

For preparation of a calibration curve, standard nifedipine solutions in methanol were prepared at 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 μg/ml. To drug-free serum, 100 μl each of the standard solutions was added instead of 100 μl of methanol, the mixtures were pretreated similarly to the samples, and a calibration curve was prepared. After the linearity of

the calibration curve was confirmed, the samples were assayed by the two-point calibration line method using the 0.4 and 0.6 μg/ml nifedipine standard solutions.

9. Analytical Methods For calculation of the values of pharmacokinetic parameters after the administration, analysis was performed by applying the data of serum concentration to a curve by the Simplex Method (non-linear least squares method), using the program of Pharmacokinetics Analysis and Graphics for Clinical Pharmacology (PAG-CP®)[6] developed by Takebe et al. The analysis was performed using the zero release of an oral administration 2-compartment model but using an oral administration, discontinuous absorption, 2-compartment model for administration method D (intranasal administration).

10. Statistical Analysis Statistical analysis was performed by student paired *t*-test. The relationships between the mean nifedipine concentration and the mean systolic blood pressure (SBP) or the mean diastolic blood pressure (DBP) were analyzed by correlation analysis. Pharmacokinetics parameters were analyzed by ANOVA using Fisher PSLD. $p<0.05$ was considered to be significant in all tests.

RESULTS

1. Serum Nifedipine Concentration Linear regression analysis gave calibration curves with coefficient or correlation of 0.9991 ($p<0.01$) for nifedipine (0—1.0 μg/ml). Assays for within-run and day-to-day reproducibility gave coefficients of variation of 4.41% ($n=6$) and 21.46% ($n=6$), respectively, at concentrations of 0.6 μg/ml. The detection limit for quantification of this assay method was 5 ng/ml.

2. Changes in the Serum Nifedipine Concentration and Blood Pressure Figure 1 shows changes in the mean serum nifedipine concentration and blood pressure (systolic, diastolic) in the 6 subjects by administration method A, B, C, D until after 480 min. As the serum nifedipine concentration increased, SBP and DBP decreased in parallel, indicating a correlation between the serum nifedipine con-

