Population Pharmacokinetic Analysis for Nimodipine

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Introduction
Nimodipine is a calcium antagonist of the 1,4-
dihydropyridine class (Fig.1). At present, nimodipine
is clinically used in over 50 foreign countries for the
treatment of acute and chronic cerebrovascular
diseases. In Japan, the drug has been investigated in
a series of clinical trials in healthy subjects and
patients with vascular dementia. We performed the
population pharmacokinetic (PPK) analysis with
plasma concentration data from these Japanese clinical
trials to investigate the factors which may affect
nimodipine pharmacokinetics as well as its intra- and
inter-individual variabilities.

Methods
1) Data set for analysis
The plasma concentration data from formal
pharmacokinetic (PK) studies in healthy subjects, as
well as PK screening in phase III long term studies
were collected for the PPK analysis. In the formal
PK studies, more than 10 blood samplings were
conducted per subject, according to the prescribed
sampling times in the study protocol. On the other
hand, only 2 to 3 blood samplings per patient were
conducted after reaching steady state in the PK
screening. These samplings were conducted at the
same time with the blood sampling for clinical
laboratory tests. Although blood sampling time was
not defined in the protocol for PK screening, it was
expected to vary patient by patient (“natural random
sampling”[1]). Plasma nimodipine concentrations
were determined by GC-ECD methods in two different
laboratories. The methods were validated in each
laboratory and finally “cross-validated” in both
laboratories.

2) PPK analysis
By using NONMEM version V level 1.0, PREDPP
version IV level 1.0 and NM-TRN version III level 1.0
which were installed on DEC alpha 4100 with open
VMS, a two-compartment model with first-order
absorption and proportional error model were applied
to the nimodipine concentration-time data. Any
variables which may influence parameters in the PK
model, such as subject backgrounds (demographic
data, clinical lab. test values), administered nimodipine
tablet (15mg or 30mg tablet), nimodipine dose per
administration (30mg, 60mg or 90 mg) and condition
for drug administration (fasting or fed), were evaluated
on their data distributions and then with a likelihood
comparison test. A p-value of 0.05 was adopted to

Fig.1 Chemical structure of nimodipine
include covariates during the model building process. Once all candidate covariates show a significance in the model building process, the covariates should be re-tested by using stepwise deletion method, after being assembled to the full model equation. A stricter p-value of 0.01 was used for deciding covariates in the final model.

**Results**

PPK analysis was conducted by using 1766 plasma concentration data from 68 healthy young male volunteers (1712 points) and 23 patients (54 points).

The final estimated model equations were as follows,

- \( CL \) (L/hr)=693 (age<65), 222 (age>=65)
- \( \frac{Vc}{f} \) (L)=1460
- \( Ka \) (1/hr)=7.34 \times 0.0572^{FD} \times 0.453^{TB}
- \( Q \) (L/hr)=120 \times 1.76^{DS}
- \( \frac{Vp}{f} \) (L)=1720
- Lag (hr)=0.223

(FD: FD=1 when fed (within 1 hour after/before meal), otherwise FD=0, TB: TB=1 when 30mg tablet was administered, otherwise TB=0, DS: DS=1 when administered single dose was 30mg, otherwise DS=0)

According to the final model equations, effects of the variables on nimodipine PK could be summarized as follows:

1. Clearance (CL) for elderly (>=65yrs.) would be reduced to 32% of young subjects.
2. Absorption rate constant (Ka) was decreased if nimodipine was administered with meal and/or as 30mg tablet.
3. Inter compartment clearance (Q) was increased by 76% if nimodipine dose per administration was 30mg.

The estimates of inter-individual variabilities (CV%) were 60% in CL, 59% in apparent volume of distribution for central compartment (Vc/F), 0.0% in Ka, 50% in Q, 95% in apparent volume of distribution for peripheral compartment (Vp/f) and 47% in lagtime (Lag). The residual variability was 38%.

**Discussion**

The results obtained by this PPK analysis seemed to be reasonable because of the following post analytical evaluations:

1. Predicted individual values based on the final model fitted to the observed values (Fig.2).
2. Simulated profiles based on the final model for each condition were in good agreement with each observed value.
3. Estimated CL value was comparable to the results in the formal PK studies with young subjects (654.3 \pm 280.2 L/hr after 60mg single dose).
4. Food effect on the nimodipine PK was suggested in both results of PPK analysis and formal PK study. (In the formal PK study, Cmax was reduced by 68%, and tmax was delayed for 15.1 hr from 0.9 hr by breakfast, while CL/f was not significantly affected.)

**References**