Table II. The area under the plasma concentration-time curve (AUC) of omeprazole, 5-hydroxyomeprazole and omeprazole sulfone, and the ratio of 5-hydroxyomeprazole AUC to omeprazole sulfone AUC[a]

Genotype	AUC (ng • h/mL)			AUC ratio
	omeprazole[b]	5-hydroxyomeprazole[c]	omeprazole sulfone[c]	5-hydroxy-omeprazole/ omeprazole sulfone
Young group				
Homozygous EMs	1441 ± 938	316 ± 124	97 ± 153	10.3 ± 12.1
Heterozygous EMs	1761 ± 474	435 ± 145	171 ± 107	3.2 ± 2.0
PMs	6892 ± 2730**	232 ± 160*	971 ± 598**	0.24 ± 0.07*
Elderly group				
Homozygous EMs	3292 ± 2376	217 ± 99	70 ± 66	5.5 ± 5.1
Heterozygous EMs	3242 ± 1156	216 ± 136	114 ± 40	2.8 ± 3.7
PMs	5650 ± 1861*	72 ± 45*	255 ± 72**	0.30 ± 0.20*

a Values are expressed as mean ± SD.

b AUC from time zero to infinity

c AUC from time zero to the last quantifiable plasma concentration.

EMs = extensive metabolisers; **PMs** = poor metabolisers; * $p < 0.05$, ** $p < 0.0001$ vs homozygous and heterozygous EMs.

For V_{ss} (mean ± SD), there was a significant difference between the young and the elderly groups (219 ± 115 and 107 ± 44.5 mL/kg, respectively; $p < 0.0001$), but no significant difference was found between the three genotypes (178 ± 142, 173 ± 79 and 110 ± 51 mL/kg for homozygous EMs, heterozygous EMs and PMs, respectively).

Discussion

We investigated the effect of aging on the relationship between the genotype and the phenotype of CYP2C19 by measuring the pharmacokinetic parameters of omeprazole after a single intravenous bolus dose. Although omeprazole is usually administered as multiple oral doses in a clinical situation, the drug was used as a probe drug to measure the effect of aging on the *in vivo* CYP2C19 activity in the present study. A number of studies showed the effect of aging on the pharmacokinetics of a drug such as phenazone (antipyrine), which undergoes hepatic metabolism.[12,13,18,19] Phenazone is frequently used as a model for the metabolising capacity of the liver and its clearance is reported to decline with age.[20,21] In phenazone metabolism, at least six CYP subfamilies are responsible for the formation of its metabolites, and combined activities of multiple CYPs are considered to contribute to phenazone clearance.[22,23] In contrast, omeprazole is metabolised to 5-hydroxyomeprazole and omeprazole sulfone by CYP2C19 and CYP3A4, respectively, and the former is mainly responsible for metabolism because many studies,[2,4-6] including the present study, have shown that omeprazole pharmacokinetics are dependent on the CYP2C19 genotype.

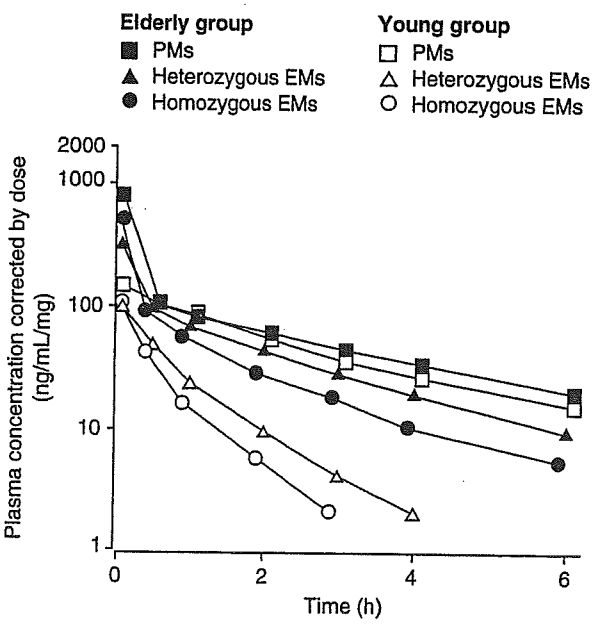

Fig. 2. The time course of dose-corrected plasma concentrations (mean) of subjects with each genotype in the young and the elderly groups. The elderly and the young subjects received a single intravenous dose of omeprazole 10mg and 20mg, respectively. **EMs** = extensive metabolisers; **PMs** = poor metabolisers.

Table III. Results of the linear regression analysis to examine the joint effects of covariates on the pharmacokinetic parameters[a]

Parameter	Mutation allele	Age	Sex	BMI
CL (L/h)	−0.434/<0.001	−0.472/<0.001	−0.182/0.096	−0.056/0.616
HI	−0.499/<0.001	−0.462/<0.001	−0.153/0.146	−0.033/0.757
MRT (h)	0.628/<0.001	0.276/0.033	−0.142/0.223	0.030/0.803
$t_{1/2\beta}$ (h)	0.441/<0.001	0.421/0.001	0.051/0.651	0.165/0.162
V_{ss} (mL/kg)	−0.208/0.071	−0.529/<0.001	−0.131/0.278	Not examined[b]

a Values are expressed as a partial correlation coefficient/p-value.

b BMI was excluded from the variables in the analysis for V_{ss} because the parameter was corrected by bodyweight.

BMI = body mass index; **CL** = systemic clearance; **HI** = hydroxylation index; **MRT** = mean residence time; $t_{1/2\beta}$ = terminal elimination half-life; V_{ss} = volume of distribution at steady state.

In the present study, omeprazole was administered intravenously to avoid aging-related changes in drug absorption,[12,13] and the dose for the elderly group was reduced to half of that for the young group because plasma omeprazole concentration was expected to be higher in the elderly group. Although the number of sampling points was not enough to evaluate the initial phase, the plasma omeprazole concentration-time curve suggested that a one-compartment model may be suitable for the young group, but a two-compartment model may be needed for the elderly group. With more frequent sampling between the time just after injection and 30 minutes post-dose, a bioexponential decline could also be observed in young subjects. Since the concentration at time zero was estimated using the initial two points, AUC of the elderly subjects was more underestimated, and CL and V_{ss} were overestimated, than those of the young subjects. In the present study, the CL of young EMs was smaller than the reported range (24–37.2 L/h).[24] Previous studies showed that omeprazole AUC in Chinese EMs was greater than that in Caucasian EMs after a single oral dose[25] and after repeated oral dose;[26] these results suggest that Japanese EMs may also have greater AUC and smaller CL compared with Caucasian EMs.

The linear regression models were used to examine the joint effects of covariates on the pharmacokinetic parameters of omeprazole and to evaluate whether possible variables besides genotype or age may exist as important determinants of the parameters. The models showed that sex was not a significant determinant in the pharmacokinetic parameters examined in this study. In the heterozygous EMs of the young or the elderly groups consisting of both sexes, the CL (mean ± SD) were 12.3 ± 1.9/13.1 ± 5.4 L/h and 4.2 ± 1.4/3.0 ± 1.1 L/h for young and elderly males/females, respectively. The V_{ss} (mean ± SD) was 190 ± 29/265 ± 86 mL/kg and 133 ± 38/127 ± 61 mL/kg for young and elderly males/females, respectively. Both parameters showed no sex-related difference. The lack of sex-related significance was consistent with previous studies reporting no effect of sex on the activity of CYP2C19.[27,28] The number of mutation alleles and age were significant covariates for all pharmacokinetic parameters, except V_{ss}. For V_{ss}, a significant difference was noted between the young and the elderly groups; this finding corresponds with a previous study showing an age-related reduction in the apparent volume of distribution during the terminal phase of omeprazole.[14]

Although most pharmacokinetic parameters examined in this study showed significant differences between EMs and PMs in the elderly group as well as in the young group, the relationship between the CYP2C19 genotype and omeprazole pharmacokinetics in the elderly group differed considerably from that in the young group. According to the Hardy-Weinberg equation, the frequencies of two mutations can account for this difference in PMs in a Japanese population[29] and it is unlikely that some unidentified mutations affect the metabolic capacity of the elderly EMs. In fact, some of the elderly EMs showed pharmacokinetic parameters similar to the elderly PMs, resulting in larger variance in the elderly EMs. Most pharmacokinetic parameters of the

Table IV. Pharmacokinetic parameters of subjects with each genotype in the young and the elderly groups and the statistical results by use of two-way ANOVA[a]

Genotype	CL (L/h)	HI	MRT (h)	$t_{1/2\beta}$ (h)
Young group				
Homozygous EMs (n = 8)	20.6 ± 11.0	0.260 ± 0.086	0.76 ± 0.20	0.74 ± 0.29
Heterozygous EMs (n = 9)	12.7 ± 4.0	0.253 ± 0.079	0.98 ± 0.24	0.84 ± 0.22
PMs (n = 6)	3.2 ± 1.0	0.033 ± 0.017	2.80 ± 0.47	2.01 ± 0.33
Elderly group				
Homozygous EMs (n = 8)	5.4 ± 4.0	0.118 ± 0.094	1.19 ± 0.49	1.64 ± 0.48
Heterozygous EMs (n = 12)	3.7 ± 1.4	0.073 ± 0.047	2.04 ± 0.70	1.71 ± 0.49
PMs (n = 8)	2.1 ± 0.7	0.016 ± 0.015	2.28 ± 0.73	2.17 ± 0.32
p-Values of effects of covariates on pharmacokinetic parameters by two-way ANOVA				
Age	<0.0001	<0.0001	<0.0001	<0.0001
Genotype	<0.0001	<0.0001	0.0366	<0.0001
Age × genotype	0.0018	0.0028	0.0005	0.0162

a Values are expressed as mean ± SD.

