STUDIES ON SUSTAINED-RELEASE DOSAGE FORMS : IV. PHARMACOKINETICS AFTER RECTAL ADMINISTRATION OF NIFEDIPINE SUPPOSITORIES IN RABBITS

KURODA, TSUTOMU

(Citation)
The Kobe journal of the medical sciences,31(3):117-131

(Issue Date)
1985-06

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

Kobe J. Med. Sci. 31, 117/131, June 1985

STUDIES ON SUSTAINED-RELEASE DOSAGE FORMS. IV. PHARMACOKINETICS AFTER RECTAL ADMINISTRATION OF NIFEDIPINE SUPPOSITORIES IN RABBITS

TSUTOMU KURODA*, TERUYOSHI YOKOYAMA**, TSUNEO UMEDA**, NORIAKI OHNISHI**, KOJI KURODA**, AND SHOZO ASADA***

*Pharmacy, Miki City Hospital
Kasa, Miki City, Hyogo 673-04, Japan

**Hospital Pharmacy
Kobe University School of Medicine

***Kobe Women's College of Pharmacy
Motoyamakitamachi, Higashinada-ku, Kobe 658, Japan

INDEXING WORDS

nifedipine; pharmacokinetic analysis; compartment model; statistical moment analysis; sustained-release suppository

SYNOPSIS

The pharmacokinetics of nifedipine after intravenous injection and rectal administration of conventional suppositories and of sustained-release suppositories in rabbits were evaluated, based on the compartment model and statistical moment method. The plasma concentration-time curves following intravenous administration were described by a two-compartment model. The half-life of elimination phase was relatively short ($t_{1/2\beta}$ = 0.682 hr). Rectal absorption from the conventional suppository dosage form was rapid and the elimination from body was more rapid. The extent of bioavailability of three dose levels was about 62 - 80% on the average. After administration of sustained-release

Received for publication : May 27, 1985
Authors' names in Japanese : 黒田 勤・横山照由・梅田常雄
大西憲明・黒田耕司・浅田昌三

suppositories, the pharmacokinetic parameters were calculated using an equation which included three or four exponential function consistent with a two-compartment model. The apparent absorption rate (k_a) of this dosage form was smaller than that of the conventional suppository, and the sustained effect was apparently attributed to the slow absorption process.

From the results of the statistical moment analysis, it was found that the mean absorption time of the sustained-release suppository was about 6 times greater than that of the conventional suppository. That is, the dissolution process with this suppository was the rate-determining step.

INTRODUCTION

Nifedipine (4-(2'-nitrophenyl)-2,6-dimethyl-3,5-dicarbomethoxy-1,4-dihydropyridine) is a calcium ion influx inhibitor and inhibits the membrane influx of calcium ions into cardiac muscle and smooth muscle. Nifedipine (NF) has been useful in treating conditions associated with vascular spasm, including variant angina,[1] Raynaud's phenomenon[4] and hypertension.[8] The plasma concentration of NF after oral administration shows considerable individual variation because of the complexity of intestinal absorption,[2, 5] and the biological half-life of this drug is relatively short.[9] Therefore, it is desired to obtain an expectant plasma concentration and to maintain it for a long time in therapeutic arena. In a previous paper,[10] we developed a double layer suppository which included NF in the outside layer using cellulose acetate phthalate (CAP) - polyethylene glycol (PEG) matrix as a base, and found that this dosage form had sufficient sustained-release effect without producing an excessively high peak level in the plasma.

A few papers about pharmacokinetics after oral administration of NF have appeared.[2, 9] Otherwise no pharmacokinetic analysis after rectal administration of NF has been reported.

In this paper, we carried out pharmacokinetic analysis of NF after intravenous injection and rectal administration of conventional suppositories and of sustained-release suppositories in rabbits by using a compartment model and statistical moment method, and investigated the utility of suppository dosage forms of NF.

MATERIALS AND METHODS

Methods of pharmacokinetic analysis

1. Compartment model method

Kinetic analysis of NF based on the compartment model was carried out a two-compartment open model, as shown in Chart 1.

