Clinical Pharmacokinetics of Diazepam

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Summary

Diazepam is still one of the most used of the benzodiazepine group of drugs. Extensive studies over 10 years have defined a fairly complete profile of its kinetics. Minor aspects relating to patterns of its metabolism and excretion in certain age groups and in some disease states remain to be described quantitatively. However, there is more than sufficient kinetic information available for the requirements of good clinical practice.

For optimum clinical benefit with minimum side-effects the following kinetic properties should be borne in mind: (a) there is a large interindividual variation (up to 30-fold) in dose/blood level ratios, especially when treatment is short-term; (b) the elimination half-life is prolonged in the elderly and the newborn and in some cases of liver disease; (c) there is accumulation of the active N-desmethylated metabolite during long-term treatment; and (d) administration of diazepam to pregnant women leads to rapid distribution from the maternal to fetal compartment: accumulation of both diazepam and desmethyldiazepam could cause prolonged sedation in the newborn. As there does not appear to be any clear relationship between the concentration of diazepam in the plasma and clinical effect, measurement of blood levels, other than for research purposes, is unnecessary.

Based on kinetic data, a single administration of diazepam at night should be adequate for hypnotic and anxiolytic effects in most patients.

There are many excellent articles on the benzodiazepines, their properties, uses and patterns of disposition (Garattini et al., 1973a, 1975; Tyrer, 1974; Greenblatt and Shader, 1974; Costa and Greengard, 1975; Lasagna, 1977). The pharmacokinetics of diazepam, still probably the most widely prescribed compound in this group, have been extensively investigated. The purpose of this review is to show how the results of these studies may be applied in general clinical practice. Previous articles in the journal have discussed the kinetic properties of diazepam relevant to its use in epilepsy (Hvidberg and Dam, 1976) and anaesthetic practice (Ghoneim and Kortilla, 1977).

There is general agreement that neither chemical manipulation of the basic diazepam molecule, nor use of its active metabolites (fig. 1) has lead to any substantial gain in therapeutic efficacy (Kesson et al., 1976; Shader and Greenblatt, 1977). However, side-effects in groups at risk because of age and/or associated disease states, may be minimised by the application of kinetic principles: either by adjusting the dosage regimen, or by choosing a benzodiazepine with a shorter half-life (and possibly no after-effects), such as oxazepam or methylxazepam (Nicholson and Stone, 1976; Fuccella et al., 1977).

The kinetic and metabolic patterns of diazepam have been extensively investigated using sensitive and
specific analytical techniques (Marcucci et al., 1968a; Van der Kleijn et al., 1971; Belvedere et al., 1972; Zingales, 1973; Arnold, 1975). Diazepam may be considered almost a classical model for the study of the various factors known to influence the disposition of a drug in the body. By far the most clinically relevant information to emerge has been the absence of any evidence of a correlation between plasma levels and therapeutic effect. Thus, measurement of blood levels is unnecessary except in a patient where knowledge of the concentration of the drug could help in clarifying an unexpected reaction, or where changes in the metabolic pattern of diazepam might be considered as a marker of other biological events, such as enzyme induction (Garattini et al., 1973b; Hvidberg and Dam, 1976; Bond et al., 1977).

1. Fundamental Pharmacokinetic Properties

1.1 Absorption

Table I summarises some of the studies dealing specifically with the absorption of diazepam follow-
### Table I. Gastrointestinal absorption of diazepam

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Dose</th>
<th>Peak time (min)</th>
<th>Peak levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz et al. (1965)</td>
<td>2</td>
<td>—</td>
<td>10mg</td>
<td>120</td>
</tr>
<tr>
<td>Garattini et al. (1973b)</td>
<td>—</td>
<td>17-59</td>
<td>0.25mg/kg</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60-80</td>
<td>0.25mg/kg</td>
<td>60</td>
</tr>
<tr>
<td>Hillestad et al. (1974a)</td>
<td>9</td>
<td>19-35</td>
<td>20mg</td>
<td>30</td>
</tr>
<tr>
<td>Kanto and Erkkola (1974)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Arnold (1975)</td>
<td>16</td>
<td>21-57</td>
<td>10mg</td>
<td>—</td>
</tr>
<tr>
<td>Gamble et al. (1975)</td>
<td>40</td>
<td>32b</td>
<td>10mg</td>
<td>90</td>
</tr>
</tbody>
</table>

a Measured in blood: a blood/serum or plasma ratio of about 0.6 should be calculated.

b Mean.

Note: Both mean and range values are reported whenever available.

### Table II. Intramuscular absorption of diazepam

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Dose (mg)</th>
<th>Peak time (min)</th>
<th>Peak level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baird and Hailey (1973)</td>
<td>4</td>
<td>—</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Hillestad et al. (1974a)</td>
<td>9</td>
<td>19-35</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Gamble et al. (1975)</td>
<td>31</td>
<td>32b</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Buttock (nurses)¹</td>
<td>10</td>
<td>33b</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Thigh (doctors)¹</td>
<td>33</td>
<td>28b</td>
<td>10</td>
<td>90</td>
</tr>
</tbody>
</table>

a See text for explanation.

b Mean.

### Discussion

ing various routes of administration. Where no contraindications exist, the oral is preferable to the intramuscular or rectal route of administration.