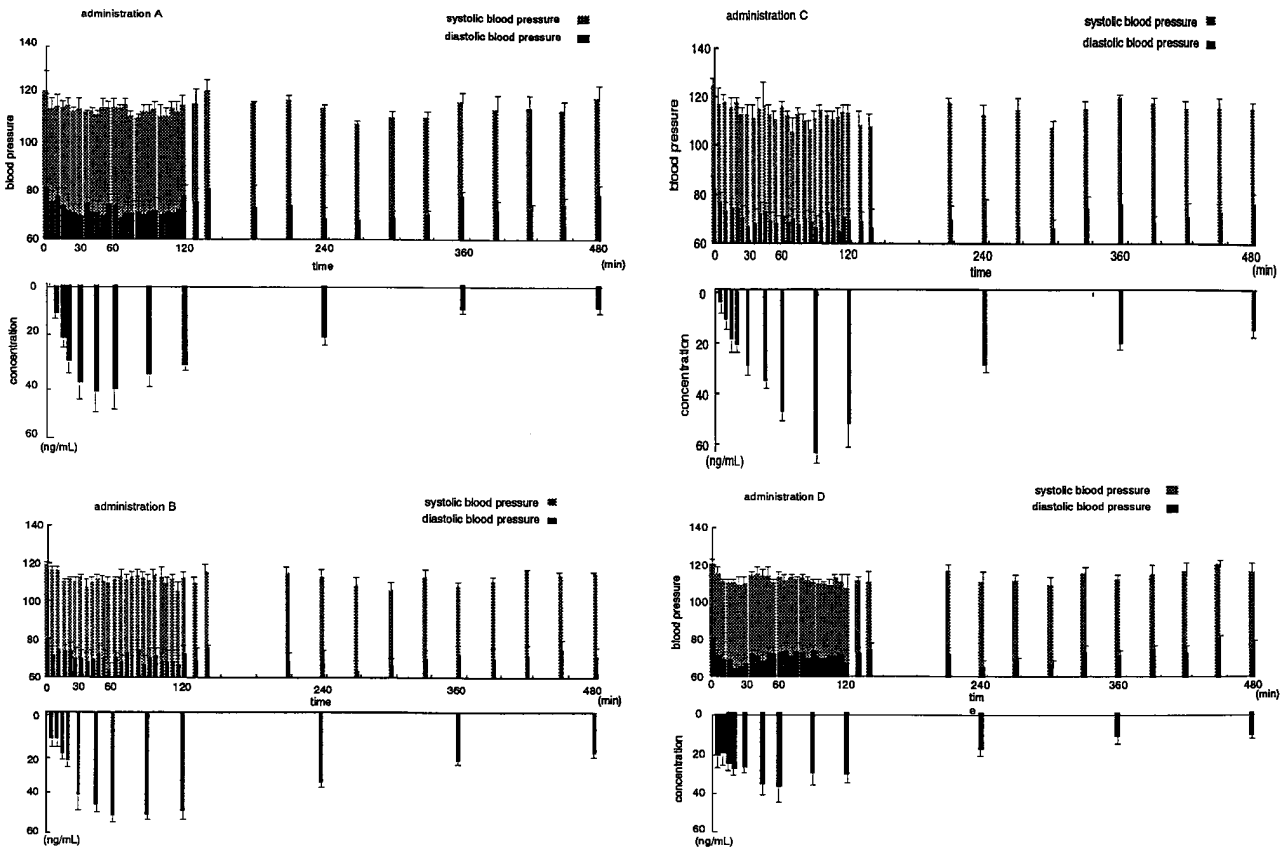

Fig. 1. Correlation of Serum Nifedipine Concentration with Systolic and Diastolic Blood Pressure in Six Normal Subjects after Administration of 10 mg Nifedipine
(Mean ± SE, $n=6$).

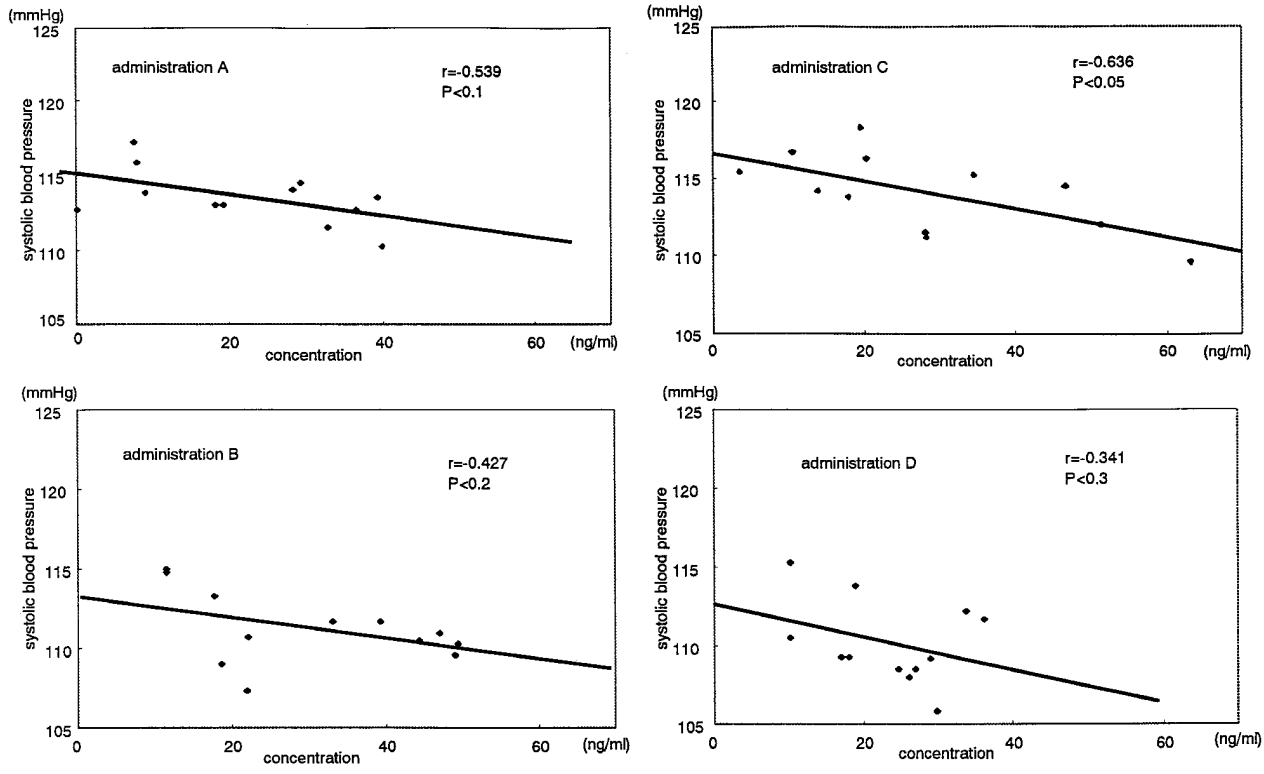

Fig. 2. Relationship between Nifedipine Serum Concentration and Systolic Blood Pressure after Administration of 10 mg Nifedipine
Values are mean for six normal subjects.