The time course of drug concentration in plasma after intravenous administration is given as equation (1).

$$C_1 = P(1)e^{-\alpha t} + P(2)e^{-\beta t} \qquad (\alpha>\beta) \qquad (1)$$

(see Appendix I)

The equation for the time course of plasma concentration after administering a conventional suppository is as follows:

$$C_1 = P(1)e^{-\alpha(t-t_0)} + P(2)e^{-\beta(t-t_0)} + P(3)e^{-k_a(t-t_0)} \qquad (\alpha>\beta) \qquad (2)$$

(see Appendix II)

On the other hand, equation (3) was applied for the kinetics after administration of a sustained-release suppository.

$$C_1 = P(1)e^{-\alpha(t-t_0)} + P(2)e^{-\beta(t-t_0)} + P(3)e^{-k_a(t-t_0)} + P(4)e^{k_1(t-t_0)} \qquad (\alpha>\beta) \qquad (3)$$

(see Appendix III)

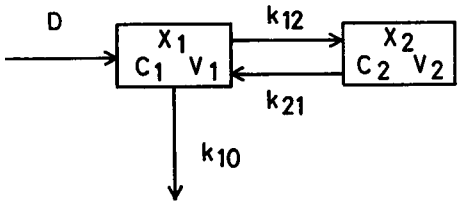
2. Moment analysis method

The statistical moment analysis is a model independent method.[12] The time course of plasma concentration can usually be regarded as a statistical distribution curve. The mean residence time (MRT) and the mean absorption time (MAT) are defined as follows:

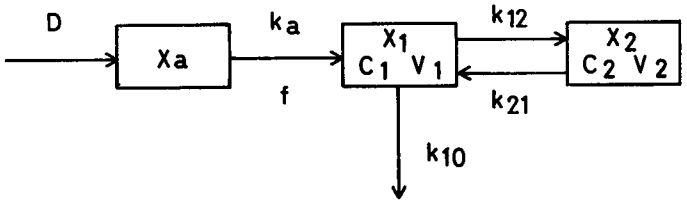
$$MRT = \frac{\int_0^\infty tC_p\,dt}{\int_0^\infty C_p\,dt} = \frac{AUMC}{AUC} \qquad (4)$$

$$MAT = MRT_{supp} - MRT_{iv} \qquad (5)$$

Model A bolus intravenous administration



Model B two-compartment model with first-order absorption



Model C two-compartment model with two consecutive first-order input steps

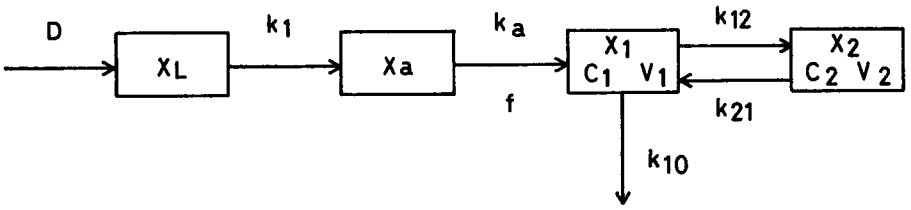


Chart 1 Pharmacokinetic compartment models used for nifedipine. D, dose administered; X_L, amount of drug in dissolution site; X_a, amount of drug in absorption site; X_1, X_2, amounts of drug in central and peripheral compartments; k_1, dissolution rate constant; k_a, absorption rate constant; k_{12}, k_{21}, distribution rate constants; k_{10}, elimination rate constant; C_1, C_2, concentrations of drug in central and peripheral compartments; V_1, V_2, apparent volumes of distribution in central and peripheral compartments; f, fraction of dose absorbed.

The mean dissolution time (MDT) is given as follows:

$$MDT = MAT_{sust.supp} - MAT_{conv.supp} \quad (6)$$

Chart 2 shows the meaning of MRT, MAT and MDT.