CL = systemic clearance; **EMs** = extensive metabolisers; **HI** = hydroxylation index; **MRT** = mean residence time; **PMs** = poor metabolisers; $t_{1/2\beta}$ = terminal elimination half-life.

elderly PMs were similar or closer to those of the young PMs, and the ratios between PMs and EMs in the elderly group were much smaller than those in the young group. The results of the elderly homozygous and heterozygous EMs were between elderly PMs and the young heterozygous EMs in terms of the profile of omeprazole pharmacokinetics and, possibly, the *in vivo* CYP2C19 activity.

In a previous study reporting the effects of age on the disposition of diazepam, the $t_{1/2\beta}$ of diazepam was increased linearly with age, from approximately 20 hours at 20 years of age to approximately 90 hours at 80 years of age. The prolongation of $t_{1/2\beta}$ with age was considered to be dependent on an increase in the initial distribution volume and, subsequently, the V_{ss} of the drug.[30] In our study, however, V_{ss} of omeprazole in the elderly group was significantly smaller than that in the young group. If the reduction in V_{ss} affects CL, MRT or $t_{1/2\beta}$, elderly PMs should show similar changes to what was found in the elderly homogenous and heterogenous EMs because the aging effect on the V_{ss} should be independent of the CYP2C19 genotype. Smaller differences in CL, MRT or $t_{1/2\beta}$ between PMs and EMs of the elderly group, and the change in HI with age, could be explained by the age-related reduction in metabolic activity of CYP2C19, but not by the age-related reduction in V_{ss}. Therefore, the reduction in the CL of the elderly group resulted from the decrease in the *in vivo* CYP2C19 activity. In addition, the aging effect on the metabolic activity may be greater in a subject with a higher CYP2C19 activity because some elderly homozygous EMs, as well as heterozygous EMs, have similar HI to PMs. Omeprazole is a racemic mixture of (*R*)- and (*S*)-isomers. Since a previous *in vitro* study reported that the intrinsic clearance of (*R*)-omeprazole was higher than that of (*S*)-omeprazole, and the contribution of CYP2C19 was greater in (*R*)-omeprazole than (*S*)-omeprazole,[31] the pharmacokinetics of (*R*)-omeprazole would more clearly show the results of age-related reduction in metabolic capacity of CYP2C19.

Although our findings suggest age-related reduction in the metabolic activity of CYP2C19, the effect of age may vary in the CYP isoenzymes. Studies on human liver microsomes showed that the activity of erythromycin *N*-demethylation, a measure of CYP3A activity, was unaffected by age over the range of 27–83 years.[32] These results were confirmed by the *in vivo* studies reporting no association of reduction in the clearance of midazolam, a CYP3A substrate, with advanced age.[33-36] In our study, mean dose-corrected concentrations in the elimination phase of the elderly PMs were very similar to those of the young PMs. Since the slope of

the plasma omeprazole concentration-time curve in PMs reflects the *in vivo* CYP3A activity, these findings appear to be consistent with the results of the previous studies.[33-36]

Conclusion

In the present study, we found that the aging process affected the relationship between CYP2C19 genotype and the pharmacokinetics of omeprazole. Elderly EMs showed wide variance in the omeprazole pharmacokinetics compared with those of the young EMs, and elderly EMs were phenotypically closer to the elderly PMs than the young EMs were to the young PMs. Some of the elderly homozygous EMs, as well as heterozygous EMs, have a metabolic activity similar to PMs, and the CYP2C19 geno-

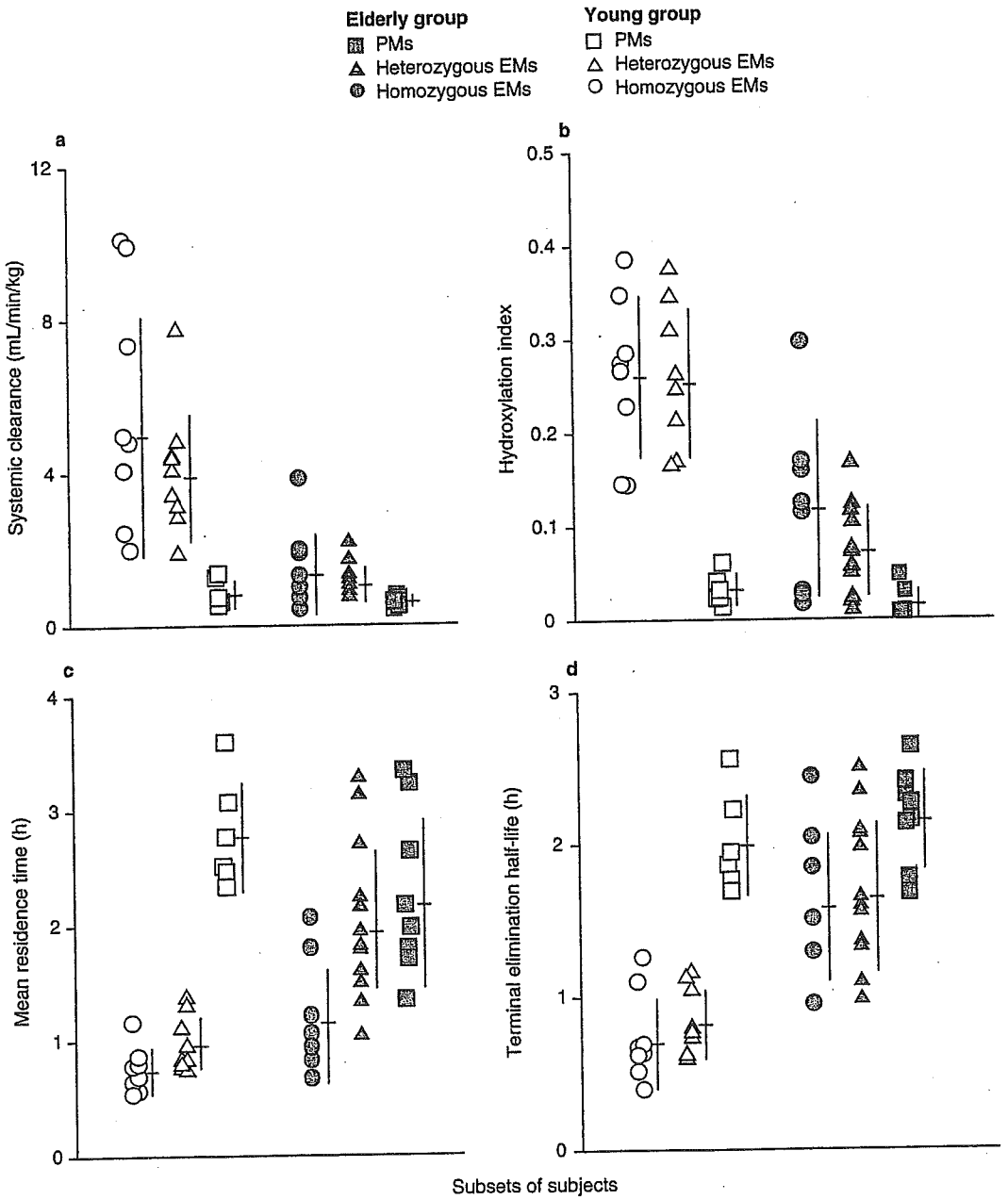

Fig. 3. Individual and mean (±SD) systemic clearance (**a**), hydroxylation index (**b**), mean residence time (**c**) and terminal elimination half-life (**d**) of omeprazole with each genotype in the young and the elderly subjects. **EMs** = extensive metabolisers; **PMs** = poor metabolisers.

type may therefore not be as useful as phenotyping in the elderly.

