Pharmacokinetics of Nisoldipine, Investigated with a Newly Developed GC/MS Method

Introduction
Nisoldipine is a long acting calcium antagonist which is clinically effective against hypertension and angina pectoris by 5 - 10 mg once daily administration). However, the pharmacokinetics of the drug was not fully investigated because sensitive assay method was not available. Therefore, we have newly established a high sensitive GC/MS method and performed a pharmacokinetic study with it.

Methods
(1) Analytical method by GC/MS (negative CI)
Extraction procedure: To 0.5 ml plasma, 50 pg internal standard (nitrendipine), 250 μl 0.1N NaOH and 5 ml CH2Cl2 were added. The mixture was shaken for 10 min and centrifuged at 3,000 rpm for 5 min. Four ml aliquot of the organic layer was evaporated to dryness under N2 stream. The residue was dissolved in 1.5 ml n-hexane/EtOAc (9:1) and applied to a BOND ELUT® NH2. Then the adsorbates were eluted with 1 ml EtOAc after washing the BOND ELUT® with n-hexane/EtOAc (9:1). The elution was evaporated to dryness under N2 stream and reconstituted in 50 μl EtOAc before analysis.

GC/MS assay: A Thermo Quest SSQ70 GC/MS system with Micro VIP™ (direct interface, ion source 140°C, 70eV) was used. One μl of the reconstituent was injected on a 15m stainless steel column, Ultra ALLOY+1(s) (FRONTIER LAB Ltd.), with He as carrier gas by a column head pressure of 5 psi. Following time program was applied: 100°C for 1 min, then 40°C/min up to 270°C, then 20°C/min up to 300°C and maintained at 300°C for 1.2 min. The injector temperature was 250°C and transfer line temperature was 270°C. The GC/MS was operated in negative ion chemical ionization mode with SIM. Nisoldipine was detected at the base peak m/z 388, and internal standard at m/z 360. Nisoldipine concentrations were calculated by peak area comparison with the internal standard. In the range of 10 - 1,000 pg/ml, the recovery was 85 - 98%. The accuracy was within ±10 % and intra-, inter-variabilities were less than 6 % at the range of 10 - 1,000 pg/ml.

(2) Pharmacokinetic study
Single oral doses of nisoldipine 5 mg and 10 mg tablets were administered under fasting condition with 150 ml water to 10 healthy adult male volunteers in a randomized crossover study with 8 days wash-out interval. Above mentioned GC/MS method was applied in this study.
Fig. Mean nisoldipine concentration profiles obtained by GC/MS method after single doses of 5mg and 10mg

Results

With the newly developed GC/MS method, plasma nisoldipine concentration could be determined until at least 24 hr after dosing (Fig.). Pharmacokinetic parameters are summarized in Tab. C\textsubscript{max} and AUC increased dose proportionally. T\textsubscript{1/2} calculated from the terminal phase was about 9 hr; which was prolonged compared to 2 - 3 hr in the previous results, due to the detection of lower concentration than before.

Tab. Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Dose</th>
<th>C\textsubscript{max} [ng/ml]</th>
<th>AUC\textsubscript{∞} [ng-h/ml]</th>
<th>t\textsubscript{max} [h]</th>
<th>t\textsubscript{1/2} [h]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5mg</td>
<td>0.93 (1.52)</td>
<td>4.03 (1.59)</td>
<td>1.5 (0.5-4)</td>
<td>8.49 (1.41)</td>
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<td></td>
<td>0.73 - 1.19</td>
<td>3.08 - 5.27</td>
<td>0.96 - 2.45</td>
<td>6.95 - 10.38</td>
</tr>
<tr>
<td>10mg</td>
<td>2.12 (1.78)</td>
<td>9.20 (1.79)</td>
<td>1.5 (0.5-4)</td>
<td>9.84 (1.21)</td>
</tr>
<tr>
<td></td>
<td>1.52 - 2.96</td>
<td>6.56 - 12.89</td>
<td>1.08 - 2.50</td>
<td>8.80 - 11.00</td>
</tr>
</tbody>
</table>

upper column : geometric mean (SD); median (range) for t\textsubscript{max}
lower column : 90% confidence interval

Discussion

Duration of nisoldipine's effectiveness had been explained by the higher and long-lasting binding to calcium receptors\textsuperscript{4-7}. According to the results of this study with a high sensitive GC/MS assay method for nisoldipine, t\textsubscript{1/2} of nisoldipine was calculated to be about 9hr, which is similar to other once daily calcium antagonists\textsuperscript{8-10}. Therefore, it was suggested that the slow elimination of nisoldipine may also attribute to the long acting effect of this drug.

References