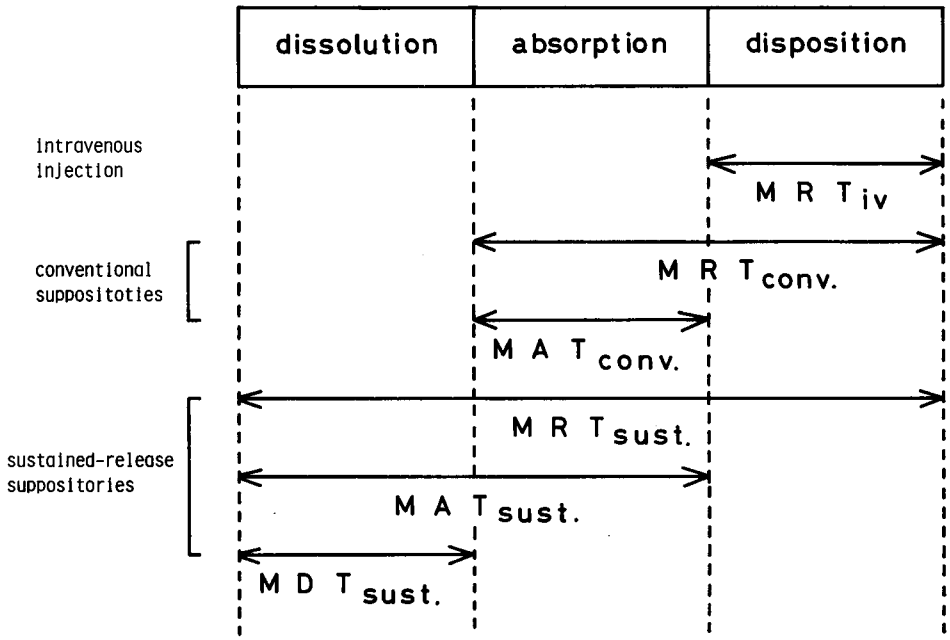


Chart 2 Illustration of the meaning of MRT, MAT and MDT.

Preparation of suppositories

The conventional suppositories were prepared by the fusion method using NF and PEG 4000 as a base. The NF content per suppository was 0.625, 1.25 and 2.5mg, respectively. The double layer suppositories were prepared by using two molds as reported previously.[10] The NF content per suppository was 2.5mg.

Animal experiments

For intravenous administration, white male rabbits weighing from 3.0 to 3.5kg were used. NF (0.625mg/ml) dissolved in 30% PEG 400 solution was intravenously injected and blood samples were taken at the appropriate times. For rectal administration, white male rabbits weighing from 3.0 to 3.5kg were fasted for 36 hr prior to the experiments but allowed free access to water. After

rectal administration, blood samples were drawn through an ear vein at regular intervals. All plasma samples obtained by centrifuging the blood were stored at -5C until assay.

Assay of nifedipine

NF concentration in plasma was assayed by using a gas chromatographic technique with electron-capture detector.[3)]

Data analysis

The computer simulations of plasma concentration by compartment model method were carried out using the SALS program[7)] on an NEAC system 1000 computer in Kobe University Data Processing Center through a TSS terminal and the MULTI program[13)] on an NEC MS-140 at Kobe University School of Medicine.

RESULTS AND DISCUSSION

Plasma concentration after intravenous administration

Fig. 1 shows the semilogarithmic plots of the time course of plasma concentration of NF after intravenous administration. These plots showed a sharp drop, then an abrupt change in slope followed by a very distinct terminal phase: accordingly, the kinetic parameters were calculated using a two compartment model.

The solid line in Fig. 1 shows a nonlinear least-squares regression curve and the estimated parameters are given in Table 1. The values of β were very large, that is, the half-life of NF was relatively short ($t_{1/2\beta}$ = 0.682 hr), as can be seen in Table 1.