Acknowledgements

This work was partially supported by the Japanese Research Foundation for Clinical Pharmacology and the Japanese Ministry of Health, Labor and Welfare (H16-tyoju-001; Quality use of drugs for the elderly based on pharmacogenetic information in Japan). The authors have no conflicts of interest that are directly relevant to the content of this study.

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J Pharmacol Sci 97, 455 – 456 (2005)

Journal of Pharmacological Sciences

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Proteasome Function and Pathological Proteins in the Pathogenesis of Parkinson's Disease

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Received February 16, 2005

Keywords: proteasome inhibitor, α-synuclein, Parkinson's disease, neurodegeneration

Parkinson's disease (PD) is a multifactorial disease that appears to arise from the effects of both genetic and environmental influences (1). Parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) showed rigidity, akinesia, stooped posture, and response to levodopa therapy; and it was indistinguishable from idiopathic PD. The discovery of MPTP demonstrated that toxic substances could cause PD. Epidemiological studies showed that pesticides and heavy metals are the principle environmental factors that appear to have an impact on the development of PD. The genetic contribution in PD has been debated for over a century. More recently, an increasing number of well-documented multigenerational parkinsonian kindreds have been reported with evidence of autosomal dominant inheritance with variable penetrance. Genes associated with either PD or Parkinson-related disorders include parkin, DJ-1, ubiquitin C-terminal hydrolase isozyme L1 (UCH-L1), nuclear receptor-related factor 1, and α-synuclein. α-Synuclein is particularly notable because it aggregates and is the main component of Lewy bodies (LBs). Because ubiquitin also accumulates in LBs, and parkin and UCH-L1 interact with the ubiquitin proteasomal system, proteasomal dysfunction is thought to contribute to the pathophysiology of PD. However, α-synuclein expression levels by themselves have no significant effect on proteasome peptidase activity, subunit expression, and proteasome complex assembly and function (2). Other mechanisms resulting in synuclein aggregation (not simply expression levels) may be the key to understanding the possible effect of aggregated synuclein on proteasome function. Aggregated α-synuclein binds to the proteasome and inhibits proteasomal activity. When rats were treated with stereotaxic unilateral infusion of lactacystin, a selective proteasome inhibitor, into the substantia nigra pars compacta, the animals became progressively bradykinetic, adopted a stooped posture, and displayed contralateral head tilting. Administration of apomorphine to lactacystin-treated rats reversed behavioral abnormalities and induced contralateral rotations (3). Lactacystin caused dose-dependent degeneration of dopaminergic cell bodies and processes with the cytoplasmic accumulation and aggregation of α-synuclein to form inclusion bodies. When proteasome inhibitors were injected systematically into adult rats over a period of 2 weeks, animals developed progressive parkinsonism with bradykinesia, rigidity, tremor, and an abnormal posture, which improved with apomorphine treatment. These findings support the notion that failure of the ubiquitin-proteasome system to degrade and clear unwanted proteins is an important etiopathogenic factor in PD (4).

On the other hand, Inden et al. found that injection of proteasome inhibitors to the substantia nigra pars compacta of rats did not cause cell loss or dysfunction of dopaminergic cells and protected dopaminergic cells from the toxic effect of 6-hydroxydopamine (6-OHDA) (5). These results showed the proteasome-involved toxic effect of 6-OHDA and inhibition of the proteasome in the animals subjected to 6-OHDA treatment caused inclusion bodies that did not cause cell loss. Accumulation of α-synuclein might protect the dopaminergic cells from the 6-OHDA toxicity as aggresomes. Parkin protein functions as a ubiquitin ligase. Mutations in the parkin gene induce ubiquitin-proteasome dysfunction and cause autosomal recessive juvenile parkinsonism. However, most patients with park2 PD did not exhibit the LBs.

The dose of proteasome inhibitors or the state of proteasome inhibited might cause the different results in

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these reports. More studies would be needed to reveal the function of the proteasome in the neurodegeneration of dopaminergic cells.

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J Pharmacol Sci 100, 59 – 64 (2006)

Journal of Pharmacological Sciences

Full Paper

Effect of Clarithromycin on the Pharmacokinetics of Cabergoline in Healthy Controls and in Patients With Parkinson's Disease

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Received August 22, 2005; Accepted November 21, 2005

Abstract. Cabergoline is used in the treatment of Parkinson's disease (PD). Clarithromycin is a potent inhibitor of CYP3A4 and P-glycoprotein and is often co-administered with cabergoline in usual clinical practice. We studied the effect of clarithromycin co-administration on the blood concentration of cabergoline in healthy male volunteers and in PD patients. Study 1: Ten healthy male volunteers were enrolled and were randomized to take a single oral dose of cabergoline (1 mg/day) for 6 days or a single oral dose of cabergoline plus clarithromycin (400 mg/day) for 6 days. Study 2: Seven PD patients receiving stable cabergoline doses were enrolled. They were evaluated for the plasma cabergoline concentration before and after the addition of clarithromycin 400 mg/day for 6 days, and again 1 month after discontinuation of clarithromycin. The dose and duration of clarithromycin were decided according to usual clinical practice. In healthy male volunteers, mean C_{max} and $AUC_{0-10\,h}$ of cabergoline increased to a similar degree during co-administration of clarithromycin. Mean plasma cabergoline concentration over 10 h post-dosing increased 2.6-fold with clarithromycin co-administration. In PD patients, plasma cabergoline concentration increased 1.7-fold during clarithromycin co-administration. Co-administration with clarithromycin may increase the blood concentration of cabergoline in healthy volunteers and in PD patients.

Keywords: cabergoline, clarithromycin, drug-drug interaction, Parkinson's disease

Introduction

Dopamine receptor agonists are widely used to treat Parkinson's disease (PD): patients who are treated early in their disease course with monotherapy show a lower incidence of motor complications and adjunctive therapy is also effective in advanced stages of the disease when combined with L-dopa (1 – 3). Structurally, dopamine receptor agonists can be divided into ergoline derivatives, non-ergoline derivatives, and apomorphines (4). Cabergoline is a synthetic ergot dopamine agonist and has the potential for the treatment of PD, acromegaly, and hyperprolactinaemia (3, 5, 6). It is metabolized mainly in the liver via hydrolysis (7, 8). Clarithromycin, a macrolide antibiotic, is a potent inhibitor of the CYP3A4 and P-glycoprotein and consequently increases the blood concentration of certain drugs. Some clinical studies suggest that fewer serious drug interactions occur with clarithromycin than with older macrolides such as erythromycin and troleandomycin (9 – 11). Clarithromycin is widely used to treat respiratory tract infections and is often used in PD patients with such infections. Pneumonia is the most frequent cause of death associated with PD. The administration of clarithromycin might potentially cause an alteration of the pharmacokinetics of cabergoline. We studied the effect of co-administration of clarithromycin on the plasma concentration of cabergoline in healthy male volunteers and PD patients to ensure the safety of cabergoline during its clinical use.

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Published online in J-STAGE: January 13, 2006
DOI: 10./1254/jphs.FP0050711

Materials and Methods

All volunteers and patients recruited to these randomized, non-blind, crossover studies gave their written informed consent prior to participation. The protocols were reviewed and approved by the Institutional Review Board of Ehime University School of Medicine, and the studies were conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Study 1

Ten healthy male volunteers, aged 20 to 52 years, were enrolled in this study. All volunteers were Japanese and selected on the basis of normal medical history, physical examination, and clinical laboratory tests. They had not taken any medication for at least 4 weeks before starting the study. Volunteers were excluded if they had confirmed or suspected cardiovascular and/or cerebrovascular disorders and if they had any history or other disorders that might compromise their safety during the study. Volunteers were randomized to cabergoline (1 mg oral tablet) (Kissei, Nagano) once daily in the morning with or without clarithromycin (200 mg oral tablet) (Taisho Toyama, Tokyo) twice daily for 6 days and crossed over to the alternate treatment after a 40-day washout period. Domperidone (10 mg oral tablet) (Kyowa Hakko Kogyo, Tokyo) was co-administered with each dose of cabergoline for prophylaxis against vomiting. Blood samples were collected on day 6 of each cycle at 0, 1, 2, 3, 4, 6, 8, and 10 h following dosing of cabergoline with or without clarithromycin.

Study 2

Seven Japanese PD patients (4 female, 3 male), aged 30 to 80 years, were enrolled in this study. All of them had been treated with cabergoline at a stable dose for more than 3 months. They were not taking any medication or food known to reduce or increase CYP activity before starting the study. All patients had been treated with the same medications for the last 4 weeks before recruitment and these were unchanged during the study. As in Study 1, the following patients were excluded: those with confirmed or suspected cardiovascular and/or cerebrovascular disorder and if they had any history or other disorders that might compromise their safety during the study. Patients received the addition of clarithromycin (400 mg) twice daily for 6 consecutive days to their previous medications, which included stable doses of cabergoline. Their signs and symptoms of PD were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) (12 – 14). Blood samples were taken 3 h after administration of cabergoline on day 1 (immediately before addition of clarithromycin) and on day 6 (with addition of clarithromycin). Patients were asked to return a month after the cessation of this study and another blood sample was taken 3 h after cabergoline administration. They were asked not to take any medication or food known to alter CYP activity prior to this visit and to ensure that the daily dose of cabergoline was not changed.

