Effect of Age on the Pharmacokinetics of Diazepam Given in Conjunction with Spinal Anesthesia

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We studied the pharmacokinetics of intravenously administered diazepam (0.15 mg/kg) given in conjunction with spinal anesthesia in 14 patients 32 to 78 years old. The disposition of this benzodiazepine derivative was described by a two-compartment open model. All of the three major determinants (elimination phase half-life, distribution volume, and total plasma clearance) had age-related pharmacokinetic changes, indicating a more prominent drug effect in the older age group. When diazepam was given in conjunction with spinal anesthesia both the increased distribution volume and the decreased total clearance increased the plasma half-life of diazepam. There was a tendency towards lower plasma levels of the major metabolite of diazepam, N-demethyl-diazepam, with advancing age.

There was no measurable amount of the hydroxylated metabolites of diazepam, N-methyl-oxazepam and oxazepam, in plasma after a single dose of diazepam, iv. The more prominent effects of diazepam in the elderly can be explained, at least in part, by age-related changes in pharmacokinetics. According to our results, for the elderly (age > 60 years) the dose of diazepam should be reduced to half to a fourth of that used for younger patients during spinal anesthesia.

Increasing evidence of an apparent sensitivity to various therapeutic agents in old age has been reported.1,2 Age-related changes in drug responses could be due to differences in the sites of drug action,3 or to alterations in drug disposition and elimination. Impairment of drug metabolism4 or of renal function5 may result in drug accumulation in the elderly.6,7

Several investigators have indicated that adverse effects of the benzodiazepine derivatives (including chloridiazepoxide,8 diazepam,9 nitrazepam,9 and flurazepam10) are more frequent in the elderly. These reactions have been explained by an increased sensitivity of the aging brain to the action of drugs without any related change in pharmacokinetics.9 On the other hand, pharmacokinetic alterations, which might be related to the increased sensitivity of elderly patients, have been found in the disposition of diazepam,11 nitrazepam,12 and chloridiazepoxide.13 To assess whether age-related pharmacokinetic changes play a significant role in the disposition of diazepam during and after spinal anesthesia, we compared the pharmacokinetics of this benzodiazepine derivative in 14 patients of various ages. We were especially interested in the effect of total plasma clearance of the drug, which did not show age-related changes in the study of Klotz and co-workers.11

Methods

Diazepam, 0.15 mg/kg, was administered iv over 1 min into an antecubital vein 10 min before spinal anesthesia. In 14 patients 32 to 78 years old (table 1), spinal anesthesia was obtained by use of 1.5–2.0 ml lidocaine, 5 per cent at L 3–4 or L 4–5. Premedication was similar in all patients: atropine, 0.01 mg/kg, and meperidine, 1.0 mg/kg, im, 1.5 hours before anesthesia. All patients except Patient 12 had normal serum creatinine values, urines, and aspartate aminotransferase values, indicating normal hepatic and renal
<table>
<thead>
<tr>
<th>Age</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Surgical Diagnosis</th>
<th>Other Diseases</th>
<th>Abnormal Laboratory Results</th>
<th>Daily Drug Treatment (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>32, F</td>
<td>64.0</td>
<td>170</td>
<td>Varicose veins, lower extremity</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Patient 2</td>
<td>36, F</td>
<td>75.0</td>
<td>167</td>
<td>Hemorrhoids</td>
<td>—</td>
<td>—</td>
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<td>Patient 3</td>
<td>46, M</td>
<td>72.0</td>
<td>167</td>
<td>Inguinal hernia</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patient 4</td>
<td>48, F</td>
<td>65.0</td>
<td>159</td>
<td>Varicose veins, lower extremity</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Patient 5</td>
<td>50, M</td>
<td>76.0</td>
<td>174</td>
<td>Inguinal hernia</td>
<td>Arterial hypertension (WHO I)</td>
<td>—</td>
</tr>
<tr>
<td>Patient 6</td>
<td>54, F</td>
<td>54.5</td>
<td>160</td>
<td>Hallux valgus</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Patient 7</td>
<td>57, M</td>
<td>83.0</td>
<td>172</td>
<td>Varicose veins, lower extremity</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Patient 8</td>
<td>60, M</td>
<td>72.0</td>
<td>168</td>
<td>Cancer of the prostate</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Patient 9</td>
<td>61, F</td>
<td>46.0</td>
<td>155</td>
<td>Varicose veins, lower extremity</td>
<td>Arterial hypertension (WHO I)</td>
<td>—</td>
</tr>
<tr>
<td>Patient 10</td>
<td>63, F</td>
<td>71.0</td>
<td>160</td>
<td>Varicose veins, lower extremity</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Patient 11</td>
<td>63, M</td>
<td>44.0</td>
<td>150</td>
<td>Inguinal hernia</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Patient 12</td>
<td>74, M</td>
<td>59.5</td>
<td>174</td>
<td>Inguinal hernia</td>
<td>Chronic bronchitis, status past ventricular carcinoma</td>
<td>Serum creatinine 178 μmol/l, ESR 46 mm/h</td>
</tr>
<tr>
<td>Patient 13</td>
<td>76, M</td>
<td>59.5</td>
<td>161</td>
<td>Cancer of the prostate</td>
<td>Chronic bronchitis</td>
<td>ESR 87 mm/h, Hemoglobin 105 g/l</td>
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<tr>
<td>Patient 14</td>
<td>78, F</td>
<td>73.0</td>
<td>167</td>
<td>Ulcer on the leg</td>
<td>Diabetes mellitus, Arterial hypertension, Chronic heart insufficiency</td>
<td>ESR 36 mm/h, Blood glucose 10.4 μmol/l</td>
</tr>
</tbody>
</table>