Plasma concentration after rectal administration of conventional suppositories

Plasma concentrations after rectal administration of conventional suppositories at three dose levels, 0.625, 1.25 and 2.5mg are shown in Fig. 2. The peak plasma level of NF was reached at 0.5 - 0.75 hr after administration with every dose. The area under the plasma concentration-time curve (AUC) was calculated according to the equation described in the Appendix. As shown in Fig. 3, an increased NF dose resulted in a linear increase in the

Table 1 The results of simultaneous fitting of NF plasma concentration by compartment model method.[a)]

Parameter	i.v.	conventional suppositories			sustained-release suppositories	
					4-exp	3-exp
Dose (mg)	0.625	0.625	1.25	2.5	2.5	
No. of animals	5	5	5	6	7	
B.W. (kg)	3.44±0.10	3.55±0.22	3.82±0.13	3.68±0.29	3.20±0.16	
AUC (ng·h/ml)[b)]	474.4±30.0	288.1±36.2	661.7±43.8	1417.3±167.9	1825.9±201.9	1144.8±185.6
P(1) (ng/ml)	1796.7±71.9	-198.1±35.6	-531.1±34.7	-624.3±34.8	0.020±1.467	-181.8±80.65
P(2) (ng/ml)	364.8±44.20	-465.7±10.20	-1067.1±50.5	-1258.4±113.4	241.8±148.9	-93.33±53.78
P(3) (ng/ml)	-	663.8±10.70	1598.2±49.40	1882.7±102.7	244.3±114.0	275.1±28.60
P(4) (ng/ml)	-	-	-	-	-486.2±395.1	-
α (h^{-1})	16.13±1.722	15.80±2.260	11.41±2.570	10.59±2.847	13.54±2.501	13.42±1.755
β (h^{-1})	1.016±0.088	1.266±0.234	1.138±0.131	1.249±0.162	1.281±0.094	1.155±0.067
k_a (h^{-1})	-	0.993±0.070	0.971±0.318	0.758±0.112	0.784±0.261	0.222±0.021
k_1 (h^{-1})	-	-	-	-	0.209±0.433	-
Lag time (h)	-	0.215±0.025	0.205±0.041	0.201±0.035	0.198±0.088	0.142±0.098
k_{21} (h^{-1})	3.567±0.544	1.870±0.227	1.714±0.300	2.574±0.301	1.985±0.384	1.585±0.353
k_{10} (h^{-1})	4.595±0.199	10.67±2.550	7.574±5.100	5.139±1.454	8.737±3.250	9.779±0.206
k_{12} (h^{-1})	8.984±0.107	4.526±0.019	3.258±1.408	4.126±1.250	4.099±1.311	3.207±1.268
f (%)[c)]	100	62.67±3.91	77.44±3.940	79.90±3.690	89.51±7.200	56.12±3.620
V_1 (l)	0.289±0.015	0.113±0.018	0.157±0.023	0.187±0.019	0.154±0.033	0.146±0.021
$t_{1/2}$ (h)[d)]	0.682±0.065	0.698±0.210	0.714±0.347	0.914±0.117	3.316±1.290	3.122±0.270

a) Each value is a mean ± S.D.

b) Calculated by the equation shown in appendix.

c) $f = \left[\frac{AUC}{D / B.W.}\right]_{supp.} \times \left[\frac{D / B.W.}{AUC}\right]_{i.v.} \times 100$

d) The half-life of elimination phase.

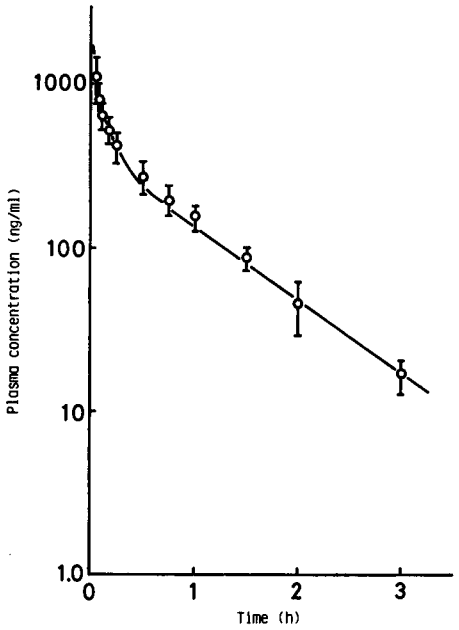


Fig. 1
Plasma concentrations of nifedipine following intravenous administration (0.625mg dose). Each point represents the mean ± S.D.