Measurement of plasma cabergoline concentration

Blood was collected in 5-ml sodium-heparinized tubes and centrifuged at 3000 rpm for 15 min. Plasma was stored at –80°C until analysis. Cabergoline in plasma was extracted to methyl *tert*-butyl ether and was measured by liquid chromatography-tandem mass spectrometry (HPLC: HP1100 Series; Hewlett Packard, Palo Alto, CA, USA) (MS/MS: TSQ7000; Thermo-Quest, Waltham, MA, USA). Symmetry Shield RP-18 (2.1 × 150 mm, 3.5 μm; Waters, Milford, MA, USA) was applied to the column and the mobile phase consisted of acetonitrile (40%) and 20 mmol·L^{-1} ammonium formate (60%). LC/MS/MS was operated in the positive mode (15). The intra-assay coefficient of variation (CV) was 4.7 – 9.2% and the detection limit was 5 pg·ml^{-1}.

Pharmacokinetic analyses

The maximum plasma drug concentration (C_{max}) and the time to reach maximum concentration (t_{max}) were determined from actual data, mean plasma concentration over 0 – 10 h ($C_{0-10\,h}$) was calculated by averaging all readings, and area under the plasma concentration-time curve from 0 to 10 h after dosing ($AUC_{0-10\,h}$) was calculated using the linear trapezoidal rule in Study 1. In Study 2, plasma drug concentration was measured 3 h after cabergoline administration.

Statistical analyses

Results are expressed as the mean ± S.D. The plasma concentration of cabergoline was compared with and without clarithromycin co-administration by the Friedman test. C_{max} and $AUC_{0-10\,h}$ were compared using the Wilcoxon matched-pairs signed-rank test. The SPSS (version 11.5 for Windows) software was employed, with $P<0.05$ as the minimum level of significance. Sample sizes were estimated from the expectation of doubled plasma concentration for drug interaction.

Results

Study 1

All volunteers completed the schedule. Table 1 sum-

Table 1. The pharmacokinetics of cabergoline given alone and with clarithromycin

Pharmacokinetic parameter	Mean ± S.D. (95%CI)	
	Cabergoline alone	Cabergoline + clarithromycin
C_{max} (pg·ml^{-1})	55.42 ± 16.11 (23.80 – 83.60)	152.85 ± 33.66* (105.70 – 203.90)
$AUC_{0-10\,h}$ (pg·h·ml^{-1})	484.24 ± 144.45 (237.60 – 752.10)	1267.91 ± 331.17* (796.45 – 1737.55)
t_{max} (h)	6.10 ± 2.42 (1.00 – 10.00)	7.20 ± 1.69 (4.00 – 10.00)
Mean $C_{0-10\,h}$ (pg·ml^{-1})	46.63 ± 15.44 (34.49 – 53.54)	121.14 ± 35.99* (87.95 – 142.12)

$AUC_{0-10\,h}$ is the area under the plasma concentration-time curve from time 0 to 10 h; C_{max} is the maximum plasma concentration; $C_{0-10\,h}$ is the mean of plasma concentration determination over 0 – 10 h; t_{max} is the time corresponding to the maximum plasma concentration (C_{max}). * $P<0.01$ *vs* cabergoline alone (Wilcoxon matched-pairs signed-rank test).

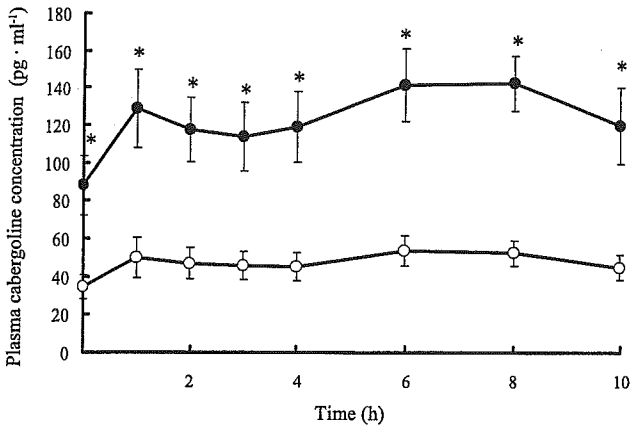

Fig. 1. Mean (±S.D.) plasma cabergoline concentration in 10 healthy volunteers after administration of cabergoline (1 mg) once daily with (closed circles) or without (open circles) clarithromycin (400 mg) twice daily for 6 days. * $P<0.01$ *vs* cabergoline alone.

marizes the mean (±S.D.) pharmacokinetic parameters for each treatment. Mean $C_{0-10\,h}$ for cabergoline was 46.6 pg·ml^{-1} without the co-administration of clarithromycin and increased significantly ($P<0.01$) to 121.1 pg·ml^{-1} with clarithromycin. At all time points, co-administration of clarithromycin increased the plasma concentration of cabergoline (Fig. 1). Individual values for C_{max} and $AUC_{0-10\,h}$ are shown in Fig. 2: mean values were significantly ($P<0.01$) increased 2.8 and 2.6 times, respectively, by clarithromycin co-administration.

Adverse effects were experienced in similar numbers of volunteers during the administration of cabergoline alone or in combination with clarithromycin (Table 2). None of these symptoms were serious and did not need any medical treatment. There was no difference in blood pressure before and after the administration of cabergoline. All of the volunteers completed the

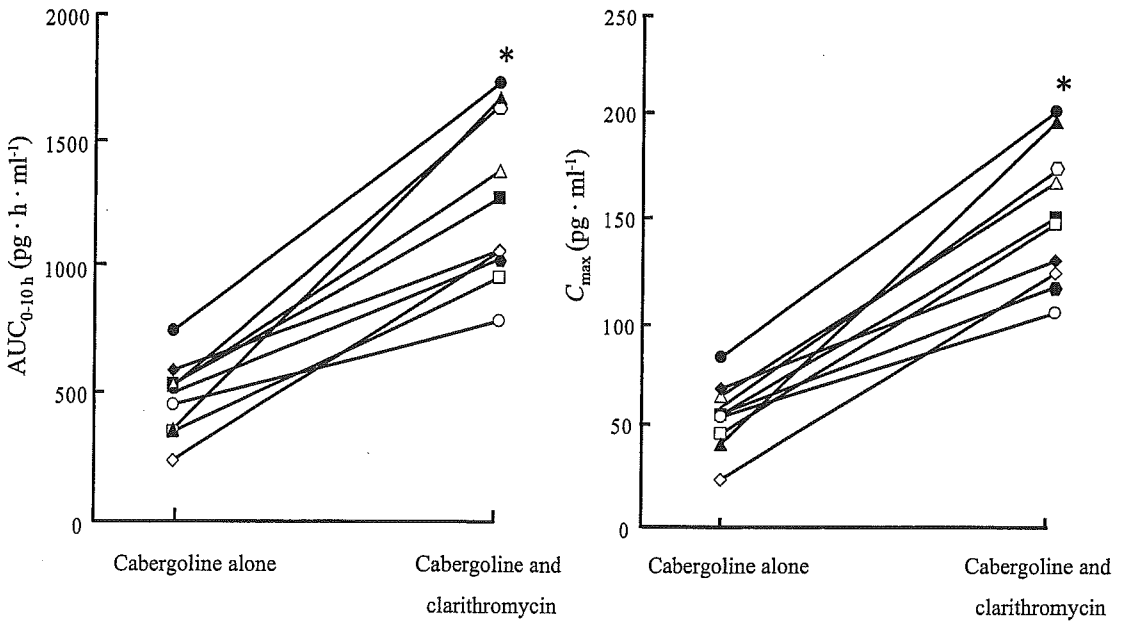

Fig. 2. Individual values for $AUC_{0-10\,h}$ and C_{max} for 10 healthy volunteers after administration of cabergoline (1 mg) once daily with or without clarithromycin (400 mg) twice daily for 6 days. * $P<0.01$ *vs* cabergoline alone.

Table 2. Symptoms and frequency of adverse events occurring in healthy volunteers

Symptoms	Cabergoline alone (n = 10)	Cabergoline and clarithromycin (n = 10)
Sleepiness	4	4
Constipation	3	4
Nausea	2	3
Dizziness	3	2
Heartburn	2	1
Diarrhea	0	1

scheduled plan.