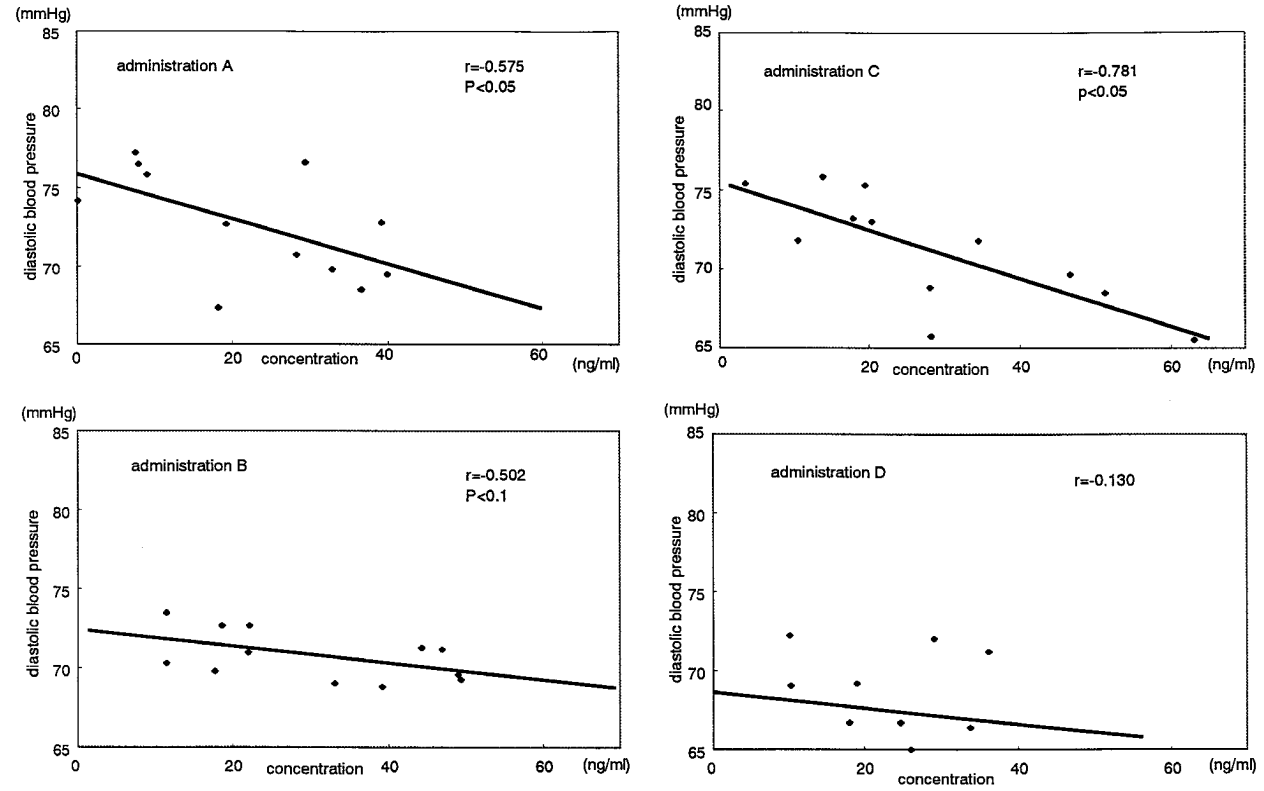

Fig. 3. Relationship between Nifedipine Serum Concentration and Diastolic Blood Pressure after Administration of 10 mg Nifedipine
Values are mean for six normal subjects.

centration and the antihypertensive effect in each administration method. The correlation coefficients between the mean serum nifedipine concentration and the mean SBP and between the mean serum nifedipine concentration and the mean DBP in the 6 subjects were calculated by each administration method. The correlation coefficient between the nifedipine concentration and SBP was -0.539, and that between the nifedipine concentration and DBP was -0.575 ($p<0.05$), by method A. They were -0.427 and -0.502, respectively, by method B, -0.636 ($p<0.05$) and -0.781 ($p<0.05$), respectively, by method C, and -0.341 and -0.130, respectively, by method D (Figs. 2, 3).

3. Pharmacokinetics of Nifedipine Figure 4 shows changes in the serum nifedipine concentration in 6 normal subjects by various administration methods. Differences were observed in changes in the serum concentration (e.g. the pattern of changes until the peak concentration was reached and the duration of the peak concentration) among the 4 administration methods.

Table 1 shows the values of pharmacokinetic parameters obtained by the analysis of the mean serum nifedipine concentration in the 6 subjects by each administration method. The area under the serum nifedipine concentration curve ($AUC_{0-\infty}$) was 177.1 $\pm$88.6 hr·ng/ml (mean$\pm$SE) by method A, being smaller ($p<0.05$) than by method B. The peak serum concentration (C_{max}) and the time until the peak serum concentration (T_{max}) also tended to be vary among the administration methods. C_{max} was highest at 65.0$\pm$10.2 ng/ml by method C and lowest at 42.9 $\pm$5.6 ng/ml by method D (intranasal administration). T_{max} was shortest at 55.7$\pm$12.3 min by method D but slowest at 81.9$\pm$12.0 min by method C. The values of elimination half-life ($T_{1/2\beta}$) and total cleasance (Clt) were in agreement with the values in the literature.