* Notice that significant disease was present in the oldest patients only.
† Normal <120 μmol/l.
‡ Normal >120 g/l.
§ Normal <6.5 mmol/l.

Function. To prevent hypotension, an intravenous infusion was started 10 min before spinal anesthesia. Approximately 1 l lactated Ringer’s solution was administered the first hour and 0.5 l hourly thereafter. Whenever the systolic blood pressure decreased by more than 30 per cent of preanesthetic value, 4 mg etilefrine (Effortil®, a sympathomimetic) were injected iv (Patients 2, 6, and 9).

Total plasma concentrations of diazepam, the demethylated major metabolite, N-demethyliazepam, and the hydroxylated metabolites, N-methyloxazepam and oxazepam, were measured by gas chromatography with a N2 electron capture detector.14 The percentage recoveries by use of the method were 95 ± 2 for plasma diazepam, 92 ± 2 for plasma N-demethyliazepam, 75 ± 3 for plasma N-methyloxazepam, and 92 ± 3 for plasma oxazepam (n = 10, mean ± SEM). The lower limit of the sensitivity of the method was 0.5 ng/ml for diazepam and N-demethyliazepam, 20 ng/ml for N-methyloxazepam, and 5 ng/ml for oxazepam. The coefficient of variation of ten determinations for the same day was always less than 5 per cent.

Samples of blood were drawn from the contralateral antebrachial antecubital vein at zero time and 5 min, 30 min, and one, three, six and 24 hours after drug administration. Thereafter at least two more samples were obtained at 32, 48, or 72 hours.

Postinjection data were analyzed as follows: the pharmacokinetic model was selected by using the AUTOAN decision-making computer program.15 Data were then fitted with the aid of NONLIN, a least-squares nonlinear fitting computer program. Computer analyses showed that the data could best be fitted by a two-compartment open model, as described by Klotz et al.14 The time course of the biexponential decline of plasma levels for this model may be described by $C_p(t) = A \cdot e^{-at} + B \cdot e^{-bt}$. According to the two-compartment open model, diazepam first distributes into an initial, central distribution compartment ($V_{de}$). After rapid intravenous injection this compartment can be estimated from the relationship $V_{de} = dose/C_m A + B = C_m$. From the central compartment there is irreversible elimination, characterized by the first-order rate constant $k_{el}$. From the
central compartment the drug reversibly distributes into a peripheral tissue compartment, which may be characterized by the first-order rate constants \( k_{12} \) and \( k_{32} \). The elimination constant \( k_{31} \) is also a function of drug distribution, as indicated by the equation 

\[
y = 0.04x - 1.01
\]

\( r = 0.84 \)

\( p < 0.05 \)

\[
y = 1.38 + 87.46
\]

\( r = 0.85 \)

\( p < 0.001 \)

and 

\[
y = 0.87x - 20.69
\]

\( r = 0.57 \)

\( p < 0.05 \)

\[
y = -1.53x + 138.22
\]

\( r = 0.58 \)

\( p < 0.05 \)

The volume of distribution at steady state \( V_{\text{dss}} \) is dependent upon distribution constants and can be estimated from the equation 

\[
V_{\text{dss}} = V_{\text{de}} (1 + k_{12}/k_{32})
\]

The total plasma clearance (\( Cl_{\text{tot}} \)), which is a model-independent parameter, can be calculated from the equation 

\[
Cl_{\text{tot}} = \text{dose/AUC}
\]

where AUC = the area under the plasma level-time curve.

Statistical analyses of the results were performed by use of the Student t test and regression analysis.