Study 2

Table 3 shows the clinical characteristics of the PD patients. They were aged 56 to 75 (mean 67.4 ± 6.02) years. There were 4 females and 3 males, and all had a diagnosis of idiopathic PD. The mean duration of the illness was 5.93 ± 5.65 years. Administration of clarithromycin increased the plasma concentration of cabergoline in all patients (Fig. 3). The mean plasma concentration of cabergoline was 145.4 ± 52.9 pg · ml^{-1} without clarithromycin and 252.7 ± 100.6 pg · ml^{-1} with clarithromycin, therefore increasing 1.74-fold with clarithromycin co-administration (P<0.01).

No patients showed adverse effects, for example, nausea, vomiting, dizziness, hypotension, during the administration of clarithromycin.

One month after cessation of clarithromycin, blood samples were collected in 4 patients who could revisit for this study. The plasma concentration of cabergoline returned to the baseline level prior to clarithromycin administration in all 4 patients (Fig. 3).

With this increase in plasma cabergoline concentration, 3 of 7 patients showed an improvement in their PD symptoms. UPDRS improved in these 3 patients from 7 to 5, 36 to 30, and 44 to 40 in cases 2, 6, and 7, respectively. The score did not change in the other 4 patients, remaining at 45, 3, 1, and 61 in cases 1, 3, 4, and 5, respectively. When UPDRS improved, it was in part II or III for motor examination, especially tremor at rest or rigidity.

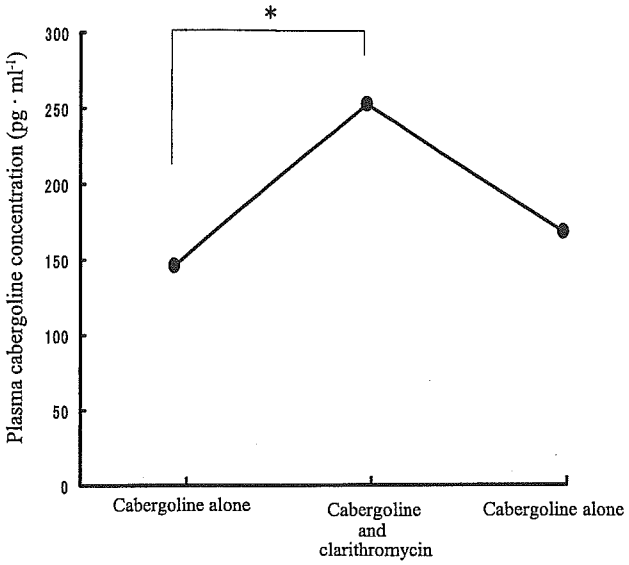

Fig. 3. Mean plasma cabergoline concentration in PD patients after 3-h therapeutic administration of stable therapeutic doses of cabergoline alone or in combination with clarithromycin (400 mg) twice daily for 6 days (n = 7) and again 1 month after discontinuationof clarithromycin (n = 4). * P<0.01.

Discussion

Cabergoline binds dopamine D_2 receptors selectively and causes functional dopaminergic activity in the brain. A distinctive characteristic of cabergoline is its long elimination half-life ($t_{1/2\beta}$) (8). In 12 healthy volunteers, mean t_{max} for cabergoline was 2.5 h and mean $t_{1/2\beta}$ was 109.7 ± 41.3 h following administration with food (16). Cabergoline has been shown to be metabolized through

Table 3. Patients clinical and demographic characteristics

Case	Gender	Age (year)	Cabergoline dose (mg/day)	L-dopa dose (mg/day)	Hoehn-Yahr stage		Disease duration (year)
					ON	OFF	
1	Male	71	3	400 (levodopa/carbidopa)	2.5	3	10.0
2	Female	68	2	200 (levodopa/benserazide)	1	1	2.7
3	Female	56	3	250 (levodopa/carbidopa)	0	2	17.0
4	Female	69	2	0	1	1	1.6
5	Male	69	1	300 (levodopa/benserazide)	3	3	2.6
6	Male	64	1	300 (levodopa/carbidopa)	2.5	2.5	5.0
7	Female	75	2	250 (levodopa/carbidopa)	3	3.5	2.6

hydrolysis and P450-mediated metabolism appears to be minimal (7, 8). In our study, the plasma concentration of cabergoline (C_{max}, $C_{0-10\,h}$ and $AUC_{0-10\,h}$) increased about 2.7 times with clarithromycin co-administration. Clarithromycin has been shown to increase the plasma concentration of certain drugs via the inhibition of P-glycoprotein (17). This suggests that the concentration of cabergoline might be increased by clarithromycin mainly through the inhibition of P-glycoprotein-mediated excretion.

Cabergoline is used in the treatment of PD in combination with other antiparkinsonian drugs. Pharmacokinetic interaction between cabergoline and levodopa has been investigated in two studies in PD patients. Plasma cabergoline concentrations were assayed over a 24-h period 3 weeks after a stable dose of cabergoline (2 mg daily). Pharmacokinetic parameters of cabergoline were unmodified by the addition of levodopa (levodopa/carbidopa, 250/25 mg daily) (18). The pharmacokinetics of levodopa before and after the concomitant administration of cabergoline has been studied in 12 PD patients (19). Plasma levodopa concentrations were measured over an 8-h period before cabergoline was added and 8 weeks after starting cabergoline. No modification of levodopa pharmacokinetics (absorption, bioavailability, $t_{1/2\beta}$) was observed when levodopa and cabergoline were co-administered. The pharmacokinetics of cabergoline and selegiline have been determined in 6 PD patients not treated with levodopa when the two drugs were given alone or in combination (20). No pharmacokinetic drug-drug interaction was found between cabergoline and selegiline, since all measured pharmacokinetic parameters of both drugs remained unchanged comparing monotherapy and combination therapy. The effect of food on the pharmacokinetics of cabergoline has also been investigated. Under both fasting and fed conditions C_{max}, AUC, $t_{1/2\beta}$, and t_{max} for cabergoline remained the same (16).

Cabergoline is an ergot alkaloid and clarithromycin is known to interfere with ergotamine metabolism. Ergot alkaloids are commonly used for migraine and have vasoactive properties. There has been a case report of clarithromycin-associated ischemia in the treatment of migraine with an ergot alkaloid (21). Itraconazole is a triazole used as local and systemic antifungal agent and is a potent inhibitor of CYP3A4 and P-glycoprotein. Christensen and colleagues (22) reported a case of PD showing increased plasma cabergoline concentration during concomitant treatment with itraconazole. Plasma cabergoline concentration was increased approximately 3-fold during treatment with itraconazole for 1 week. In our study, the concentration of cabergoline increased 2.7-fold in PD patients during the treatment of clarithromycin for 6 days. Our results were compatible with the previous study of itraconazole. Clarithromycin and itraconazole are both inhibitors of CYP3A4 and P-glycoprotein, although itraconazole is a more potent inhibitor (23, 24). Clarithromycin might elevate the concentration of cabergoline by the inhibition of both CYP3A4 and P-glycoprotein.

Drug-drug interactions between levodopa and DOPA decarboxylase inhibitors (carbidopa, benserazide), levodopa and COMT inhibitors, or levodopa and selegiline are applied practically in the treatment of PD. Co-administration of carbidopa increased the plasma concentration of levodopa approximately 400% (25) and entacapone 140% (26) in patients with PD. When adjunctive selegiline is used with levodopa, the extracellular concentration of dopamine increased several fold in the brain of monkeys (27). In the treatment of PD, drug-drug interaction is used for more efficient drug therapy. In our study, no patients or healthy volunteers showed dose-dependent serious adverse effects. Nonetheless, physicians should be aware of the potential for interaction between clarithromycin and cabergoline: in particular, their co-administration should be avoided in PD patients who show marked dyskinesia or levodopa-induced psychosis.