Absorption after oral administration is rapid and complete; peak plasma levels being reached within 30 to 90 minutes. Age is a major factor influencing absorption; an earlier peak is seen in children, a delayed and lower one is observed in the elderly (fig. 2; Garattini et al., 1973b). In chronic alcoholic cirrhosis, a substantially lower (44% at 2 hours), but not delayed, absorption peak has been observed (Sellman et al., 1975a).
Fig. 2. Diazepam blood levels in children, adults and elderly people after a single oral dose (0.25mg/kg).

- ● - Children (0.3-4 years)
- ★ - Adults (17-59 years)
- ▲ - Elderly people (60-80 years)

$\bullet p < 0.05$ in respect to children

Fig. 3. Individual variability of diazepam blood levels 180min after oral administration of 15mg.
Solid dosage forms with different dissolution rates (5 cf 48min) yield the same blood levels (Arnold, 1975) but faster absorption is seen following the use of a suspension compared with tablets (Berlin et al., 1972). Therapeutic or symptomatic effects first appear 60min after administration. Interindividual variability in plasma concentration (up to 30-fold) has been noted in patients receiving the same oral dose (fig. 3; Garattini et al., 1973b; Gamble et al., 1973, 1975). A plasma concentration of 400ng/ml is considered necessary to produce a demonstrable and lasting effect (section 1.5).

Suppositories are rarely used. When their use seems to be clinically justified, lower and more erratic absorption can be expected: plasma levels are only 50% of those obtained with the same dose by mouth, and pharmaceutical preparations with different dissolution rates (6 cf 60min) achieve peak levels at different times (1.8 to 4.4h) [Schwartz et al., 1966; Arnold, 1975].

Similarly, poor and irregular absorption is seen after intramuscular administration. Plasma levels are only 60% of those attained with the same oral dose. Possible contributing factors are the site and depth of the injection, the amount of adipose tissue, and perhaps precipitation at the injection site. In routine practice the influence of these variables can be great. Table II shows the differing results attributable to variation in injection site (with higher plasma concentrations after injection in the thigh than the buttock) and injection technique (higher concentrations being achieved when a group of doctors, injecting into the buttock, paid deliberate attention to ensuring penetration into muscle, than when injections, at the same site, were given by nurses not thus briefed) [Gamble et al., 1975].

After intravenous injection, no linear increase in plasma levels has been found with increasing doses; boluses of 10 and 20mg result in concentrations after 15min of about 400 and 1,200ng/ml respectively (Hillestad et al., 1974a). After a few minutes all subjects are relaxed and drowsy, with slurring of speech. 10 to 15 minutes after administration of the drug the patient is usually asleep. These effects persist for 120 minutes; the sleep can be easily broken at any time, with the subjects being comfortable and alert (Baird and Hailey, 1972; Hillestad et al., 1974a).

1.2 Plasma Protein Binding

Diazepam is highly bound to plasma proteins; reported values according to different methods ranging from 96.8 to 98.6% (Van der Kleijn et al., 1971; Klotz et al., 1975, 1976a; Thiessen et al., 1976). The percentage of the free drug fraction is independent of the total amount of drug present. Samples loaded with up to 16μg/ml and up to 10μg/ml were tested respectively by Van der Kleijn et al. (1971) and Thiessen et al. (1976). In the fetus and newborn, a lower degree of binding (84%) has been reported by some investigators (Kanto et al., 1974a). Significant differences have been observed for other age groups, but a highly significant (p<0.001) increase of the free fraction is seen in cirrhotic patients (Klotz et al., 1975). The same binding values as for diazepam have been reported for desmethyldiazepam (Klotz et al., 1976a).

1.3 Distribution in Various Body Tissues

1.3.1 Cerebrospinal Fluid (CSF)

In a study in neurological patients, the distribution from plasma to CSF has been shown to correspond to the free fraction of diazepam (2 to 3%) and of desmethyldiazepam (1 to 4%). The pattern is the same following single and repeated doses (Kanto et al., 1975). A long-term high dose regimen (15 to 30mg/day for many months) does not produce any change in diazepam concentration (8.7% of plasma level), but is accompanied by a significant accumulation of desmethyldiazepam (30.9% of plasma level) [Hendel, 1975].

1.3.2 Brain

A detailed study of the kinetics of diazepam and its metabolites in the brain has been made in cats (Morselli et al., 1973a). A rapid distribution phase in the
grey matter is followed by a longer accumulation phase of diazepam and its metabolites in the white matter. This accumulation is more marked following repeated dosages of the drug; the lipid-rich white matter is proposed as a deep compartment. Measurement of diazepam concentrations in various parts of the brain strongly suggests that there is early preferential distribution in those areas, mainly grey matter, with the highest blood flow.

1.3.3 Adipose Tissue

As it is highly lipophilic, diazepam might be expected to be readily distributed to, and possibly stored in, adipose tissue, being released during lipolysis or under other conditions of physiological change (Marcucci et al., 1968b). However, direct measurement in humans is insufficient to give reliable quantitative evidence of this. Following a single intravenous injection of 10 mg of diazepam, concentrations of 300 and 345 ng/g adipose tissue were measured in 2 patients at 30 min and 200 and 239 ng/g at 60 min. No desmethyldiazepam was detected at 180 min (Marcucci et al., 1968c).