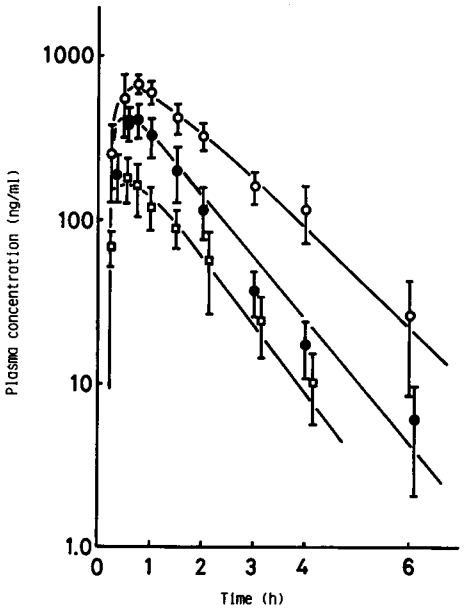


Fig. 2
Plasma concentrations after rectal administration of conventional suppositories. —□—, 0.625 mg; —●—, 1.25mg; —○—, 2.5mg. Each point represents the mean ± S.D.

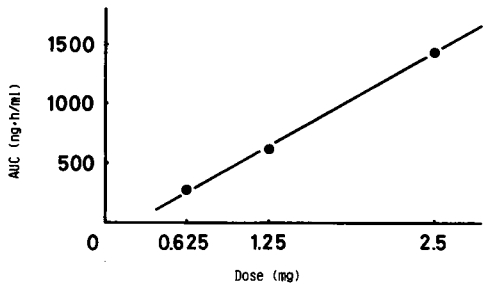


Fig. 3
Relationship between AUC and the dose of nifedipine conventional suppositories.

value of AUC over the dose range from 0.625 to 2.5mg, suggesting the passive absorption of NF in the rectum. The extent of bioavailability (EBA) after rectal administration of each suppository is shown in Table 1. EBA of three dose levels (0.625, 1.25 and 2.5mg) was about 62 - 80% on the average.

The pharmacokinetic analysis of plasma concentration-time course was carried out according to a two-compartment model with first-order absorption. The computer analysis was done by simultaneous fitting of the equation for both the intravenous and suppository dosage forms. In this case, the estimation of pharmacokinetic parameters was achieved by combining the Simplex method (MULTI program) and Marquardt method (SALS program).[6] The calculated concentration curve fitted well with the observed plasma data, as shown in Fig. 2. This suggests that the plasma concentration-time course of NF after rectal administration followed the two-compartment model with first-order absorption. The parameters converged were given in Table 1. Each absorption rate (k_a) was 0.758 - 0.993 h^{-1}. From these results, it appeared that the absorption of NF from the rectum was very rapid.

Plasma concentration after rectal administration of sustained-release suppositories

Fig. 4 shows the time course of plasma concentration after administration of sustained-release suppositories. The maximum concentration was only about 200ng/ml and the plateau plasma level was observed until 10 hr after administration. The pharmacokinetic analysis was tried by using a 4-exponential equation to clarify the release rate from a suppository (see equation (3)). As shown in Table 1, the value of P(1) was neary equal to zero. It may therefore be difficult to analyze by using a 4-exponential equation. Consequently, the pharmacokinetic analysis was carried out with a 3-exponential equation in a way similar to that for conventional suppositories. In the latter analysis, the rate constant k_a represents both the dissolution process in sustained-release suppositories and the absorption process of NF by a crossing of the rectal mucous membrane. The k_a value obtained was much smaller than that of conventional suppositories. From these results, the sustained effect achieved by this suppository was apparently attributed to the slow absorption process of NF.

However, we were unable to clarify sufficiently the dissolution rate of NF in the sustained-release suppository by means of the compartment model method. To elucidate this process, statistical moment analysis was employed.