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特集／神経疾患治療薬の現状と今後の開発

2．パーキンソン病

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1．はじめに

パーキンソン病は黒質神経細胞の選択的細胞死により，神経伝達物質であるドパミンが不足し発症する神経変性疾患であり，神経変性疾患の中ではアルツハイマー病に次いで多く認められる．黒質神経細胞から線維連絡を受けている線条体におけるドパミン低下により，振戦，筋強剛，寡動などの種々の神経症状を呈する．この病態に基づいて数多くの抗パーキンソン病薬が開発され臨床応用されている．現在の治療薬の中心はドパミン系に作用するものであるが，最近ではアデノシン受容体やグリア細胞に作用するパーキンソン病治療薬も開発されており，現在治験の段階である．さらに，パーキンソン病に対する対症，補充療法とともにドパミン神経細胞の変性抑制という原因療法も検討されるようになってきている．本稿では現在日常診療で用いている治療薬と今後の薬について概説する．

2．現在の治療薬

Levodopa製剤が1961年にパーキンソン病治療に初めて使用されてから40年以上の歳月が経過したが，現在もなおlevodopaがパーキンソン病治療の中心であることには変わりない．パーキンソン病治療においては下記に述べる作用機序の異なる複数の抗パーキンソン病薬が開発されており，年齢，症状，副作用等を考慮し，これらの薬を組み合わせて治療が行われている．

1）Levodopa製剤

Levodopaは脳血液関門を通過し，脳内の黒質，線条体などでドパミンに代謝され抗パーキンソン病作用を示す．経口投与されたlevodopaは，酸性下の胃内で溶解し小腸で吸収される．しかし，投与されたlevodopaの大部分は腸管などの末梢組織でドパ脱炭酸酵素によりドパミンに代謝され，脳内に移行するlevodopaは投与量の1～3%にすぎない．このため，現在ではドパ脱炭酸酵素阻害薬（dopa-decarboxylase inhibitor：DCI）とlevodopaの合剤が用いられている．DCIは末梢でlevodopaからドパミンへの代謝を防ぎ，脳内へ移行するlevodopa量を約5倍に増加させる．しかし，DCI自体は脳血液関門を通過しにくいため脳内でのlevodopaからドパミンへの代謝は阻害しない．DCIとしてcarbidopaとbenserazideが使用されている．臨床の現場ではlevodopa含有量が同じならば，これら2種のDCI配合剤は同等に使用されている．しかし，パーキンソン病患者を対象としたlevodopa薬物動態を検討した結果，benserazide合剤使用群では血中levodopaのC_{max}，AUCがそれぞれ6.7 μM，796.8 μMminと，carbidopa合剤使用群の3.9 μM，646.2 μMminに比較してC_{max}で1.7倍，AUCで1.2倍の上昇を示した（Fig. 1）[1]．一般にlevodopaは内服後30～90分後で最高血中濃度に達し，その後約60分の半減期で消失する．Levodopa製剤の吸収には胃内酸性度，胃内容物排出時間，上部小腸での吸収能が影響を与えるため，種々の要因で吸収が変化する．Levodopa製剤は酸性で溶解しやすく，胃酸の分泌が低下した症例ではlevodopaの吸収が低下することがある．このような場合はビタミンCやレモン水との服用で吸収が改善することがある．制吐薬であるdomperidoneは上部消化管運動を高める作用があり，胃内容物排出時間短縮作用によりlevodopa吸収を高める．我々の検討ではdomperidone併用によりlevodopa血中C_{max}は約1.9倍，AUCは約1.4倍の上昇を認めた（Fig. 2）．Levodopaの腸管から血液への吸収，血液から脳内への移行には中性アミノ酸トランスポーターが使用される．したがって，タンパク質由来のアミノ酸は

Key words：Parkinson's disease, levodopa, pharmacokinetics, neuroprotection, dopamine
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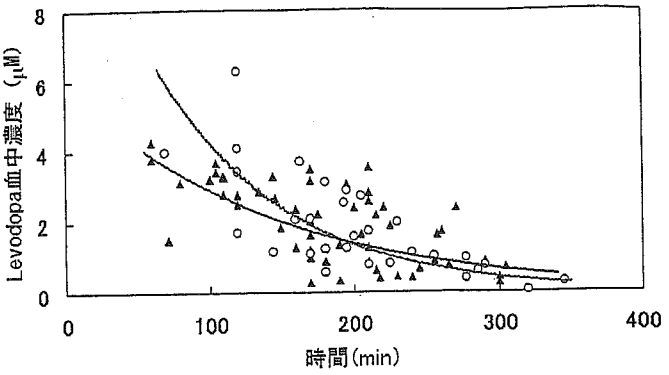


Fig. 1　DCI の違いによる levodopa 薬物動態の相違
パーキンソン病患者を対象に population pharmacokinetics 法で解析（○：benserazide 合剤，▲：carbidopa 合剤）

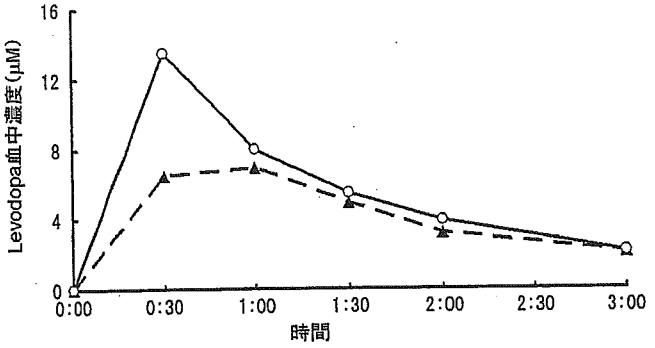
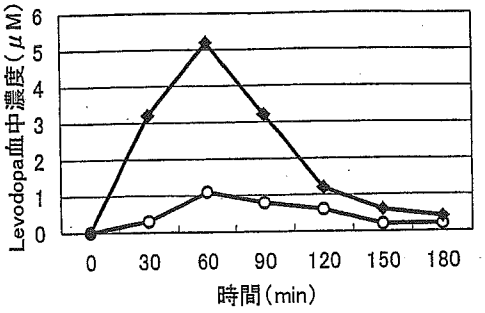


Fig. 2　Domperidone 併用による levodopa 血中濃度の上昇
（○：domperidone 併用，▲：levodopa 単独）



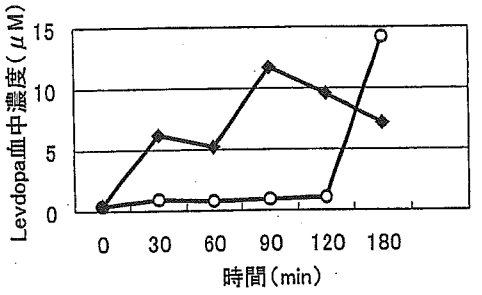


Fig. 3　低タンパク食による levodopa 血中濃度の上昇．パーキンソン病 2 症例（上段，下段）における levodopa 血中濃度
（○：通常食，◆：低タンパク食）

levodopa の吸収，移行を競合阻害する．このため levodopa の吸収は食事による影響を受けやすく，空腹時の吸収はよいが，タンパク質の多い食事の後では吸収が悪くなる．Levodopa の効果が不十分な時には，低タンパク食療法により levodopa 吸収が改善する場合もある（Fig. 3）．

2）ドパミンアゴニスト

ドパミンアゴニストは，線条体のドパミン受容体を直接刺激することにより抗パーキンソン病作用を示す．ドパミンアゴニストは levodopa と比べて半減期が長く，安定した血中濃度を維持することができる．ドパミンアゴニスト使用により，levodopa 長期使用時にみられるような wearing-off 現象やジスキネジアなどの問題症状の発生を遅らせることがエビデンスとして明らかになっている．現在，本邦で用いられているドパミンアゴニストには，麦角アルカロイド系の bromocriptine，pergolide，cabergoline と，非麦角系の talipexole と pramipexole がある．麦角系ドパミンアゴニストの副作用としては悪心，嘔吐などの消化器症状の頻度が高い．まれではあるが肺線維性変化，胸水などの特異的な副作用があり念頭においておく必要がある．また，最近，心臓弁膜症の合併が報告されている[2]．非麦角系ドパミンアゴニストは，消化器系副作用は少ないが，眠気の副作用が強く，睡眠発作なども報告されており，服薬中の自動車運転は避けたほうがよい．麦角系アゴニストは肝臓のチトクローム P450（CYP）3A4 および 2D6 によって代謝される．したがって，マクロライド系抗生物質，抗真菌薬，グレープフルーツジュースなど同 CYP の阻害作用を有する製剤との併用はドパミンアゴニストの上昇をもたらしうる（Fig. 4）．また，非麦角系ドパミンアゴニストは腎臓からの排泄が多い．このため，腎機能低下により血中濃度に影響を受けやすい．

3）モノアミン酸化酵素（MAO）-B 阻害薬

MAO は消化管，肝臓，血管内皮細胞など生体組織に広く分布する酵素であり，ドパミン，ノルアドレナリン，セロトニンやチラミンなどのアミン類の酸化的脱アミノ反応を介在する．脳内のドパミンは MAO サブタイプの 1 つである MAO-B と COMT により最終代謝産物である homovanillic acid（HVA）まで代謝される．MAO-B の特異的阻害は脳内におけるドパミンの作用を増強し，levodopa の効果を高め