Figure 5 shows changes in the mean serum nifedipine concentration in the 6 subjects until 30 min after the administration by the 4 methods. The mean

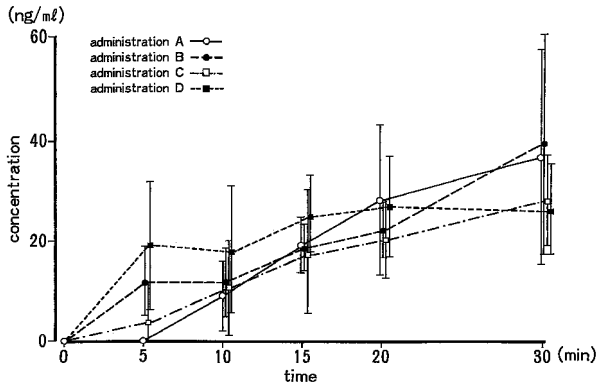

Fig. 4. Serum Nifedipine Concentration in Six Normal Subjects after Administration of 10 mg Nifedipine
(Mean$\pm$SE) The data of serum concentration was applied to a curve by the Simplex Method (non-linear least squares method).

Table 1. Pharmacokinetic Parameters after Administration of 10 mg Nifedipine in Each Administration Method

Parameters	Administration			
	A	B	C	D
$AUC_{0-\infty}$ (hr · ng/ml)	177.1 $\pm$88.6	434.0 $\pm$96.7	343.9 $\pm$55.9	211.3 $\pm$48.9
C_{max} (ng/ml)	50.5 $\pm$10.1	61.8 $\pm$ 5.4	65.0 $\pm$10.2	42.9 $\pm$ 5.6
T_{max} (min)	64.2 $\pm$13.5	77.8 $\pm$14.4	81.9 $\pm$12.0	55.7 $\pm$12.3
K_a (hr^{-1})	30.6 $\pm$11.5	144.0 $\pm$67.1	16.8 $\pm$ 6.2	163.8 $\pm$42.1
$T_{1/2\beta}$ (hr)	2.9 $\pm$ 0.7	5.2 $\pm$ 1.6	4.6 $\pm$ 0.8	5.8 $\pm$ 1.6
V_{dss}/F (l)	204.1 $\pm$41.3	166.5 $\pm$21.6	183.5 $\pm$27.6	294.5 $\pm$44.6
K_{el} (hr^{-1})	1.62$\pm$ 1.07	3.12$\pm$ 1.89	0.72$\pm$ 0.27	3.07$\pm$ 1.69
Clt (l/hr)	69.0 $\pm$14.2	27.6 $\pm$ 3.5	33.0 $\pm$ 5.1	47.0 $\pm$11.0

* $p<0.05$; **: $p<0.01$ obtained from a comparison between the four administrations by ANOVA. (Mean$\pm$SE, $n=6$)

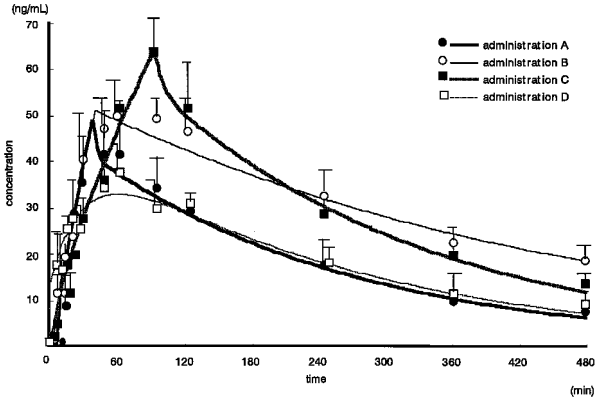

Fig. 5. Serum Nifedipine Concentration in the First 30 min (Mean±SD, $n=6$)

serum concentration at 5 min was highest at 18.92± 12.84 ng/ml (mean±SD) by method D, showing the most rapid increase among the 4 methods, and remained highest until after 15 min. Following method D, the 5-min value was 11.46±6.71 ng/ml by method B, but the subsequent increase was gradual. At 5 min, which was the first point of measurement, the serum nifedipine concentration showed significant differences ($p<0.05$) by methods D and B compared with method A, indicating rapid increases in the serum concentration by these two methods.

4. Serum Nifedipine Concentration and Antihypertensive Effect Figure 6 shows changes in the mean serum concentration, SBP, and DBP in the subjects until 30 min after the administration. The blood pressure was expressed as the difference in the value at each point of measurement compared with the value before the administration. SBP and DBP decreased with the increases in the serum nifedipine concentration by each administration method. The differences in the DBP among the administration methods were particularly notable. The serum concentration was highest until after 15 min by method D, the DBP also decreased significantly ($p<0.05$) and most notably among the 4 methods after 5—30 min after the administration. By method B, by which the increase in the serum concentration was the most rapid next only to method D, DBP at 5 min was $\Delta=-7.2\pm9.8$ mmHg, but its decreases until after 25 min were not significant.