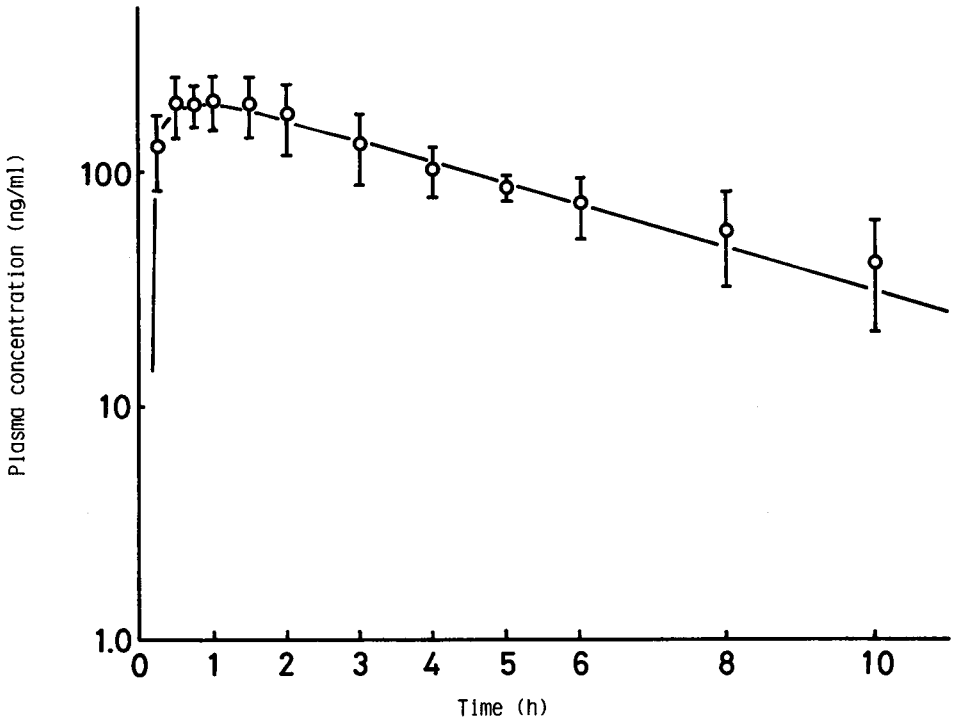


Fig. 4 Plasma concentrations after rectal administration of sustained-release suppositories (2.5mg dose). Each point represents the mean ± S.D.

Pharmacokinetic analysis by moment method

Table 2 shows the results of pharmacokinetic analysis by means of the moment method. The mean absorption time (MAT) after administration of conventional suppositories was 0.6 - 1.0 hr; i.e. absorption of NF was rapid after rectal administration. On the other hand, the mean dissolution time (MDT) in sustained-release suppository was about 5.0 hr. Therefore, it was found that the dissolution process in sustained-release suppositories was the rate-determining step.

In general, low bioavailability is observed because of excessive restrictions on drug dissolution in sustained-release dosage form. But the EBA value of this sustained-release suppository was

similar to the values of conventional suppositories, as shown in Table 2 (not significantly different at p value of 0.05). From these results, it was found that this dosage form gave a sufficient sustained-release effect without producing an excessively high peak level in the plasma, by controlling the dissolution rate from the suppository.

Table 2 The results of NF pharmacokinetic analysis by moment method.[a)]

		i.v.	conventional suppositories			sustained-release suppositories
Dose	(mg)	0.625	0.625	1.25	2.5	2.5
AUC (ng·h/ml)[b)]		472.6±130.5	268.5±103.7	642.2±184.3	1359.1±237.7	1419.8±296.4
MRT	(h)	0.768±0.073	1.398±0.215	1.421±0.203	1.772±0.212	6.852±4.567
MAT	(h)	-	0.630	0.653	1.004	6.084
MDT	(h)	-	-	-	-	5.080
EBA[c)]	(%)	100	58.63	75.45	76.91	69.87

a) Each value is a mean ± S.D.

b) Calculated by the trapezoidal rule with extrapolation to infinity.