1.4 Plasma Level Profile and Elimination Kinetics

A two compartment open model, consisting of a rapid distribution (α), followed by a longer elimination phase (β) is usually employed to describe the disappearance profile of diazepam. Recently published studies on single dose intravenous administration (table III) are in substantial agreement with earlier results obtained with an oral preparation for both the α and β phases (De Silva et al., 1966). A third, deep compartment described as a γ phase has been proposed by Kaplan et al. (1973), but its existence does not seem to be justified and it has not been quantitatively documented.

Overall consideration of available data on the terminal elimination half-life (t_{1/2β}), indicates that values of 1 to 2 days (24 to 48 h) are a good reference for clinical application. However, a linear increase of half-life has been reported with increasing age from 20 to 80 years (Klotz et al., 1975). This is not due to

Table III. Diazepam apparent half-lives after single intravenous administration

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Dose</th>
<th>t_{1/2α}(h)</th>
<th>t_{1/2β}(h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz et al. (1975)</td>
<td>33</td>
<td>0.1 mg/kg</td>
<td>20-90</td>
<td></td>
</tr>
<tr>
<td>Andreasen et al. (1976)</td>
<td>4</td>
<td>10 mg</td>
<td>14.3-61.2</td>
<td>(32.1)^a</td>
</tr>
<tr>
<td>Klotz et al. (1976a)</td>
<td>10</td>
<td>0.1 mg/kg</td>
<td>19.3-46.9</td>
<td>(32.9 ± 8.8)^a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a Mean.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table IV. Apparent volume of distribution (V_d) and plasma clearance (Cl) of diazepam after single dose administration

<table>
<thead>
<tr>
<th>Author</th>
<th>No. pts</th>
<th>V_d (L/kg)</th>
<th>Cl (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz et al. (1975)</td>
<td>5</td>
<td>1.13</td>
<td>26.8</td>
</tr>
<tr>
<td>Andreasen et al. (1976)</td>
<td>4</td>
<td>1.16</td>
<td>35</td>
</tr>
<tr>
<td>Hvidberg and Dam (1976)</td>
<td>1-2</td>
<td>1-2</td>
<td>—</td>
</tr>
<tr>
<td>Klotz et al. (1976a)</td>
<td>7</td>
<td>0.95</td>
<td>26</td>
</tr>
</tbody>
</table>
### Table V. Diazepam apparent half-life after repeated administration

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Daily dose</th>
<th>Route</th>
<th>Duration of treatment</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>(mg)</td>
<td></td>
<td>(days)</td>
<td>(h)</td>
</tr>
<tr>
<td>Van der Kleijn et al. (1971)</td>
<td>5</td>
<td>30</td>
<td>oral</td>
<td>15</td>
<td>20-42</td>
</tr>
<tr>
<td>Berlin et al. (1972)</td>
<td>7</td>
<td>15</td>
<td>oral</td>
<td>10</td>
<td>26-53</td>
</tr>
<tr>
<td>Hillestad et al. (1974b)</td>
<td>3</td>
<td>15</td>
<td>oral</td>
<td>15</td>
<td>54</td>
</tr>
<tr>
<td>Arnold (1975)</td>
<td>16</td>
<td>10</td>
<td>oral</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Kaplan et al. (1973)</td>
<td>4</td>
<td>10</td>
<td>IV</td>
<td>15</td>
<td>21-37</td>
</tr>
<tr>
<td>Klotz et al. (1976a)</td>
<td>5</td>
<td>---</td>
<td>IV + oral</td>
<td>sub-chronic</td>
<td>53.0 ± 17.4</td>
</tr>
</tbody>
</table>

Changing plasma clearance values, which were reported in the same study to be fairly stable (ranging from 20 to 32ml/min), but rather a larger initial distribution space \( V_f \) reflecting a larger volume of distribution at steady state \( V_{dSS} \) seems the more likely explanation of these findings (Klotz et al., 1975). Values for volume of distribution and plasma clearance after a single dose are summarised in table IV.

Studies performed during multiple dose and long-term treatment suggest a longer elimination half-life and less interindividual variability (table V). The variations, although statistically significant, are not substantial, and have been related to accumulation of the active metabolite desmethyldiazepam having an inhibitory influence on the rate of diazepam metabolism (Klotz et al., 1976b). Animal data seem to support this interpretation (Klotz et al., 1976b). Conversely, a diminution of both diazepam and desmethyldiazepam steady state plasma levels has been shown during continuous (1 to 6 weeks) treatment, suggesting an autoinduction phenomenon (Kanto et al., 1974c). The induction could apply first to the demethylating step; this is suggested by the fact that a higher percentage of desmethyldiazepam is found in previously treated patients given an intravenous dose of diazepam than in patients never exposed to the drug. Accelerated degradation of the desmethylated metabolite could then follow (Kanto et al., 1974c). Another possible explanation for the lower plasma concentrations is the accumulation of diazepam and desmethyldiazepam in erythrocytes after 11 or more weeks of therapy (Zingales, 1973).

The steady state plasma level of diazepam depends on the daily dose (table VI). The most striking feature is the report that the values measured over a period of 2 to 5 years were 1/5 to 1/10th those found after 15 days’ treatment (Kanto et al., 1974c). Causes such as lack of patient compliance, cannot be ruled out with certainty. However, the role of metabolic autoinduction discussed above seems a more likely explanation. Changes from fixed to flexible dosage regimens or vice versa are not an important factor in the plasma level profile. This is not surprising in a drug with a long half-life.