**RESULTS**

There was a significant positive correlation between age and elimination-phase half-life (\( t_{1/2d} \); \( P < 0.05 \)), age and total drug plasma clearance (\( Cl_{\text{tot}} \); \( P < 0.05 \)), and age and the volume of distribution at steady state (\( V_{\text{dss}} \); \( P < 0.05 \)). Similarly, the elimination half-life (\( t_{1/2d} \)) and total plasma clearance (\( Cl_{\text{tot}} \); \( P < 0.001 \)) correlated (fig. 1). No correlation was found between the age and distribution phase half-life (\( \alpha \)-phase, \( t_{1/2a} \); \( P < 0.10 \)), age and central distribution volume (\( V_{\text{dc}} \); \( P < 0.10 \)) age and distribution ratio (\( k_{12}/k_{32} \); \( P < 0.10 \)), and age and the elimination rate constant (\( k_{31} \); \( P < 0.10 \)).

The pharmacokinetic mean (±SD) data from the 14 patients are shown in table 2.

Of the three main metabolites of diazepam, \( \alpha \)-demethylidiazepam, \( \alpha \)-methylidiazepam, and oxazepam, only \( \alpha \)-demethylidiazepam was detectable in all plasmas, at low levels. No correlation between age and the plasma levels of this major metabolite of diazepam was found. In plasmas of younger patients \( \alpha \)-demethylidiazepam was first detected after 30 min to one hour. Thereafter it increased to reach a maximum between

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**Table 2. Pharmacokinetic Indices (Mean ± SD) Derived from Data Obtained after a Single Administration of Diazepam, 0.15 mg/kg, iv, to 14 Patients 32–78 Years Old**

<table>
<thead>
<tr>
<th></th>
<th>( C_L^* ) (mg/ml)</th>
<th>( k_{12} ) (h(^{-1}))</th>
<th>( k_{32} ) (h(^{-1}))</th>
<th>( k_{12} ) (h(^{-1}))</th>
<th>( \alpha ) (h(^{-1}))</th>
<th>( \beta ) (h(^{-1}))</th>
<th>( t_{\alpha} ) (h)</th>
<th>( V_{\text{d}} ) (V/kg)</th>
<th>( V_{\text{cc}} ) (V/kg)</th>
<th>( Cl_{\text{tot}} ) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>535.8</td>
<td>0.414</td>
<td>0.216</td>
<td>1.542</td>
<td>2.363</td>
<td>0.5</td>
<td>0.045</td>
<td>28.8</td>
<td>0.22</td>
<td>1.19</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>207.2</td>
<td>0.270</td>
<td>0.199</td>
<td>1.212</td>
<td>1.469</td>
<td>0.4</td>
<td>0.036</td>
<td>21.0</td>
<td>0.11</td>
<td>0.83</td>
</tr>
</tbody>
</table>

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24 and 48 hours, and then decreased until 72 hours. In the elderly, N-demethyl Diazepam was detected later (after two to six hours), and peak concentrations were lower, but occurred generally at the same time or only a little later than in younger subjects. Figure 2 shows the mean (±SEM) values of N-demethyl diazepam in the plasmas of patients less than and more than 60 years of age.

DISCUSSION

Elderly patients often manifest an apparent sensitivity to diazepam. For example, side effects related to the central nervous system during chronic diazepam treatment have been reported to increase between the ages of 40 and 70 years. There are two hypotheses explaining this phenomenon: increased sensitivity to drugs in old age, and pharmacokinetic age-related changes in the disposition and elimination of diazepam, resulting in an increased concentration of the pharmacologically active drug at receptor sites. The main determinants in a two-compartment open model are elimination phase half-life, distribution volume, and total plasma clearance. The discrepancy may lie in the diseases of our patients or in the effects of spinal anesthesia and operation. Spinal anesthesia and surgical intervention together have been shown to cause abnormal hepatic function tests in patients with normal livers. Similarly, changes in renal function are possible. On the other hand, Shader et al. found a decreased clearance and an increased distribution of chlordiazepoxide with increased elimination half-life in healthy elderly individuals without spinal anesthesia, but Kangas et al. reported only an increased distribution volume and elimination phase half-life of nitrazepam in older patients, without any change in total plasma clearance. Pharmacokinetically, clearance is the major determinant of the amount of drug accumulation during chronic treatment. Therefore, plasma levels accumulate at a rate proportional to the elimination phase half-life. When only the distribution volume, but not the total clearance, is changed, the steady-state levels will be similar. However, these conditions are achieved more rapidly in young than in elderly subjects. When total plasma clearance is decreased, steady-state plasma levels will be higher in the older age group. The mean plasma clearance value in our study was higher than that found by Klootz et al., mainly because of the higher values in younger patients. However, we have no explanation for this discrepancy.