Figure 7 shows serial changes in the mean serum nifedipine concentration and DBP (difference compared with the value before the administration: ΔDBP) in the 6 subjects by the administration

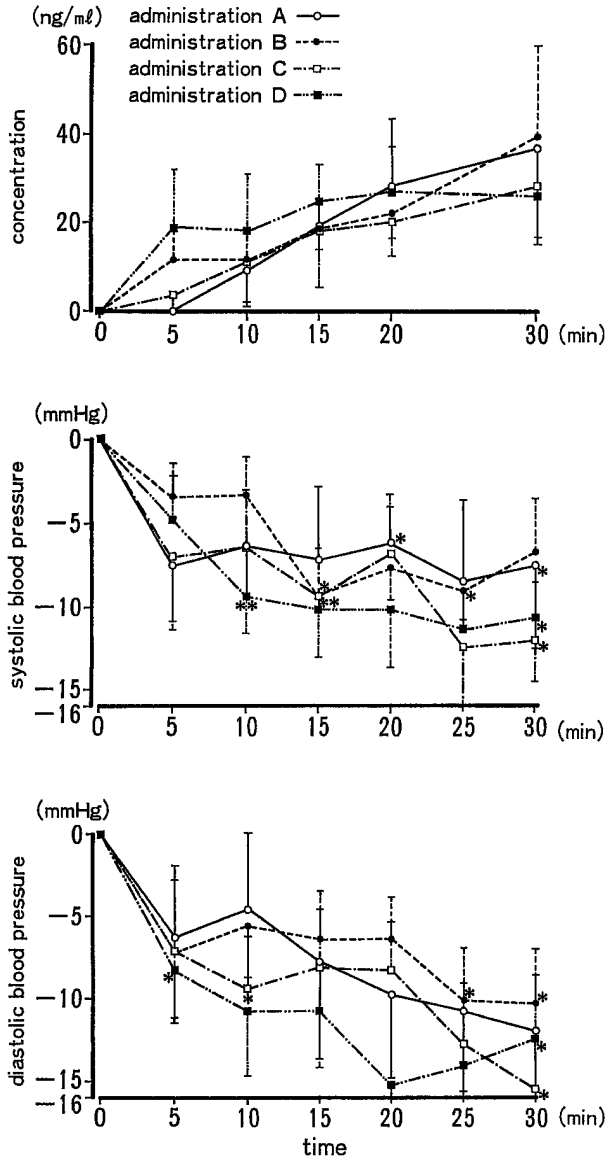

Fig. 6. Mean Serum Nifedipine Concentration and Mean Change in Blood Pressure in the First 30 min

*Significant at $p<0.05$, **Significant at $p<0.01$, The first and last values significantly different from baseline are indicated.

methods. Concerning the relationship between the serum concentration and ΔDBP at 5 min, which reflects the quickness of the onset of the antihypertensive effect, they were both greatest at 18.92 ng/ml and −8.3 mmHg, respectively, by method D, followed by 11.46 ng/ml and −6.3 mmHg, respectively, by method B.

The heart rate, examined as a parameter of the effect, showed no significant or notable change by any administration method.

