Clinical effects and metabolism of diazepam in patients with chronic liver disease

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Summary

1. After a fixed weight-related dose given intravenously, plasma diazepam concentrations were significantly lower in 11 cirrhotic patients than in controls matched for age and sex, in the 4 h after diazepam administration but not thereafter.

2. When measured at a single fixed time point, a greater proportion of the drug was in the unbound form in the plasma of cirrhotic patients, but non-bound diazepam concentrations were not significantly different in the two groups.

3. Several psychomotor tests showed that cirrhotic patients, although having significantly impaired liver function, did not as a group have increased sensitivity to diazepam compared with their matched controls.

4. Only those cirrhotic patients who at the time of drug administration had impaired cerebral function, as judged by baseline performance of psychomotor tests, showed increased sensitivity to the effects of intravenous diazepam.

5. Psychomotor tests, particularly the Reitan trail test, seem more useful than tests of liver function or drug metabolism for identifying those patients with liver cirrhosis at risk of excessive sedation after diazepam administration.

Key words: diazepam, liver cirrhosis, metabolism, psychomotor tests.

Introduction

Patients with chronic liver disease are less tolerant of neurotropic drugs than are normal subjects [1–3]. Diazepam, often used as a sedating premedication for minor procedures, has been reported as being relatively safe in small doses in patients with chronic liver disease [4], although Branch et al. [5] found that patients with liver disease had an increased sensitivity to the drug. Clinical experience suggests that patients with liver disease vary in their response to the drug. In a study of the clinical effects and metabolism of diazepam in cirrhotic patients we have therefore attempted, by means of several psychomotor tests, to identify those patients likely to experience adverse effects from the drug. Cirrhotic patients were compared with control subjects matched for age and sex, since metabolism of diazepam alters with age [6].

Patients and methods

Fourteen patients with biopsy proven liver cirrhosis were studied after giving their informed consent. According to clinical and histological criteria, the aetiology of the cirrhosis was alcohol abuse in eight patients, chronic active hepatitis in four and cryptogenic in two. Eleven of these patients were compared with control subjects matched for age and sex, six normal healthy laboratory staff, four in-patients without evidence of liver disease, and one patient with mild fatty
changes without cirrhosis on liver biopsy. Five of
the 14 cirrhotic patients had been en-
cephalopathic in the 2 months before the study,
usually as a consequence of gastro-intestinal
bleeding, but all had recovered before testing. The
other nine patients had no history of en-
cephalopathy. All but three of the patients studied
were male, and none had received diazepam in
the previous week.

The day before investigation patients were
familiarized with the psychomotor tests to be
used. The tests were repeated the next day before
intravenous injection of diazepam, and the best
performance of two attempts in each test was
taken as the baseline. Patients were then retested
40 min and 2, 4 and 8 h after diazepam. The
following tests were used.

1. Reitan trail test: a sensitive index of hepatic
encephalopathy [7]. The sum of the times taken
to complete the two parts of the test constituted
the score.

2. Card sorting test. Playing cards, without
the face cards and with a specially designed unit,
were sorted into the four suites. On each run, two
variable numbers were sorted into a fifth com-
partment. The time taken to complete the test was
scored.

3. Digit symbol substitution test: a subtest of
the Wechsler adult intelligence scale [8]. Patients
substituted symbols for an assigned set of digits
according to a code provided. Scoring was based
on the number of symbols substituted in 1 min.

4. Word memory test: a test of the patient’s
ability to memorize a list of 10 words presented
at a rate of one word every 3 s [9]. The words
used were of two or three syllables, with a
frequency occurrence in normal language of less
than 15/million. Recall was tested immediately
after 5 min (delayed). The number of words
remembered was scored.

5. Visual analogue scale of subjective feelings
was also used [10]. The ranges of feelings
alert/drowsy, clear-headed/confused and well
co-ordinated/clumsy were used.

After the patient had performed the psy-
chomotor tests to obtain baseline values,
intravenous diazepam (0-25 mg/kg) was ad-
ministered slowly over 1 min. Blood samples were
taken from each subject before and \( \frac{1}{4}, 1, 2, 4, 8, 24, \) and 32 h after dosing. The subjects continued
to take their usual meals at normal times during
the study. Later blood samples were also taken,
usually one sample daily, on the next 3 days.
Plasma was separated immediately and stored at
\(-20^\circ C\) until diazepam and N-desmethyl-
diazepam concentrations were measured.

### Assay of diazepam and N-desmethyldiazepam

Plasma samples were analysed in batches. Diazepam and N-desmethyldiazepam were ex-
tracted into ether, which was then evaporated to
dryness. After the drug had been redissolved in
ethanol, the quantities present were determined
by gas chromatography with electron capture
detection [11–13]. This method has a minimum
limit of sensitivity of 0-25 ng/ml.