Total body water diminishes with age. Therefore, accumulation of the lipophilic diazepam in lipid compartments could explain the change in the apparent volume of distribution. Antipyrine, which is evenly
distributed throughout the total body water, has a decreased apparent volume of distribution in the elderly.\textsuperscript{21} The value of the apparent volume of distribution can be used to estimate the amount of drug in the body during the elimination phase (β-phase) by the two-compartment open model.\textsuperscript{17} In the elderly (higher $V_{\text{obs}}$), a greater amount of the administered drug will be present at a steady state in the tissue compartment.

The extensive plasma protein binding of diazepam\textsuperscript{22} may also play an important role in the distribution and hepatic metabolism of diazepam.\textsuperscript{11,22} In this respect, however, no age-related change has been found.

The mean reduction of about 55 per cent in the plasma clearance of diazepam in the oldest of our patients shows that according to this major pharmacokinetic determinant, the plasma concentrations of unchanged drug, and consequently, the clinical effects, would be greater in this group of patients. After a single dose of diazepam in both human and animal studies, a correlation between the plasma or serum concentration of diazepam and the sedative, muscle-relaxing, amnestic, and ataxic effects was observed.\textsuperscript{24,25} Thus, when diazepam is given to the elderly in conjunction with spinal anesthesia, side effects such as unpredictable reduction of blood pressure or depression of respiration (even apnea),\textsuperscript{26,27} as well as long-lasting postoperative sedation, confusion, and amnesia,\textsuperscript{26,28} may even be more prominent than in young patients. In this study we did not measure the clinical effects of diazepam, but generally, the drug effects were clearly marked, lasting in some cases until next morning (Patients 10–14).

The major metabolite of diazepam, η-demethyl-diazepam, has similar or somewhat weaker pharmacologic effects than the parent drug.\textsuperscript{30} Knowledge of its age-related pharmacokinetic changes is still scanty.\textsuperscript{11} After a single administration of chloridiazepoxide,\textsuperscript{13} reduced levels of the demethylated metabolite were observed. The clinical significance of this phenomenon may be of little importance because of the low levels of η-demethyl-diazepam compared with diazepam. Concentrations of the hydroxylated metabolites, η-methoxazepam and oxazepam, were below the lower limit of sensitivity of our method, as was found in our earlier studies as well.\textsuperscript{31} In plasmas of diazepam-intoxicated patients, however, they have been measured in significant amounts.\textsuperscript{32}

In conjunction with spinal anesthesia, all of the major determinants of the pharmacokinetics of diazepam (elimination phase of half-life, distribution volume, and total plasma clearance) were altered with advancing age. Therefore, the more prominent effects of this benzodiazepine derivative in the elderly can be explained, at least in part, by age-related changes in the disposition and elimination of the drug. According to these pharmacokinetic alterations the dose of diazepam for the elderly should be reduced to half to a fourth of that used for younger patients.

References

Objective Measurement of Succinylcholine-induced Fasciculations and the Effect of Pretreatment with Pancuronium or Gallamine

Erik C. Jansen, M.D.,* and Paul Howard Hansen, M.D.†

Succinylcholine induces fasciculations at the onset of the depolarizing block. Pretreatment with a non-depolarizing agent e.g., pancuronium or gallamine, is known to attenuate the fasciculations. An objective method for measurement of fasciculations was not found in literature. A system was developed and applied in a clinical trial.

Materials and Methods

The circumference of the upper arm was chosen as the point of measurement. Variations in circumference were recorded by a strain gauge, an elastic tube filled with mercury (0.15 × 0.04 inch, length 16 cm, from Parks Electronics, Beaverton, Oregon). The gauge was part of a bridge network. The signal was converted from a DC into an AC signal, as only the alterations of circumference were of interest. The signal was amplified and stored on a Philips Minilog® four-track tape recorder and later demonstrated on an x/y recorder. The system meets the safety requirements of IEC regulations. To obtain the wanted quantification of fasciculations we used a Tektronix® DC 504 pulse counter with variable threshold. The threshold was set so that all deflections larger than those of the brachial artery were registered by the pulse counter. In this way the fasciculation count consists of the muscular fasciculations and the transmitted movements associated with a few controlled respirations.

The study comprised three groups of 20 patients each, scheduled for elective surgical procedures. All patients were of ASA class I, and all body weights were similar. Patients with diseases of the arm were excluded from the study.

The patients were premedicated orally with diazepam (0.2 mg/kg). They were randomly allocated to one of three induction techniques: 1) Thiopental, iv, from...