In its clinical implications, the plasma level profile of diazepam at steady state cannot be considered separately from that of its active metabolite desmethyldiazepam. Desmethyldiazepam was shown very early to be the main metabolic degradation product of diazepam (De Silva et al., 1966; Schwartz et al., 1965; Kvetina et al., 1968), but only recently,
Table VI. Steady state plasma concentrations of diazepam

<table>
<thead>
<tr>
<th>Author</th>
<th>Daily dose (mg)</th>
<th>Duration of treatment</th>
<th>Plasma concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Kleijn et al. (1971)</td>
<td>30</td>
<td>14 days</td>
<td>700-1500</td>
</tr>
<tr>
<td>Berlin et al. (1972)</td>
<td>15</td>
<td>10 days</td>
<td>285-395</td>
</tr>
<tr>
<td>Garattini et al. (1973b)</td>
<td>15</td>
<td>48 days</td>
<td>104-243&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dasberg et al. (1974)</td>
<td>20</td>
<td>5 days</td>
<td>264-647</td>
</tr>
<tr>
<td>Kanto et al. (1974c)</td>
<td>15, 15, 20-40</td>
<td>15 days, 2-5 years, 2-5 years</td>
<td>200-400, 42-207, 85-422</td>
</tr>
<tr>
<td>Bond et al. (1977)</td>
<td>10</td>
<td>2-4 weeks</td>
<td>70-392</td>
</tr>
</tbody>
</table>

<sup>a</sup> Blood concentration.

with the development of more sensitive analytical techniques, has it been possible to describe the kinetics of its appearance and accumulation pattern following both single and repeated dose administration of diazepam by all routes (Hillestad et al., 1974a,b; Kanto et al., 1974c; Arnold, 1975).

As can be seen from tables VII and VIII, desmethyldiazepam has a longer elimination half-life (51 to '120h) than diazepam (24 to 48h), possibly because of the lower rate of hydroxylation to oxazepam. Both the protein binding and the volume of distribution of desmethyldiazepam are similar to those for diazepam. Because of this longer half-life, the accumulation of desmethyldiazepam to steady state can continue over a treatment-period of more than 3 weeks. Moreover, dose-dependent elimination kinetics of desmethyldiazepam has been suggested (Tognoni et al., 1975). In 3 out of 6 anxious depressed patients who received long-term desmethyldiazepam treatment, a biexponential decay was observed with a very slow first component (K<sub>e</sub>[h<sup>-1</sup>] range 0.0019 to 0.0072; t<sub>1/2</sub> range 96 to 349 hours) followed by a faster one when plasma levels approached 550ng/ml (K<sub>e</sub>[h<sup>-1</sup>] range 0.0085 to 0.0205; t<sub>1/2</sub> range 26 to 33 hours). While the data are too scanty to allow clear conclusions to be

Table VII. Some pharmacokinetic properties of desmethyldiazepam

<table>
<thead>
<tr>
<th>Author</th>
<th>Protein binding (%)</th>
<th>t&lt;sub&gt;1/2p&lt;/sub&gt; (h)</th>
<th>V&lt;sub&gt;d&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt; (L/kg)</th>
<th>TBCP&lt;sup&gt;b&lt;/sup&gt; (ml/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillestad et al. (1974b)</td>
<td>—</td>
<td>92</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Klotz et al. (1976b)</td>
<td>97.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tognoni et al. (1975)</td>
<td>— 51 ± 7</td>
<td>1.11 ± 0.18</td>
<td>16.73 ± 2.19</td>
<td></td>
</tr>
<tr>
<td>Mahon et al. (1976)</td>
<td>— 120</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> Apparent volume of distribution.
<sup>b</sup> Total body clearance.
derived, dose-dependent elimination kinetics can be suggested.

From the above referred values of elimination half-life, a very long duration of pharmacological effect can therefore be expected after discontinuation of therapy. These facts and the interindividual variation in the ratios of diazepam to desmethyldiazepam plasma levels, ranging from 0.21 to 1.7 (Bond et al., 1977), should be borne in mind when considering the clinical implications of an accumulative effect of the 2 drugs.

Methyllozepam and oxazepam, the other 2 active metabolites of diazepam, are only found in small amounts when β-glucuronidase is added to samples of adult plasma or serum before extraction procedures. (For different findings see sections 1.6 and 2.4). Quantitative measurement of these compounds using a specific and sensitive analysis has only relatively recently become possible (Belvedere et al., 1972). The formation of these metabolites after administration in man does not seem to have any clinical relevance, although in certain animal species they explain the long duration of action of diazepam (Marcucci et al., 1968b; Marcucci et al., 1970). The overall consideration of data presented up to this point seems to allow a practical suggestion, the validity and efficacy of which could be checked in clinical practice. An individually tailored treatment schedule based on a single daily administration of diazepam at night should be adequate for a prolonged anxiolytic effect over the following day. No significant accumulation should take place following this regimen, thus avoiding the risk of excessive sedation during repeated dose treatment mainly in elderly people, and a too long wash-out period after stopping the treatment.