c) $EBA = \left[\frac{AUC}{D / B.W.}\right]_{supp.} \times \left[\frac{D / B.W.}{AUC}\right]_{i.v.} \times 100$

APPENDIX I

The time function of plasma concentration in model A shown in Chart 1 is as follows:

$$C_1 = P(1)e^{-\alpha t} + P(2)e^{-\beta t}$$

where

$$P(1) = \frac{D(k_{21}-\alpha)}{V_1(\beta-\alpha)}, \qquad P(2) = \frac{D(K_{21}-\beta)}{V_1(\alpha-\beta)}$$

$$AUC = \frac{P(1)}{\alpha} + \frac{P(2)}{\beta}$$

$$\alpha + \beta = k_{12} + k_{10} + K_{21}$$

$$\alpha \cdot \beta = k_{21}\, k_{10}$$

$$k_{21} = \frac{P(1)\beta + P(2)\alpha}{P(1) + P(2)}$$

$$k_{10} = \frac{\alpha \cdot \beta}{k_{21}}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10}$$

and

$$V_1 = \frac{D}{P(1) + P(2)}$$

APPENDIX II

The time function of plasma concentration in model B is as follows:

$$C_1 = P(1)e^{-\alpha(t-t_0)} + P(2)e^{-\beta(t-t_0)} + P(3)e^{-k_a(t-t_0)}$$

where t_0 indicates the lag time,

$$P(1) = \frac{k_a \cdot f \cdot D}{V_1} \left(\frac{k_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)} \right)$$

$$P(2) = \frac{k_a \cdot f \cdot D}{V_1} \left(\frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)} \right)$$

$$P(3) = \frac{k_a \cdot f \cdot D}{V_1} \left(\frac{k_{21} - k_a}{(\alpha - k_a)(\beta - k_a)} \right)$$

$$P(1) + P(2) + P(3) = 0$$

$$C_0 = \frac{f \cdot D}{V_1} = \frac{P(1)(K_a - \alpha) + P(2)(k_a - \beta)}{k_a}$$

$$AUC = \frac{P(1)}{\alpha} + \frac{P(2)}{\beta} + \frac{P(3)}{k_a}$$

$$k_{21} = \frac{P(1)\beta k_a + P(2)\alpha k_a + P(3)\alpha\beta}{P(1)(k_a - \alpha) + P(2)(k_a - \beta)}$$

$$k_{10} = \frac{\alpha \cdot \beta}{k_{21}}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10}$$

and

$$V_1 = \frac{k_a \cdot f \cdot D}{P(1)(k_a - \alpha) + P(2)(K_a - \beta)}$$

APPENDIX III

The time function of plasma concentration in model C is as follows:[11]

$$C_1 = P(1)e^{-\alpha(t-t_0)} + P(2)e^{-\beta(t-t_0)} + P(3)e^{-k_a(t-t_0)} + P(4)e^{-k_1(t-t_0)}$$

where

$$P(1) = k_1 k_a C_0 \left(\frac{k_{21} - \alpha}{(\beta - \alpha)(k_1 - \alpha)(k_a - \alpha)} \right)$$

$$P(2) = k_1 k_a C_0 \left(\frac{k_{21} - \beta}{(\alpha - \beta)(k_1 - \beta)(k_a - \beta)} \right)$$

$$P(3) = k_1 k_a C_0 \left(\frac{k_{21} - k_a}{(\alpha - k_a)(\beta - k_a)(k_1 - k_a)} \right)$$

$$P(4) = k_1 k_a C_0 \left(\frac{k_{21} - k_1}{(\alpha - k_1)(\beta - k_1)(k_a - k_1)} \right)$$

$$P(1) + P(2) + P(3) + P(4) = 0$$

$$(k_1 + k_a - \alpha - \beta)[k_1 k_a(\beta P(1) + \alpha P(2)) + \alpha\beta(k_1 P(3) + k_a P(4))] - (P(3) + P(4))$$

