Age Difference in Kinetics of Diazepam and Lorazepam in Man

Satoru MINESHITA*1 Shigeyuki NAKANO*2 Hiroshi YANAIBARA*3 Tamotsu FUKUDA*3 Kikuo TAKANO*4 Atsushi TOYOSHIMA*5 Yumiko HONDA*6

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*1 Department of Clinical Pharmacology, Medical Research Institute, Tokyo Medical and Dental University, 2-3-10, Chiyoda-ku, Kandasurugadai, Tokyo 101, Japan
*2 Department of Pharmacology, Ehime University, School of Medicine
*3 Department of Hospital Pharmacy, Ehime University Hospital
*4 Department of Medicine, School of Medicine, Juntendo University
*5 Department of Urology, School of Medicine, Teikyo University
*6 Department of Medicine, Aoyama Kyosai Hospital

The effect of age on the pharmacokinetics of two benzodiazepines, diazepam and lorazepam, was studied. Seven young healthy male volunteers, 22 to 25 years old, and 10 elderly people, aged 67 to 90, participated in this study after giving informed written consent. One mg of lorazepam was administered orally to the elderly volunteers, and 2 mg was given to the young volunteers. Using two weeks drug-free interval, 5 mg of diazepam was administered orally to the two groups using randomized experimental protocol based on a Latin square design.

Blood samples were drawn for 72 hr and plasma concentrations of diazepam, N-desmethyl-diazepam, and lorazepam were determined by electron-capture gas-liquid chromatography. Pharmacokinetic parameters were calculated and comparisons were made between the young and the elderly.

With diazepam, elimination half-lives (t1/2) of the elderly group (Mean±SD: 86.3±65.4 hr) were prolonged compared with those of the young (38.6±8.2 hr) at the 5% significance level.

The volumes of distribution (Vd) of diazepam in the elderly (1.42±0.83 l/kg) were significantly larger than those of the young (0.79±0.20) (P<0.05). The t1/2 and Vd of lorazepam in the elderly (29.6±16.7 hr, 1.35±0.46 l/kg respectively), were not significantly different from those of the young (18.4±3.7 hr, 1.48±0.58 l/kg respectively); however, clearance of lorazepam in the young (57.0±21.09 ml/hr/kg) was higher than in the elderly (35.42±10.63 ml/hr/kg) (P<0.05). Clearances of diazepam in the young and in the elderly were nearly identical.

Key words: diazepam, lorazepam, pharmacokinetics, elderly, young
**Introduction**

The elderly are generally considered to be different from young people in terms of drug response. It is reported that the frequency of intoxication caused by drugs is higher in the elderly than the young.\(^1\) While altered drug handling is a major potential source of difference in responsiveness to drugs, the relative contribution of pharmacokinetics and pharmacodynamics to this difference is not clear.

Recently benzodiazepines have been used not only as a sedative but also as a premedicant drug.\(^2\) In the present study two benzodiazepines (BDP), diazepam (DZP) and lorazepam (LZP), were studied to elucidate age differences in the kinetics of these drugs.

**Volunteers and Methods**

Seven young Japanese men (Y: 22-25 yr) and 10 aged Japanese men and women (A: 67-90 yr) took part in this study. Mean±SD body weight was 60.1±4.7 kg (51-65 kg) in the young, and 54.4±7.0 kg (47-68 kg) in the elderly. All subjects submitted informed written consent before participating in the study. Subjects were free of identifiable medical or psychiatric disease and none had a history of regular drug use.

The schedule of drug administration in subjects was randomized according to a Latin square design and at least 2 wk elapsed between trials. Each subject took diazepam (one 5-mg tablet) or lorazepam (one or two 1-mg tablets) between 08:15 and 08:30 am, with 180 ml of water after fasting overnight.

Subjects remained fasting for 4 hr after each benzodiazepine dose after which time they resumed their normal diet. Blood samples (5 ml) were drawn from the ante-cubital vein prior to the dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 33 and 48 hr after dosing of both benzodiazepines and additionally obtained 57 and 72 hr after oral diazepam administration. Blood samples were immediately centrifuged and plasma was separated and kept frozen at -20°C until the time of assay.

Total plasma concentrations of diazepam and N-desmethyldiazepam, which is one of main metabolites of diazepam, and lorazepam were determined by electron-capture gas-liquid chromatography.\(^3,4\) The elimination rate constant (k) was determined from plasma concentrations using linear regression on a natural logarithm concentration-versus time curve. Half-life was calculated by dividing the elimination rate constant into 0.693.