1.5 Plasma Levels and Clinical Response

No simple correlation exists between clinical response and plasma levels of diazepam and desmethyldiazepam, either separately or together. Besides the well known problem of obtaining reliable markers for anxiolytics or sedative drugs in a popula-
tion of widely differing individuals, there are also differences between the levels which are effective after single dose and long-term administration. Whereas 400ng/ml produces a clearly detectable clinical effect after a single dose, no signs of functional impairment or evidence of therapeutic activity could be observed with much higher steady state plasma levels of both diazepam and desmethyldiazepam (Bond et al., 1977; Tansella et al., 1975; Kanto et al., 1974c; Garattini et al., 1973b). In only a few cases has a correlation been found between desmethyldiazepam levels and response; as determined by results of psychiatric rating scales (Curry, 1974) or the appearance of autonomic side-effects (Dasberg, 1975). The lack of correlation between plasma levels and clinical effect has been confirmed in a carefully controlled multiple dose study in hospitalised patients (Tansella et al., 1978).

Dasberg et al. (1974) and Zingales (1973) consider that there are advantages in measuring diazepam plasma levels in order to ensure that steady state levels above 400ng/ml are reached and maintained, but this does not seem to reflect clinical experience, where a therapeutic effect is obtained with a wide range of dosage from 2 to 20mg (Bond et al., 1977). Diazepam does have an anticonvulsant effect at a peak plasma level of 400 to 500ng/ml, which is usually reached following a bolus intravenous injection of 10 to 20mg (Booker and Celesia, 1973; Hvidberg and Dam, 1976).

The extensive metabolism of diazepam, the likelihood that different clinical conditions will require different plasma concentrations, and the probability that plasma and brain concentrations of diazepam and desmethyldiazepam will vary depending upon whether treatment is short or long-term (Morselli et al., 1973a), all confirm the lack of indication for routine measurement of plasma levels of the drug (Garattini et al., 1973b).

1.6 Biliary Excretion

The study of biliary excretion of diazepam has received particular attention in recent years, mainly for kinetic reasons; the existence of a substantial enterohepatic circulation being hypothesised to explain partially the long elimination half-life of the drug and the secondary peak observed during the elimination phase (Van der Kleijn et al., 1971; Baird and Hailey, 1972). However, diazepam is not excreted in bile in significant amounts after single or repeated doses in post-cholecystectomy patients with a normal liver function (Klotz et al., 1975, 1976b), and evidence for the existence of enterohepatic circulation in patients with biliary disease is controversial.

The biliary excretion of diazepam in patients undergoing biliary tract surgery has been investigated by 2 groups. Sellman et al. (1975b) compared levels of diazepam and desmethyldiazepam in patients whose bile was collected with a T-tube with levels in a group of cholecystectomised controls; they interpreted their results as providing good evidence of the existence of enterohepatic circulation of diazepam but not of desmethyldiazepam. However, the work of Mahon et al. (1976) does not support this conclusion. Using $^{14}$C-5-diazepam given as an intravenous bolus to 5 patients with T-tube biliary drainage, these authors found that a mean of only 5.35% (range 1.7 to 7.4%) of the radioactivity was present in the bile over a period of 5 to 14 days. Even when corrected to bile flow of 700ml, this value is still too low (15%) to allow for a clinically significant enterohepatic circulation. Furthermore, the radioactivity was not due to either diazepam or desmethyldiazepam (which accounted respectively for 0.056% and 0.152% of the dose), but rather to the same hydroxylated metabolites which were found in the urine. The existence of an enterohepatic circulation has been confirmed for free and glucuronated oxazepam by studies in animals (Bertagni et al., 1972, 1978).

Indirect evidence of enterohepatic circulation is offered by Linnola et al. (1975) on the basis of secondary peaks in diazepam plasma levels after a fatty meal; the disappearance curve being linear following water ingestion. While excluding any influence of decreased binding to proteins due to higher concentrations of free fatty acids, a more general mechanism of mobilisation from storage sites is pro-
posed by Korttia and Kangas (1977), who showed the same pattern of transient increase of diazepam levels following a carbohydrate meal.

1.7 Urinary Excretion

Data on urinary excretion of diazepam and its metabolites is scanty. 71% of the radioactivity of a 10mg oral dose of \(^3\)H-diazepam is found in the urine. Only a very small percentage of this is in the free form, the major part being excreted as either the glucuronide or sulphate. Insufficient quantitative data exist to confirm whether desmethyldiazepam (Arnold, 1975) or oxazepam (Schwartz et al., 1965; Kanto et al., 1974a) is the more important urinary metabolite (see also section 2.4).

2. Influence of Physiological and Disease States on Kinetics

2.1 Liver Diseases

As might be expected for a drug like diazepam, which is extensively metabolised by hepatic microsomal enzymes, and exhibits capacity-limited protein binding sensitive hepatic clearance, it is primarily in liver disease that significant disease-induced alterations of kinetic properties have been shown (table IX). Although there is no indication for the routine use of diazepam in patients with liver disease, an understanding of the kinetic changes likely to occur is necessary so that the dose may be adjusted if necessary in a patient in whom the use of diazepam is thought warranted. Precise guidelines for any dose adjustment cannot be given at this time and clinicians so using diazepam in the presence of liver diseases must titrate dosage on the basis of both careful patient observation and available kinetic findings.

Impaired absorption is suggested by the lower peak plasma levels observed in alcoholic patients given oral diazepam (Sellman et al., 1975a). A larger (50 to 60% increase) volume of distribution in alcoholic cirrhosis (Klotz et al., 1975; Andreasen et al., 1976) and in patients with biliary disease (Mahon et al., 1976), is a possible explanation for their lower steady state plasma levels.