$$C_0 = \frac{(k_1 - \alpha)(k_a - \alpha)(K_1 - \beta)(k_a - \beta)}{k_1^2 k_a^2 - k_1 k_a \alpha\beta}$$

$$AUC = \frac{P(1)}{\alpha} + \frac{P(2)}{\beta} + \frac{P(3)}{k_a} + \frac{P(4)}{k_1}$$

$$k_{21} = \frac{\alpha \cdot \beta \cdot AUC}{C_0} = \frac{k_1 k_a(P(1)\beta + P(2)\alpha) + \alpha\beta(P(3)k_1 + P(4)k_a)}{k_1 k_a C_0}$$

$$k_{10} = \frac{C_0}{AUC}$$

$$k_{12} = (\alpha + \beta) - (k_{10} + k_{21})$$

$$V_1 = \frac{f \cdot D}{C_0}$$

$$EBA = \left(\frac{AUC}{D \,/\, B.W.}\right)_{supp.} X \left(\frac{D \,/\, B.W.}{AUC}\right)_{i.v.} X\ 100 = f$$

REFERENCES

1. Dunn, R.F., Kelly, D.T., Sadick, N., and Uren, R.: Circulation 1979. 60. 451/455. Multivessel coronary artery spasm.
2. Foster, T.S., Hamann, S.R., Richards, V.R., Bryant, P.J., Gravers, D.A., and McAllister, R.G.: J. Clin. Pharmacol. 1983. 23. 161/170. Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects.
3. Jakobsen, P., Pedersen, O.L., and Mikkelsen, E.J.: Chromatogr. 1979. 162. 81/87. Gas chromatographic determination of nifedipine and one of its metabolites using electron-capture detection.
4. Kahan, A., Weber, S., Anrons, B., Spata, L., and Hodara, M.: Ann. Int. Med. 1981. 94. 546. Nifedipine and Raynaud's phenomenon.
5. Kuroda, T., Yokoyama, T., Umeda, T., Ohnishi, N., Kuroda, K., Inoh, T., Inatome, T., Yamaguchi, A., and Asada, S.: Kobe J. Med. Sci. 31. 1985. Pharmacokinetics of nifedipine and prediction of plasma concentration on essential hypertensive patients. (to be published)
6. Murata, K., Kohno, K., and Suzuki, T.: Yakugaku Zasshi 1983. 103. 1068/1076. Estimation of pharmacokinetic parameters with a microcomputer using a program SIMPLEX.
7. Nakagawa, T., Koyanagi, T., and Togawa, H.: In:Nakagawa, T., and Koyanagi, T., eds., Users' Manual for SALS, 2nd ed. (Computer Center of University of Tokyo, Tokyo). 1979. 1-1/7-6.
8. Pedersen, O.L., Christensen, N.J., and Ramsch, K.D.: J. Cardiovasc. Pharmacol. 1980. 2. 357/366. Comparison of the acute effects of nifedipine in normotensive and hypertensive man.
9. Raemsch, K.D., and Sommer, J.: Hypertension 1983. 5. (Supp. II). 18/24. Pharmacokinetics and metabolism of nifedipine.

10. Umeda, T., Yokoyama, T., Ohnishi, N., Kuroda, T., Kita, Y., Kuroda, K., and Asada, S.: Chem. Pharm. Bull. Studies on sustained-release dosage forms. III. Preparation and bioavailability of nifedipine suppositories. (in press)
11. Wagner, J.: In:Wagner, J., ed., Fundamentals of clinical pharmacokinetics (Drug Intelligence Publications, Inc. Hamilton, Illinois). 1979. 107/110. The two compartment open model with two consecutive first order input steps and where elimination only occurs from compartment No.3 - single dose.
12. Yamaoka, K., Nakagawa, T., and Uno, T.: J. Pharmacokin. Biopharm. 1978. 6. 547/558. Statistical moments in pharmacokinetics.
13. Yamaoka, K., Tanigawara, Y., Nakagawa, T., and Uno, T.: J. Pharm. Dyn. 1981. 4. 879/885. A pharmacokinetic analysis program (MULTI) for microcomputer.