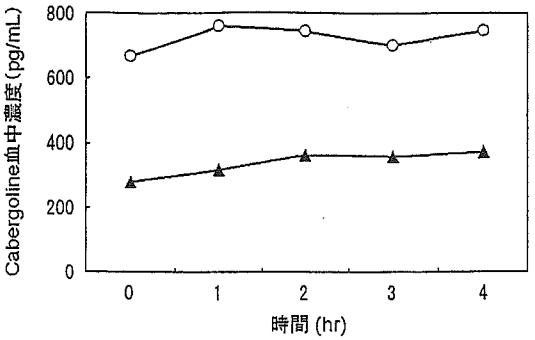


Fig. 4　グレープフルーツジュース7日間併用によるcabergoline血中濃度の上昇
(○：グレープフルーツジュース併用，
▲：cabergoline単独)

る[3]．現在，selegilineが治療薬として臨床で使用されている．Selegilineは麦角系ドパミンアゴニストと同様にCYP 3A4および2D6によって代謝される．したがって，同CYPの阻害作用を有する製剤との併用はselegiline血中濃度の上昇をもたらす．また，三環系抗うつ薬，選択的セロトニン再取込み阻害薬との併用はセロトニン症候群などの重篤な副作用の発現が報告されているため併用禁忌となっている．Selegilineには実験的な神経細胞保護作用が認められているが，大規模臨床試験の効果は，神経細胞保護作用よりは症候性のものと考えられている．

4）抗コリン薬

抗コリン薬は最も古いパーキンソン病治療薬であり，現在も使用されているtrihexyphenidylによる治療は1949年に報告されている．中枢性抗コリン作用によって記銘力の低下やせん妄が引き起こされることがあるため，高齢者への使用は控えたほうがよく，最近は抗コリン薬の使用頻度は減少してきている．

5）NMDA受容体拮抗薬

AmantadineはA型インフルエンザに対する抗ウイルス薬として開発されたが，偶然にパーキンソン病症状改善作用が認められ，以後，パーキンソン病治療薬として用いられるようになった．動物実験ではドパミン神経細胞終末からのドパミン遊離促進等の報告があるが，ヒトでの作用機序は不明な点が多い．近年では線条体におけるNMDA（N-methyl-D-aspartate）受容体の拮抗作用がその作用機序に関与すると考えられている．また，amantadineはlevodopa誘発性ジスキネジアに対して有効であるとの報告がなされている[4]．副作用として血中濃度の上昇に伴い幻覚，興奮あるいは不随意運動（ミオクローヌス）が出現することがある．Amantadineは腎排泄性の薬剤であり，腎機能低下症例（Ccr 50 mL/min以下）では血中濃度が上昇するため投与量を調整する．

3．開発中の治療薬

現在，数多くのパーキンソン病治療薬が開発されている．その中には，A）ドパミンアゴニスト貼付剤や水溶性levodopaなどのように，既存の抗パーキンソン病薬を改良，発展させたもの，B）COMT阻害薬などドパミン代謝系に働く新しい薬剤，C）zonisamideのようにすでに他疾患に使用されていた薬剤のパーキンソン病への応用，そして，D）現在使用されているドパミン系に作用する薬剤とは作用機序が全く異なる薬剤，などがある．本章ではとくにD）に含まれる薬剤を概説する．

1）KW-6002

アデノシンA_{2A}受容体は脳内において，線条体から淡蒼球にいたるindirect pathwayを構成しているGABA，エンケファリンを含む中型有棘ニューロンに特異的に発現していることが知られている．パーキンソン病においてはドパミン神経細胞変性による脱抑制のため，indirect pathwayが興奮状態にある．KW-6002はアデノシンA_{2A}受容体拮抗薬であり，中型有棘ニューロン上のアデノシンA_{2A}受容体を阻害することによりindirect pathwayの興奮状態を是正する作用を有する[5]．本薬剤はMPTP投与パーキンソン病モデル動物において運動障害を改善し，また，levodopaの効果を増強，延長することが認められている．海外での後期第II相試験では，プラセボに比べ有意にオフ時間の減少が認められている．現在，国内において前期第II相試験が施行されている．治験薬（20 mg，40 mgまたはプラセボ）1日1回12週間投与時の有効性（症状日記を用いてオフ時間平均割合の変化を評価），安全性を二重盲検群間比較法で評価している．

2）ONO-2506

アストロサイト特異的タンパク質であるS-100βはパーキンソン病，アルツハイマー病などの神経変性疾患や脳血管障害患者脳組織，脳脊髄液で上昇することが報告されており，アストロサイト機能異常がこれら中枢神経疾患に関与することが推測されている．ONO-2506はアストロサイトにおけるS-100β増加抑制，NGFβ産生亢進，グルタミン酸トランスポーター減少，GABA受容体減少および炎症性酵素誘導抑制などの作用機序を有するアストロサイト機能改善剤である．本薬剤はMPTP投与パーキンソン病モデ

ル動物において，パーキンソン病様症状を軽減させることが認められており[6]，パーキンソン病治療薬としての臨床応用が期待されている．現在，国内において第II相試験が施行されている．治験薬（100 mg，600 mg またはプラセボ）1日1回16週間投与時の有効性（UPDRS：Unified Parkinson's Disease Rating Scale，症状日記を用いて評価），安全性を二重盲検群間比較法で評価している．

3）TCH-346

MAO-B 阻害薬である selegiline が *in vitro* において神経細胞死抑制作用を有することは以前より報告され，実際，パーキンソン病患者においても，進行抑制の効果を有するのかを実証すべく大規模臨床試験がなされてきた．そこで，selegiline と類似構造を有する TCH-346 が開発された．TCH-346 は selegiline とは異なり MAO-B 阻害作用を有していない．TCH-346 は培養細胞の細胞死抑制やサル MPTP 投与パーキンソン病モデルのドパミン神経細胞死抑制など *in vitro* および動物実験系において，神経細胞死抑制作用を示している[7]．パーキンソン病患者を対象として，国内において前期第II相試験まで施行された．パーキンソン病患者における治験薬（2.5 mg，10 mg またはプラセボ）1日1回4週間投与時の安全性を二重盲検群間比較法で評価している．

4．開発の今後の方向

パーキンソン病治療薬の今後の方向であるが，病気自身の進行を抑制する神経細胞保護薬のさらなる開発が期待される．今後，高齢化に伴う神経変性疾患患者数の増加も予想され，神経細胞保護薬の開発はパーキンソン病に限らずアルツハイマー病，筋萎縮性側索硬化症など他の神経変性疾患の治療においても重要性を増す分野である．しかし，パーキンソン病に対する神経保護作用薬開発の問題点は，神経細胞死抑制作用を臨床上評価することの難しさである．パーキンソン病の進行は緩徐であり，また，症状は抗パーキンソン病薬使用により修飾されるため臨床的にパーキンソン病自体（ドパミン神経細胞の変性）の進行に対する治療薬の効果を評価するには困難が伴う．しかも，評価のための抗パーキンソン病薬の中断は倫理的に難しいのが現状である．β-CIT や ^{18}F-dopa などドパミン神経に取り込まれる物質を用いた画像検査による残存ドパミン神経細胞数の定量が用いられてきてはいるが，その信頼性にはいくつかの問題点があり，今後，より信頼できる非侵襲的な評価法の開発が，薬効評価の鍵となる．薬剤以外のパーキンソン病治療ではグリア細胞株由来神経栄養因子（GDNF）などの神経栄養因子，自己神経幹細胞を用いた細胞移植，ウイルスベクターを用いた遺伝子治療（ドパミン代謝系酵素の遺伝子導入）などが開発されてきている．

5．おわりに

パーキンソン病治療の中心をなす levodopa は，前述のとおり吸収が不安定であり薬物血中濃度に基づいた治療時の工夫が必要であると思われるが，現実はごく一部の施設で行われているにすぎない．また，ドパミンアゴニストなどの薬物相互作用の情報も十分なものではなく，神経疾患治療学において，臨床薬理学の果たす役割は今後も増していくものと思われる．また，パーキンソン病治療薬開発においても今後の貢献が期待される．

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＜シンポジウム 5—1＞パーキンソン病の病態と治療

パーキンソン病治療の個人差と薬物動態

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（臨床神経，45：895—898, 2005）
Key words：パーキンソン病，個人差，薬物動態，相互作用，食事

はじめに

薬は体内へ入り受容体に作用して効果を現わす．処方した薬は服薬の過程（コンプライアンス）を経て，吸収・分布・代謝・排泄により血中濃度が決まり（bioavailability），拡散およびタンパク結合して作用部位での薬物量が決まる．この過程を pharmacokinetics（薬物動態）と呼ぶ．さらに受容体へ作用して薬理作用が発現し臨床薬理効果が現れる．この過程は pharmacodynamics（薬力学）と呼ばれる．治療薬は作用部位へ届くまでの間に食事，消化管の変化，代謝，排泄等により影響を受け，日によって効果がことなる．さらに，パーキンソン病では服用を始めて数年経過するとジスキネジアや wearing off 等がおこりはじめ，効果がことなってくる．パーキンソン病治療において日常診療でみられる治療薬の効果における個人差や日内変動，日間変動を薬物動態をもとに検討した．