Decreased protein binding (from 97.8 to 95.3%) together with diminished (50%) plasma clearance (Klotz et al., 1975; Andreasen et al., 1976) and in-
creased volume of distribution (Klotz et al., 1975) has also been observed in cirrhotic patients. Values for the elimination half-life are increased about 2-fold in acute viral hepatitis, but return to normal on recovery from the illness (Klotz et al., 1975). A more marked (2 to 5-fold) increase in the elimination half-life is seen in patients with alcoholic cirrhosis (Klotz et al., 1975; Andreasen et al., 1976). These authors, however, could not find any correlation between half-life and various hepatic function tests.

A delay in the appearance of the active metabolite desmethyldiazepam and of the peak plasma level (from 43 to 85h) has also been reported in cirrhotics (Andreasen et al., 1976), further supporting the decreased rate of metabolism of diazepam in cirrhosis. However, the net consequence of a slower rate of elimination of diazepam and slower production of desmethyldiazepam is probably negligible when diazepam is used intravenously in status epilepticus (Hvidberg and Dam, 1976). Blaschke (1977) has discussed in more detail the clinical consequences of and changes in disposition of diazepam (and other drugs) in liver diseases.

2.2 Hypoalbuminaemic States

A larger free drug fraction can be measured in hypoalbuminaemic states (Thiessen et al., 1976), with a resultant larger volume of distribution and a significant increase in plasma clearance of diazepam (p < 0.05) [Klotz et al., 1976a]. Thus, the expected increase in clinical effects is probably only temporary; the initial increased availability of the free drug being compensated for by a faster elimination rate, as also proposed by Thiessen et al. (1976) for tolbutamide in cirrhotics. A higher incidence of diazepam side-effects has indeed been observed in patients with hypoalbuminaemia than in patients with normal serum proteins (Greenblatt and Koch-Weser, 1974); the number of patients with liver or renal disease being the same in both groups. An explanation for the increase in clinical effects in hypoalbuminaemia may relate to an earlier and greater diffusion in the central nervous system due to the larger free fraction of both diazepam and desmethyldiazepam available for activity firstly on the grey and then on the white matter of the brain (section 1.3.2). The role of the dose-dependent elimination kinetics suggested for desmethyldiazepam (section 1.4) at higher free drug plasma concentration could also be considered as a supplementary factor explaining the frequency of side-effects, which could result from an increased accumulation in the cerebral compartment.

No linear relationship between albumin concentration and binding capacity of diazepam was observed in patients with acute renal failure (Andresen, 1974). Elevated serum free fatty acids do not modify the protein binding of diazepam (Tsutsumi et al., 1975).

2.3 Pregnancy and Labour

Studies of diazepam metabolism and kinetics in different stages of pregnancy fall under 2 main headings, dependent upon the emphasis given to the evaluation of the metabolic activity of the fetal liver, as distinct from the kinetic behaviour of the drug and its metabolites in crossing the placenta. The clinical interest of the data obtained in the first type of study lies mainly in the information provided on maturation of the hepatic drug metabolising enzymes of the fetus. On the other hand, knowledge of the extent and pattern of transplacental passage of diazepam following single and repeated administration, mainly during the late stage of pregnancy, is important both in monitoring the effects of diazepam and desmethyldiazepam on the fetus and the newborn, and studying their disposition in the first days of life.

2.3.1 Transplacental Passage

As may be expected, in view of the changes which take place in the anatomical structure of the placenta and in the uterine circulation as pregnancy advances, transfer of diazepam across the placenta has been shown to be slower in early pregnancy than in the later stages and during labour (Erkkola et al., 1973;
Table X. Diazepam transplacental kinetics after single dose treatment (after Mandelli et al., 1975)

<table>
<thead>
<tr>
<th>Dose</th>
<th>No. pts</th>
<th>Time course of plasma concentrations</th>
<th>CP/MP&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>minutes between last dose and delivery</td>
<td>NDZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>corresponding levels (ng/ml)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mother</td>
<td></td>
</tr>
<tr>
<td>10mg IV</td>
<td>6</td>
<td>12 -- 215</td>
<td>95 -- 19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10mg IV</td>
<td>7</td>
<td>40 -- 160</td>
<td>248 -- 14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>122 -- 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>272 -- 29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>69 -- 23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.9 -- 1.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.77 -- 2.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.34 -- 3.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a Ratio between cord plasma (CP) and mother plasma (MP) concentrations.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b DZ = Diazepam.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c NDZ = Desmethyldiazepam.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kanto and Erkkola, 1974; Kanto et al., 1974a). These authors showed that the ratio of fetal:maternal plasma levels changed from 1.2 in early pregnancy to 1.8 in the later stages, when diazepam was given as a single parenteral dose, and from 0.4 to 0.8 when diazepam was given by repeated oral administration. Measurable amounts of diazepam were found in all samples from the placenta, fetal liver and fetal brain but not in amniotic fluid. This last finding is at variance with the reports of others (Indanaapan-Heikkila et al., 1971).

Concentrations of diazepam and desmethyldiazepam following repeated treatment were measured in various organ tissues of a fetus aborted at 31 weeks (Mandelli et al., 1975). The ratio of desmethyldiazepam to diazepam was approximately 2.3 in all tissues with 2 notable exceptions: desmethyldiazepam was highly concentrated in both lung and placenta (10:1 of diazepam).

Available knowledge of the transplacental kinetics of diazepam during late pregnancy and labour is summarised in tables X and XI, showing data obtained after single dose and long-term administration respectively. Distribution from the maternal to fetal compartment is rapid, after both intravenous and intramuscular administration. Long-term treatment leads to accumulation of both diazepam and desmethyldiazepam on the fetal side.