5. Side Effects Some subjects complained of mild headache, a heavy feeling of the head, blush,

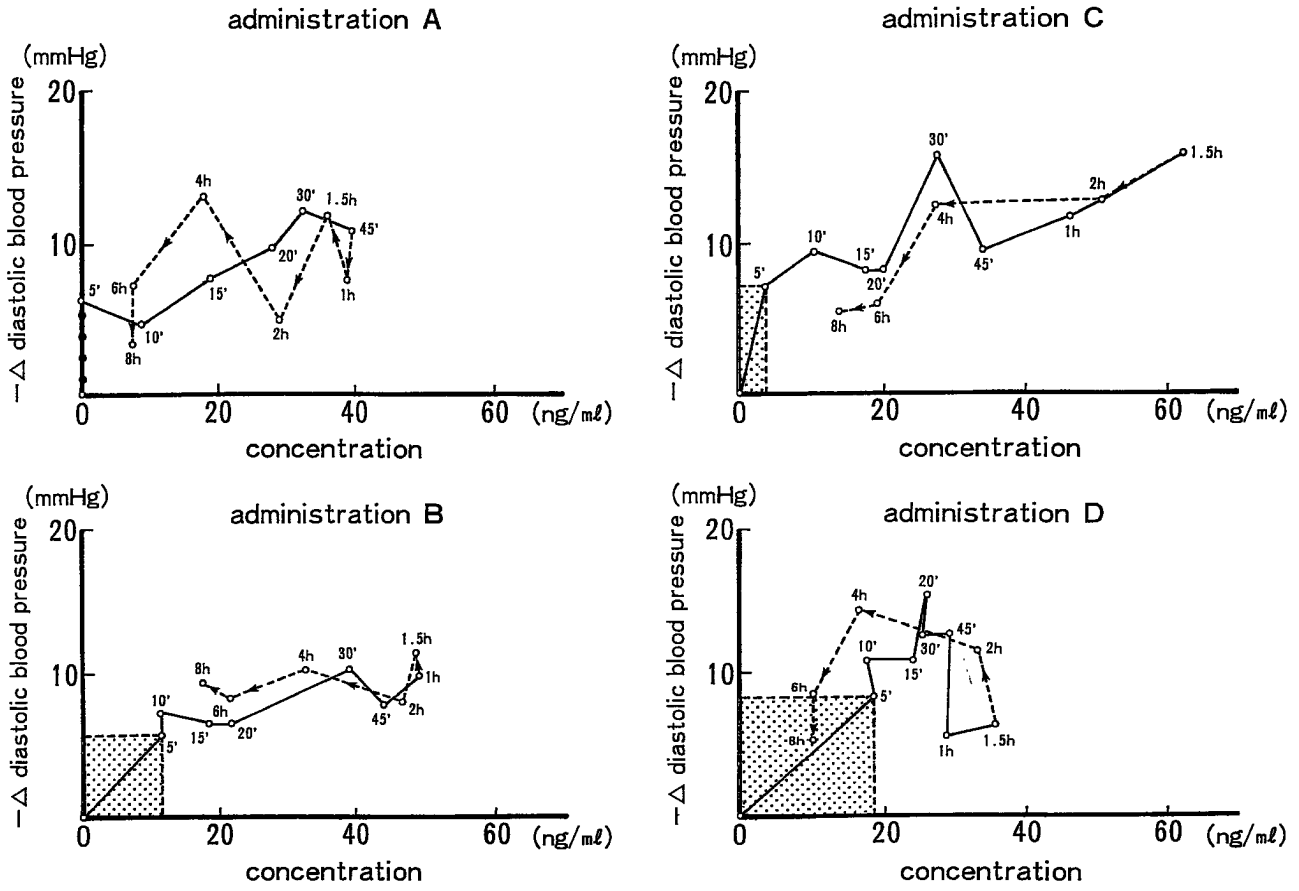

Fig. 7. Correlation between Mean Change in Diastolic Blood Pressure and Serum Nifedipine Concentration at Each Time
Points are connected in order of time after nifedipine administration.

and a hot feeling during the test, but these symptoms were resolved within 2 hours after the end of the test. No serious side effects were observed.

DISCUSSION

Nifedipine is administered to obtain a rapid reduction of elevated suddenly and temporarily blood pressure for inpatients or hypertensive pseudoemergencies such as unstable hypertension, angina pectoris, or hypertension after surgery.[7—11] The "Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" recognize that parenteral drugs for treatment of hypertensive emergencies are vasodilators, such as sodium nitroprusside and nitroglycerin.[12] Grossman et al.[2] reported that sublingual nifedipine capsule given for hypertensive emergencies might produce severe adverse effects such as cerebrovascular ischemia, stroke, hypotension, acute myocardial infarction and death. However, nifedipine is still widely used for treatment of emergency, especially pseudoemergency hypertension, because it has been said that it has rarely induced excessive hypotension and has had no serious side effects.[13]

Brown et al.[14] compared sublingual administration of nifedipine with oral administration and reported that the increase in the serum nifedipine concentration was more rapid by the sublingual administration. On the other hand, there have been reports that nifedipine was not almost absorbed through the oral mucosa, and sublingual nifedipine was not effective.[15,16] It was reported that intranasal administration of nifedipine was also effective[17] although the intranasal absorption was not inspected sufficiently. Comparative studies of changes in the serum nifedipine concentration and differences in the antihypertensive effect among oral administration and various types of sublingual administration have been carried out to date, but contradicting results have been reported. Additionally, comparative studies of sublingual and intranasal administration have not been reported.

Aoki et al.[18—20] reported that the serum nifedipine concentration correlated closely with the blood pressure in patients with hypertension orally administered nifedipine. Nifedipine usually shows no marked antihypertensive effect in normal individuals, because the diastaltic sympathicotonia through pressoreceptor with decreases of peripheral arterial resistance induces the increases of heart rate, and prevents blood pressure decreases.[20] However, there have been reports[21—28] that nifedipine significantly reduced the blood pressure by oral and sublingual administration and that the serum nifedipine concentration was correlated with the antihypertensive effect in normal individuals. In our study, also, the serum concentration was correlated with blood pressure, especially DBP, by each administration method. The serum concentration of nifedipine has been reported to be correlated more closely with DBP than with SBP.[18] Thus, the serum concentration and blood pressure are parameters useful for efficacy evaluation. Changes in the serum concentration of nifedipine are considered to be useful information for the judgment of its antihypertensive effect particularly in normal individuals.