Area under the plasma concentration-time curve (AUC\(_{0-\infty}\)) was calculated by the following equation\(^5\):

\[
AUC_{0-\infty} = \sum_{i=0}^{n-1} \frac{t_{i+1}-t_i}{2} (C_i + C_{i+1}) + C_n/k,
\]

where \(C_i\) is the plasma drug concentration at the sampling time of \(t_i\), \(k\) is the elimination rate constant and \(C_n\) means the predicted plasma drug concentration at the last sampling time. The volume of distribution and the clearance were estimated by:

\[
V_d = \frac{D \times F}{k \times AUC_{0-\infty}}, \quad \text{and} \quad Cl = \frac{D \times F}{AUC_{0-\infty}}
\]

where \(D\) is the dose administered and \(F\) is the extent of absorption of the drug.\(^5\) As \(F\) could not be calculated in the present study it was assumed for purposes of comparison to be unity. In this respect Greenblatt and his coworkers showed 97.2% absorption in the elderly i.e. \(F\approx1\). This fact may support the assumption of \(F=1\) in our calculation.\(^6\)

**Statistical analysis**

The mean and standard deviation of each parameter were calculated for each group. The variances of means were tested for homoscedasticity and when variances were found to be homogeneously distributed values were compared by Student's t-test, Wilcoxon two sample test.

**Results**

There was considerable inter-individual variation in plasma concentrations of both benzodiazepines. Mean plasma lorazepam and diazepam concentrations are given in Figs. 1 and 2 and concentrations of one of the metabolites, N-desmethyldiazepam, are shown in Fig. 3. Table 1 shows the individual details of the young and elderly volunteers. Table 2 shows the pharmacokinetic parameters of the two benzodiazepines in the young and elderly.

**Diazepam**

The elimination half-life was prolonged in the elderly compared with the young (\(P<0.05\)) and the volume of distribution was increased in the elderly (\(P<0.05\)). However there were no significant differences between the two groups in the
other pharmacokinetic parameters.

**Lorazepam**

Peak plasma concentration was higher in the young than in the elderly (P<0.01), and the clearance was also higher in the young volunteers compared with the elderly group (P<0.01). There were no differences between the two groups in the elimination half-lives at the 5% level of significance.

**N-Desmethyldiazepam**

Figure 3 shows the plasma concentration-time curve of N-desmethyldiazepam up to 72 hr. The
Fig. 3 Time course of N-desmethyldiazepam. Plasma concentration of N-desmethyldiazepam level following a single oral administration of 5 mg diazepam: young (*), elderly (○).

Tab. 1 Age, Body Weight, and Gender of the Volunteers

<table>
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<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>B·W (kg)</th>
<th>Sex</th>
<th>No.</th>
<th>Age (yr)</th>
<th>B·W (kg)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>83</td>
<td>47</td>
<td>F</td>
</tr>
</tbody>
</table>

Mean 23.5 60.1 60.1 Mean 78.3 54.4
SD     1.4 4.7 4.7       SD     9.3 7.0

The area under the plasma concentration-time curve from 0 to 72 was calculated; in the young the value was $1.77 \pm 0.43 \mu g \cdot hr/ml$ whereas a value of $2.11 \pm 0.50$ was obtained in the elderly. Although there was a tendency towards accumulation of N-desmethyldiazepam in the elderly, this was not significant between the two groups at the 5% significance level.

Discussion

The effects of age on the pharmacokinetics of benzodiazepines have already been studied in Western people, but there has not as yet been a systematic study carried out in Japanese people. In the present study, the pharmacokinetics of diazepam and lorazepam in Japanese young and elderly people were studied and compared.

Lorazepam

The study of lorazepam pharmacokinetics in Western elderly subjects, 60 to 84 yr of age, gave a value for the elimination half-life of 15.9 hr, and in the young volunteers from (19 to 38 yr), the half-life was 14.1 hr and 14.3 hr. In this report there were no significant differences between the young and the elderly. It was also shown that the half-life of lorazepam was independent of dose and route of administration.

We gave 1 mg of lorazepam to the elderly and 2 mg to the young in order to comply with dose levels used in normal clinical practice. The peak plasma concentration was significantly higher in the young according to the administered dose. This significant difference in peak plasma levels is.
However, rather artificial. When we correct the plasma concentration for dose by dividing 'young' values by 2, the values are almost identical with those of the elderly. In this study the mean half-life in the elderly, 67 to 90 yr of age, was 29.6 hr and in young subjects, ranging in age from 22 to 25, it was 18.4 hr. The mean values are fairly different, but the interindividual variation in the elderly was large and thus there were no statistically significant differences at the 5% level. It is of interest to note that in young Japanese people the elimination half-life of diazepam was relatively long compared with European, but as to lorazepam the differences were not prominent. For example the time to the peak plasma concentration was approximately 2 hr. Thus the values obtained in our study are fundamentally consistent with those of Western people.