2.3.2 Fetal Drug Metabolising Capacity

Human fetal liver microsomes can metabolise diazepam to desmethyldiazepam and methyloxazepam as early as the 13th week of gestation (Ackermann and Richter, 1977). The metabolising capability of the fetus for some major biotransformation pathways of diazepam is further supported by studies conducted at birth, comparing diazepam and desmethyldiazepam in arterial (AC) and venous (VC) cord blood (Mandelli et al., 1975). AC/VC ratios of 0.71 ± 0.12 and 0.94 ± 0.13 were found for diazepam in short and long-term treated cases respectively; the corresponding AC/VC ratios found for desmethyldiazepam were 1.75 ± 0.38 and 0.87 ± 0.05. These figures suggest an important demethylating activity in the fetus, with plasma concentrations reaching an equilibrium in the feto-maternal unit only after repeated dosing.

2.4 Neonates, Infants and Children

Differences in the kinetics of diazepam in newborn infants and children are shown in table XII. It
Table XI. Diazepam transplacental kinetics after repeated dose (RD) treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>No. pts</th>
<th>Time course of plasma concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>hours between last dose and delivery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cree et al. (1973)</td>
<td>RD &lt; 30mg</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>RD &gt; 30mg</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Kanto et al. (1974b)</td>
<td>10-15mg for</td>
<td>5</td>
<td>12-15</td>
</tr>
<tr>
<td></td>
<td>6-21 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mandelli et al. (1975)</td>
<td>RD</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} DZ = Diazepam.
\textsuperscript{b} NDZ = Desmethyldiazepam.

Table XII. Some pharmacokinetic properties of diazepam in premature, newborn infants and children

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>Treatment</th>
<th>t\textsubscript{1/2}\textsuperscript{b}</th>
<th>TBCI (ml/kg/h)</th>
<th>V\textsubscript{d} (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morselli et al. (1973b)</td>
<td>4 premature (28-34 wk)</td>
<td>0.33mg/kg</td>
<td>75 ± 37</td>
<td>27.49 ± 8.53</td>
<td>1.80 ± 0.29</td>
</tr>
<tr>
<td>Mandelli et al. (1975)</td>
<td>11 newborns (1-2 days)</td>
<td>10mg IM to the mother before delivery</td>
<td>31 ± 2.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Morselli et al. (1973b)</td>
<td>5 children (4-8 y)</td>
<td>0.33mg/kg</td>
<td>18 ± 3</td>
<td>102.10 ± 9.72</td>
<td>2.60 ± 0.53</td>
</tr>
</tbody>
</table>

seems worth recalling that no clear consensus exists with regard to variations in the volume of distribution according to age. Whereas some studies (Morselli, 1976) refer to data suggesting a tendency for the volume of distribution to be lower in the newborn (1.40 to 1.82 L/kg) than that calculated in adults (2.20 to 2.60 L/kg), comparison of values in table XII with results reported in table IV indicates no major differences in the volume of distribution between newborn infants and adults. Some studies have shown diazepam to be less bound to umbilical cord plasma than to the corresponding maternal plasma.
(Kanto et al., 1974), but others have found no difference between cord and adult serum in binding properties of diazepam (Krasner and Yaffe, 1975).

Conclusive data on the type and extent of diazepam transformation to hydroxylated metabolites in the newborn are not available, but it is usually considered that hydroxylation of both diazepam and desmethyl Diazepam is very limited or lacking in premature and full-term infants, while the hydroxylated compounds are present in subjects over 2 to 3 weeks of age and in children (Morselli et al., 1973b). However, hydroxylation activity in the fetal liver can apparently be induced by administration of inducing agents to the mother. Thus, administration of phenobarbitone to the mother during pregnancy resulted in an elimination half-life of diazepam in premature infants of around 16h (Morselli et al., 1974), close to the value observed for young children (table XII).

A demethylating activity relatively lower than that in children has been observed in premature and full-term infants [rate of demethylation (K) in newborns of 0.097h compared with 0.179h in children] (Morselli, 1976).

Data on the usually expected low glucuronidation capacity in the newborn are more clear cut. While desmethyl Diazepam, mainly conjugated, represented the main metabolite detected in the urines of newborns (Morselli et al. 1973b, 1974), only small amounts of the conjugated form of both methylexazepam and oxazepam were found but these were higher when the mother had been treated with phenobarbitone. The presence of methylexazepam, both as free and as glucuronide derivative, in cord and in the plasma of newborns, reported only in those cases in which the concentration of both hydroxylated and conjugated compounds can cross the placenta (Mandelli et al., 1975). Glucuronised oxazepam constituted about 70% of all diazepam products in the urine of 5 newborn in another study, where no glucuronised form of desmethyl Diazepam was found (Kanto et al., 1974a,b). In the same study the measurement of free oxazepam in plasma (13 to 220ng/ml with 1 value of 121ng/ml) is justified by the authors through a low glucuronising capacity in the newborn.

2.5 Breast Feeding

Levels of diazepam in human breast milk are of the order of 1/10 of that in plasma, but administration of therapeutic (10mg) doses to the mother leads to fairly high levels in the newborn (491ng/ml and 172ng/ml respectively after 4 days; 601ng/ml and 74ng/ml after 6 days). The low figure in the breast-fed infant after 6 days is possibly due to an increasing rate of metabolism by the infant (Erkkola and Kanto, 1972).