Changes in the serum nifedipine concentration and blood pressure until 30 min after the administration also differed according to the administration method. By method D, by which the serum nifedipine concentration 5 min after the administration was highest among the 4 methods, DBP showed significant and largest decreases from after 5 min. DBP decreased after 5 min also by method B, by which the increase after the administration was the fastest next only to method D. The changes in heart rates were not observed because blood pressure decreased significantly though the degree of antihypertensive effect was low. From the serum concentration and antihypertensive effect 5 min after the administration, the method D is expected to produce the most rapid onset of the antihypertensive effect, followed by method B.

It was reported that nifedipine was not absorbed sufficiently through the oral mucosa, however, it was indicated that nifedipine was absorbed partly through the oral and nasal mucosa in this study. According to Waller et al.,[29] nifedipine is likely to undergo first-pass metabolism in the gastrointestinal wall. Also, the drug concentration and absorption rate at the absorption site are estimated to vary according to the administration method.

By method A, *i.e.* swallowing the contents of the capsule aspirated with a syringe, the drug directly reaches the absorption site in the gastrointestinal tract. However, there is a time lag until the beginning of absorption, and the drug may be affected by first-pass metabolism in the gastrointestinal tract. Moreover, the dose is uncertain, because the small contents of the capsule is aspirated with a syringe.

By method C, the capsule was swallowed after breaking it by biting. Therefore, absorption of nifedipine through the oral mucosa is expected, but absorption begins mostly after the drug reaches the gastrointestinal tract. Therefore, the time lag until the beginning of absorption is large, and the drug is liable to first-pass metabolism. These factors are considered to have been involved together in the low nifedipine concentration in the initial phase. Furthermore, some nifedipine soft capsule products are relatively hard and difficult to break by biting. Therefore, the administration by this method is considered to be difficult in such patients as those exhibiting acute symptoms of myocardial infarction, those with reduced level of consciousness, and elderly patients.

Nifedipine absorbed through the oral mucosa or nasal mucosa enters the systemic circulation without passing the portal system so that it escapes first-pass metabolism. Also, in mucosal absorption, the absorption rate is generally considered to be fast. These are considered to be reasons for the rapid increase in the serum nifedipine concentration in the initial phase by administration methods B and D.

By method D, *i.e.* intranasal administration, the actual dose tends to be unsteady, and the bioavailability is low. Also, the drug is retained in the nasal cavity and is absorbed through the mucosa, but part of it flows into the gastrointestinal tract via the internal nares and pharynx. Therefore, the serum nifedipine concentration shows several peaks, and the whole pharmacokinetics is unclear. The results of this study suggest that the increase in the serum concentration early after the administration and the effect of a reduction in blood pressure were the best by this method among the 4 methods. However, the greatest problem with intranasal administration of nifedipine using currently available commercial preparations is irritation of the nasal mucosa by the mint oil compounded as a corrigent, which causes great discomfort to patients.

By method B, *i.e.* making a needle hole in the

capsule and placing the capsule sublingually, which showed the most rapid increase in the serum nifedipine concentration next only to method D, the drug flows out gradually from the capsule placed sublingually and is absorbed partly through the oral mucosa but is also considered to be absorbed partly through the gastrointestinal tract. Also, the method is advantageous for sustaining a stable serum concentration, because absorption progresses gradually so that frequent repetition of administration may be avoided. However, there is the risk of injuring the fingers during puncture of the capsule with a needle.

From the pharmacokinetics, the effect of a reduction in blood pressure, safety and ease of administration, sublingual administration of a capsule preparation after making a needle hole is considered to be clinically the most recommendable for the administration of nifedipine to obtain a rapid onset of effect. Close clinical monitoring is indicated until 30 min after administration of nifedipine. However, the development of dosage forms and preparations catering to clinical needs and evaluation of safer and more effective administration methods are considered to be necessary.