L-dopa：L-dopa の薬物動態には約 4 倍の個人差をみとめた（Fig. 1a）．また，同じ個人であっても日間変動がみられ，L-dopa の吸収は服用後に安静にすることにより吸収は高まった（Fig. 2b）．L-dopa の吸収は食事の影響を受けやすく，食事中のタンパク質が多くなると吸収は低下あるいは遅延し，No ON や Delayed ON をおこす（Fig. 1c, d）．麺類やおに

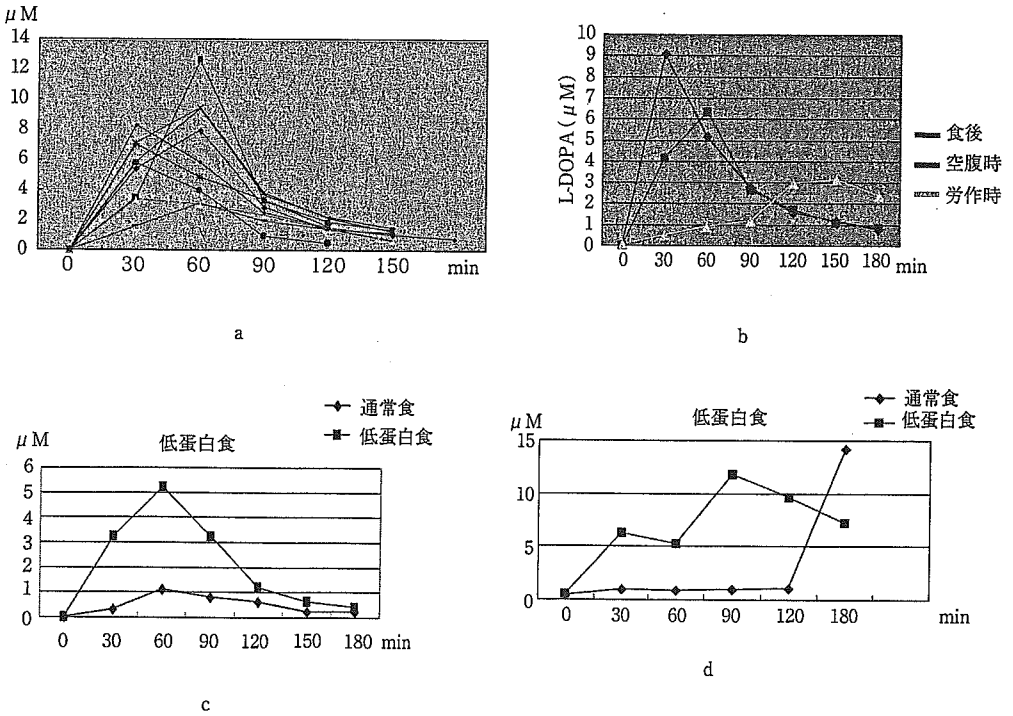

Fig. 1

a：L-dopa 血中濃度の個人差
b：L-dopa の吸収の日間変動　L-dopa/benserazide 100/25 mg
c：低タンパク食と L-dopa 吸収　48 歳男性　L-dopa/carbidopa100/10mg
d：低タンパク食と L-dopa 吸収　74 歳女性　L-dopa/carbidopa200/20mg

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（受付日：2005 年 5 月 26 日）

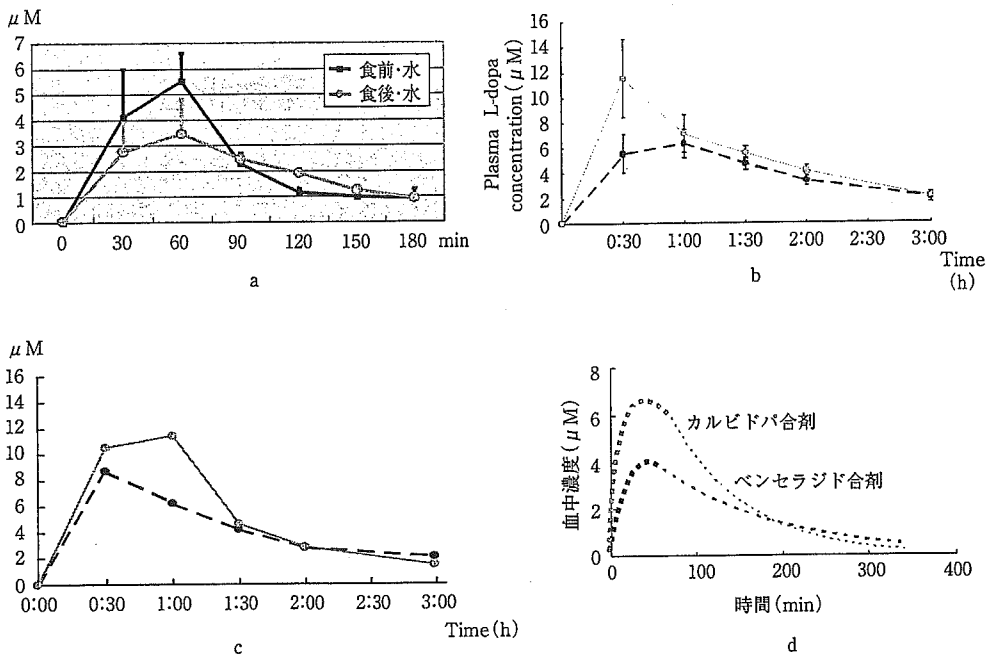

Fig. 2

a：食前と食後服用の血中 L-dopa 濃度
L-dopa/benserazide 100/25mg，Mean±SD　n=4

b：Domperidone 併用による L-dopa 血中濃度の変化
■ L-dopa/benserazide（100/25mg）
■ L-dopa/benserazide（100/25mg）+ domperidone（10mg）Mean±SD　n=5

c：カマグ併用による L-dopa 血中濃度の変化
■ L-dopa/benserazide（100/25mg）+ magnesium oxide（1g）
■ L-dopa/benserazide（100/25mg）Mean±SD　n=5

d：L-ドパ予想血中濃度（Tmax=60min）

ぎりなどの低タンパク食は吸収を改善する効果がある．また，食前の服用は L-dopa の吸収を改善させた（Fig. 2a）．鎮吐薬としてパーキンソン病治療薬と併用されるドンペリドンは Auerbach 神経叢のアセチルコリン細胞に分布する D2 受容体に作用して消化管機能を高めることから，薬物の吸収に対する作用を検討するために L-dopa 服用後の血中濃度を測定したところ，ドンペリドンの併用により吸収が増加することを明らかにした（Fig. 2b）．また，便秘の治療にもちいられるカマグは制酸薬でもあるために，その併用は L-dopa の吸収を低下させると記載されている．このことから L-dopa の吸収に対する作用を検討したところ変化はなかった（Fig. 2c）．L-dopa 製剤にはカルビドパ製剤とベンセラジド製剤があるが，L-dopa 量が同じであっても切りかえ時には効果のことなる症例を経験する．このことから両者の血中濃度を population PK study で検討したところ，ベンセラジド製剤で血中濃度がより高いことが示された（Fig. 2d）．L-dopa の抗パーキンソン病作用は，結核治療薬の isoniazid（INH）との併用で低下する[1]．これは，INH が L-dopa 脱炭酸酵素を抑制し，脳内における L-dopa からドパミンへの代謝を抑制するためと考えられる．鉄剤は L-dopa をキレートし，吸収を低下させるために，同時刻の併用は避けて服用したほうがよい[2]．

ドパミン受容体作動薬：麦角系ドパミン受容体作動薬にも L-dopa と同程度の個人差をみとめた．また，麦角系アルカロイドのカベルゴリンは，抗真菌薬のイトラコナゾール，マクロライド系抗生物質のクラリスロマイシンやグレープフルーツとの併用により健康成人においてもパーキンソン病治療例においても血中濃度が 2～3 倍に上昇した[3)～5)]．ブロモクリプチンも同様に血中濃度の上昇をみとめる[6]．この作用はペルゴリドでは観察されなかった．

セレギリン：セレギリンは CYP3A で代謝される．このために一部の女性ホルモン剤との併用はセレギリンの代謝を抑制する[7]．

アマンタジン：アマンタジンはインフルエンザの予防や脳血管障害後遺症にももちいられている．アマンタジンは未変化体として腎から排泄されるために，腎クレアチニンクレアランスの低下にともない血中濃度が上昇する．とくに体重の少ない女性ではクレアチニンが基準値内であっても血中濃度が上昇し副作用のおこることがある．

チサニジンとフルボキサミンは神経疾患の治療では時に併用される組み合わせである．チサニジンの代謝酵素である