As expected, desmethyl Diazepam can be found with diazepam in plasma of a newborn breast-fed by a mother on treatment with the drug (Cole and Hailey, 1975), with levels of desmethyl Diazepam in milk (12 to 85ng/ml) consistently higher than those of Diazepam (17 to 43ng/ml) after 10mg daily for 6 days (Brandt, 1976). There has been a single case report of lethargy and weight loss with EEG evidence of sedative medication, in a breast-fed infant of a mother treated with diazepam 10mg 3 times daily. Maternal plasma and milk levels were not measured but oxazepam could be traced in the urine of the infant (Patrick et al., 1972).

These studies suggest that a daily dose of 10mg diazepam is probably too small to cause untoward effects in the breast-fed infant. However, if higher daily doses of diazepam must be given repeatedly, breast-feeding should probably be discontinued.

2.6 The Elderly

As discussed in section 1.4, there is an increase in elimination half-life of diazepam with increasing age such that at age 80 years the half-life is 90h compared with 20h at age 20 years, as a consequence of an increase in volume of distribution. Plasma clearance did not change. The therapeutic implications of these kinetic findings are not clear but for other reasons
(e.g. risk of postural hypotension, unsteadiness and falls), lower dosage of diazepam should be used, at least initially, in the elderly.

2.7 Renal Diseases

Protein binding of diazepam is decreased from 98 to 92% in patients with renal insufficiency (Kangas et al., 1976) but the implications of this finding are not clear. Renal disease does not appear to affect the rate of elimination of diazepam. There are no data on the role of hypoalbuminaemia associated with uraemia on the disposition of diazepam, but Andreassen (1974) has shown that there is no linear relationship between the albumin concentration and binding capacity of diazepam in patients with acute renal failure.

3. Use of Diazepam in Pregnancy and Labour

Recent studies (Aarskog, 1975) have raised suspicions about the potential dysmorphogenicity of some antianxiety drugs. Pending more definite results expected from prospective studies, the routine use of diazepam should be discouraged during the first trimester of pregnancy, as part of the general recommendation to avoid the unnecessary use of drugs during this period.

Administration of diazepam should, however, be considered with great caution throughout pregnancy, as both the drug and its metabolites can accumulate in all fetal tissues (section 2.3) and cause problems at birth. The clinical significance of high plasma and tissue levels of these compounds in the newborn should be carefully considered when evaluating vital signs before and during labour and in the presence of behavioural and physiological impairment in the first 10 to 15 days of extrauterine life. Lower Apgar scores, apnoea spells, hypothermia, reluctance to feed, and impaired metabolic response to cold stress (Cree et al., 1973; Shannon et al., 1972) have been reported after large doses, as has respiratory depression (Andre et al., 1973). Alterations of fetal heart rate have been observed (Scher et al., 1972; Sagen and Haram, 1973), but their clinical significance has not been determined (Mandelli et al., 1975).

No major complications should be expected following a single dose of diazepam during labour, but certainly the possible effects of diazepam on the newborn must be taken into account when large (40 to 100 mg) intravenous doses of diazepam are used in the treatment of eclampsia and severe pre-eclampsia.

4. Pharmacokinetic Drug Interactions

The effects of combined ingestion of ethanol and diazepam have been the subject of many publications. The impairment by this combination of various indices of performance of driving-related skills has been well documented (Linnoila and Mattila, 1973), but data on possible underlying kinetic mechanisms of interaction are scanty. No modification of absorption has been observed following an alcoholic (dose of alcohol being 0.5 g/kg body weight) bitter ingestion (Linnoila et al., 1974) using diazepam capsules, but approximately 100% higher peak plasma levels were seen when the absorption pattern of an alcoholic solution of diazepam was compared with that of diazepam in distilled water (Hayer et al., 1977). The former experiment seems possibly to be closer to the situation in clinical practice and enhancement of absorption should not therefore be considered a major factor in determining the clinical effects of the diazepam-ethanol interaction.

The influence of smoking on diazepam metabolism has also received some attention. No differences in plasma elimination half-life or steady state levels have been reported between smokers and non-smokers, suggesting that there is no important induction of the metabolic pathway of diazepam elimination (Klotz et al., 1975). These data are, however, at variance with those from the Boston Collaborative Drug Surveillance Program (1973) showing a markedly lower incidence of side-effects (mainly sedation) in elderly smokers, compared with non-
smokers. Despite the fact that no plasma levels were obtained in that retrospective study, clinical evidence suggests that lower concentrations of both diazepam and desmethyldiazepam may be due to increased formation of glucuronated and readily excreted hydroxylated derivatives of diazepam. The existence and clinical significance of increased hydroxylation has been documented in newborn infants of mothers on treatment with phenobarbitone (Morselli et al., 1973b; Sereni et al., 1973; see section 2.4).

Despite its high protein binding to plasma proteins, diazepam does not seem to be able to displace other highly bound drugs such as warfarin (Orme et al., 1972). A displacing effect on bilirubin has not been confirmed and was attributed to a chemical impurity present in the pharmaceutical preparation (Adoni et al., 1973; Schiff et al., 1971).

References


Krasner, J. and Yaffe, S.J.: Drug-protein binding in the neonate; in Morselli, Garattini and Sereni (Eds) Basic and Therapeutic


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