REFERENCES

1) Hart L. L., Mowers R. M., *Drug Intell. Clin. Pharm.*, **21**, 432–433 (1987).
2) Grossman D., Messerli F. H., Grodzicki T., Kowey P., *JAMA*, **276**, 1328–1331 (1996).
3) Kubota R., Kumazawa J., Komiyama T., *JJSHP*, **34**, 1341–1346 (1998).
4) Miyazaki K., Kohri N., Arita T., *J. Chromatogr.*, **310**, 219–222 (1984).
5) Kohri N., Miyazaki K., Arita T., Shimono H., Nomura A., Yasuda H., *Chem. Pharm. Ball.*, **35**, 2504–2509 (1987).
6) Takebe M., Azuma J., Yafune A., Tei S., Kishimoto S., *Jpn. J. Clin. Pharmacol. Ther.*, **20**, 139–140 (1989).
7) Beer N., Gallegos I., Cohen A., Klein N., Sonnenblick E., Frishman W., *Chest*, **79**, 571–574 (1981).
8) Ellrodt A. G., Ault M. J., Riedinger M. S., Murata G. H., *Am. J. Med.*, **79**, 19–25 (1985).
9) Abraham G., Shukkur A., van der Meulen J., Johny K. V., *Br. J. Clin. Pract.*, **40**, 478–481 (1986).
10) Haft J. I., Litterer III W. E., *Arch. Intern. Med.*, **144**, 2357–2359 (1984).
11) Krichbaum D. W., Malone P. M., *Drug Intell. Clin. Pharm.*, **22**, 891–892 (1988).
12) Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, *Arch. Intern. Med.*, **157**, 2413–2446 (1997).
13) Ferguson R. K., Vlasses P. H., *JAMA*, **255**, 1607–1613 (1986).
14) Brown G. R., Fraser D. G., Castile J. A., Gaudreault P., Platt D. R., Friedman P. A., *Int. J. Clin. Pharmacol. Ther. Toxicol.*, **24**, 283–286 (1986).
15) Mcallister R. G., *Am. J. Med.*, **81**, 2–5 (1986).
16) Van Harten J., Burggraaf K., Danhof M., van Brummelen P., *Lancet*, **2**, 1363–1365 (1987).
17) Lopez-Herce J., Dorao P., Ruza F., de la Oliva P., *Crit. Care. Med.*, **16**, 914 (1988).
18) Aoki K., Sato K., Kawaguchi Y., Yamamoto M., *Eur. J. Clin. Pharmacol.*, **23**, 197–201 (1982).
19) Hanawa K., Kobayashi H., Togashi M., Tsuzuki M., Fujise Y., Iimura O., *Rinsho to Kenkyu*, **59**, 1703–1712 (1982).
20) Kikuchi K., Kobayashi H., Nakao T., Kondo A., Mito T., Tsuzuki M., Iimura O., Fujise Y., Hanawa K., *Jpn. J. Clin. Pharmacol. Ther.*, **13**, 623–637 (1982).
21) Kleinbloesem C. H., van Brummelen P., van de Linde J. A., Voogd P. J., Breimer D. D., *Clin. Pharmacol. Ther.*, **35**, 742–749 (1984).
22) Traube M., Hongo M., McAllister Jr R. G., McCallum R. W., *J. Clin. Pharmacol.*, **25**, 125–129 (1985).
23) Kleinbloesem C. H., van Brummelen P., Breimer D. D., *Clin. Pharmacokinet.*, **12**, 12–29 (1987).
24) Walley T. J., Heagerty A. M., Woods K. L., Pohl J. E., Barnett D. B., *Br. J. Clin. Pharmac.*, **23**, 693–701 (1987).
25) Graefe K. H., Ziegler R., Wingender W., Ramsch K. D., Schmitz H., *Clin. Pharmacol. Ther.*, **43**, 16–22 (1988).
26) Holford N. H., Sheiner L. B., *Clin. Pharmacokinet.*, **6**, 429–453 (1981).
27) Kleinbloesem C. H., van Brummelen P., Danhof M., *Clin. Pharmacol. Ther.*, **41**, 26–30

(1987).
28) Kleinbloesem C. H., van Harten J., de Leede L. G. J., van Brummelen P., Breimer D. D., *Clin. Pharmacol. Ther.*, **36**, 396–401 (1984).
29) Waller D. G., Renwick A. G., Gruchy B. S., George C. F., *Br. J. Clin. Pharmac.*, **18**, 951–954 (1984).

要旨

一時的な血圧上昇を来した患者に対して直ちに降圧作用を期待する場合には，血管拡張薬の注射剤が投与されることは少なく，ニフェジピンが舌下投与をはじめとする様々な方法で投与されている．今回，繁用されている4種類の投与方法（カプセルをかみ砕いて飲み込む，カプセルに穴をあけて舌下に保持する，カプセル内容液をシリンジで抜き取り飲み込む，シリンジを使用して点鼻投与する）の有効性と安全性，使用性を評価するため，6名の健康成人についてクロスオーバー臨床試験を実施し，即効性を期待する時のニフェジピン最適投与方法を検討した．各投与方法において，収縮期血圧と拡張期血圧は，ニフェジピンの血中濃度と相関性を示した．またニフェジピンの薬物動態は4種類の投与方法によって異なり，消化管からの吸収ばかりでなく，口腔粘膜や鼻粘膜からの吸収も速やかであった．降圧作用も点鼻投与，舌下投与で優れていた．しかし点鼻投与は，カプセル内に添加されているハッカ油が鼻粘膜を刺激する．迅速な降圧作用を期待する時の臨床使用には，カプセルに1箇所穴を開けて舌下投与する方法が，即効性と簡便において最も適していた．