A large proportion (approximately 75% of administered dose) of lorazepam is conjugated with glucuronic acid and the glucuronide conjugate is rapidly excreted into urine. However, a small proportion of lorazepam is metabolized by hepatic oxidation processes and some derivatives, such as quinazoline derivatives, hydroxylorazepam and unidentified metabolites have been reported. In this study it was shown that apparent volumes of distribution were not different, and total clearance in the elderly was reduced. Kraus and co-workers observed a weak negative correlation of lorazepam clearance with age among 11 subjects, 15 to 75 yr of age.

From these interesting findings it can be conceived that lorazepam metabolism is not extensively affected by aging. The capacity for glucuronidation of lorazepam appears to decline slightly with age but further studies are needed to determine whether this change is of clinical significance.

### Diazepam

Diazepam is widely used in the management of anxiety and tension and as an anticonvulsant. Despite this extensive clinical experience, there is only limited quantitative information upon the disposition and elimination of this drug. Most studies of the plasma elimination of diazepam have been limited to data obtained after oral administration of the drug, particularly after prolonged therapy. Such estimates of the half-life of diazepam in normal volunteers and psychiatric patients range from 9 to 35 hr. Kaplan et al. showed it was 33 hr in four normal subjects. Klotz and co-workers have already shown that elimination of this drug is age dependent ranging from about 20 hr in 20 yr old to about 90 hr at 80 yr of age.

In Japanese people, however, there have been no studies undertaken to investigate age-related differences in pharmacokinetics for diazepam. In our study the elimination half-life in the young was 38.6 ± 8.2 hr and in the elderly it was 86.3 ± 65.4 hr. This shows that the elimination half-life of diazepam in Japanese young people is relatively long compared with that of Western young people. However, in the elderly group the half-lives were shown to be consistent with those of Western elderly people.

The volumes of distribution were larger in elderly people (5% significance level) whereas clearance was almost identical. Thus it appears

<table>
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<th>Diazepam</th>
<th>Lorazepam</th>
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<tbody>
<tr>
<td></td>
<td>Young</td>
<td>Elderly</td>
</tr>
<tr>
<td>Peak plasma concentration (ng/ml)</td>
<td>187.0 ± 18.1</td>
<td>163.3 ± 61.5</td>
</tr>
<tr>
<td>Time to peak (hr after dose)</td>
<td>1.7 ± 0.8</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Elimination half-life (hr)</td>
<td>38.6 ± 8.2</td>
<td>86.3 ±65.4**</td>
</tr>
<tr>
<td>AUC0→∞ (µg·hr/ml)</td>
<td>6.1 ± 1.9</td>
<td>9.7 ± 7.2</td>
</tr>
<tr>
<td>Vd area (l/kg)</td>
<td>0.79± 0.20</td>
<td>1.42± 0.83*</td>
</tr>
<tr>
<td>Cl (ml/hr/kg)</td>
<td>14.6 ± 3.7</td>
<td>15.7 ±11.9</td>
</tr>
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</table>

Values shown are mean±standard deviation.
AUC0→∞: area under the plasma concentration-time curve from 0 to infinity after dosing. Vd area and Cl: volume of distribution and clearance of the drug respectively. On Vd area or Cl estimation, F was taken as 1.0. *: P<0.05, **: P<0.01 when compared between young and elderly.
that the prolongation of elimination half-life of diazepam in the elderly is primarily dependent on an increase in the volume of distribution of the drug. Diazepam is primarily metabolized by the microsomal mixed function oxidases in the liver. In humans, the main pathway of diazepam biotransformation is N-demethylation, yielding N-desmethyldiazepam. N-Desmethyldiazepam is then oxidized at the 3-position to convert it to oxazepam, which is eliminated almost entirely as glucuronide conjugates.\textsuperscript{14,15} The effect of age on glucuronide conjugation of foreign chemicals by man is not well understood. Studies with acetaminophen, another drug metabolized principally by glucuronide conjugation, were suggestive of prolonged t\textsubscript{1/2} and reduced clearance in the elderly.\textsuperscript{16,17} Although in our study the half lives of lorazepam were not statistically different in the 2 groups, in the case of over 85 yr, t\textsubscript{1/2} tended to be prolonged and clearance was reduced. Even with lorazepam the capacity of glucuronidation appears to be limited in extremely elderly people.

The accumulation of the main metabolite of diazepam, N-desmethyldiazepam, showed no statistical significance between the two groups with respect to AUC and profile, but further evaluation needs to be performed by measuring plasma N-desmethyldiazepam concentrations over a longer time period after dosing than in the present study, in order to clarify the exact mechanism of the accumulation of diazepam and its metabolites.

These results indicate that age has probably different influences on the kinetics of diazepam and lorazepam due to the different metabolic characteristics of the two drugs, since lorazepam is directly metabolized to glucuronide conjugates whereas diazepam is metabolized oxidation prior to glucuronide conjugation.

Reference