### Protein binding

Protein binding of diazepam in individual
samples was determined with \(^{3}H\)-labelled
diazepam (obtained from The Radiochemical
Centre, Amersham, Bucks, U.K.) by a technique
of isotope dilution and equilibrium dialysis [14].
No impurities were detectable in the radiolabelled
compound by thin layer chromatography, and so
the material was considered 99% pure. In all
experiments, which were conducted at room
temperature, both dialysate and residual plasmas
were measured to allow for losses by adsorption
or absorption on to or into tubes or membranes.
Samples in which dialysate contained protein
were rejected. The specific radioactivity of the
\(^{3}H\)diazepam was 47 Ci/mmol. Approximately
50 pg of the purified material was added to each
dialysis tube.

Serum albumin concentration was measured
with an SMA 12/60 automatic analyser, and
prothrombin time by a standard method [15].
Correlations were calculated by linear regression
using the method of least squares, and results
from the matched patients and control subjects
were compared by the paired Student’s \( t \)-test;
results from the unmatched groups were com-
pared by the unpaired test.

### Results

The eleven pairs of cirrhotic patients and control
subjects were matched for age and sex, and did
not differ significantly in body weight. Hepatic
function as gauged by serum albumin concen-
tration and prothrombin time was significantly
impaired in the 11 cirrhotic patients (Table 1). How-
ever, there was no significant difference
between the paired groups in the baseline perfor-
ance of any of the psychomotor tests (Table 1),
although some cirrhotic patients, usually those
with a recent history of encephalopathy, per-
formed poorly in several tests. Thus, of the 14
cirrhotic patients, the five who were recently
encephalopathic performed significantly less well
than those patients without a history of en-
cephalopathy in the Reitan trail test \( (P < 0.05)\)
TABLE 1. Comparison of age, weight, liver function and psychomotor test results and peak diazepam concentrations in 11 age and sex matched pairs of cirrhotic patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Mean results ± 1 SD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>40.6 ± 13.3</td>
<td>42.5 ± 12.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.6 ± 9.2</td>
<td>69.7 ± 13.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42.5 ± 6.9</td>
<td>28.0 ± 6.6</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Prolongation of prothrombin time (s)</td>
<td>0.2 ± 0.6</td>
<td>7.4 ± 3.5</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Initial Reitan trail test time (s)</td>
<td>91.1 ± 31.3</td>
<td>112.1 ± 42.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Maximum deterioration in Reitan trail test (s)</td>
<td>18.7 ± 23.4</td>
<td>56.6 ± 73.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Initial card sorting test (s)</td>
<td>61.7 ± 10.0</td>
<td>71.9 ± 18.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Maximum deterioration in card sorting test (s)</td>
<td>12.7 ± 8.0</td>
<td>11.9 ± 15.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Initial digit symbol substitution test (no.)</td>
<td>36.4 ± 9.7</td>
<td>30.4 ± 10.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Maximum deterioration in digit symbol substitution test (no.)</td>
<td>2.3 ± 4.4</td>
<td>1.7 ± 5.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diazepam concentration at 30 min (µg/ml)</td>
<td>0.531 ± 0.185</td>
<td>0.263 ± 0.080</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Non-bound drug (%)</td>
<td>0.94 ± 0.25</td>
<td>2.21 ± 1.65</td>
<td>P &lt; 0.005</td>
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and digit symbol substitution test (P < 0.05). The performances of these recently encephalopathic patients were also significantly poorer than those of control subjects in the Reitan trail test (P < 0.01), card sorting test (P < 0.01) and digit symbol substitution test (P < 0.05; Table 2). Control subjects showed a significant correlation between age and both baseline Reitan trail test (P < 0.001), card sorting test (P < 0.001) and digit symbol substitution test (P < 0.005), the older subjects performing less well.

Total serum diazepam concentrations in the cirrhotic patients were significantly lower than those in their matched controls in the first 4 h after diazepam administration, but thereafter the differences were not significant (Fig. 1). For several patients the data were unsuitable for complex pharmacokinetic analysis because of late increases in plasma diazepam concentration during the period of blood sampling. Protein binding studies showed that the proportion of non-bound diazepam in the plasma of cirrhotic patients was greater than that in controls (Table 1). Although total diazepam concentrations in the cirrhotic group were significantly lower than those in control subjects in the first 4 h after diazepam administration, non-bound plasma concentration did not differ significantly in the two groups. The principal metabolite of diazepam, N-desmethyl-diazepam, was usually detected in small concentrations in the plasma sample at 4 h after diazepam administration but peak concentrations of the metabolite were not achieved until 24 h or later. This pattern was similar in both cirrhotic patients and controls and differences in concentration of the metabolite between the groups were not significant.

There was no significant difference between the matched patient and control groups in the degree or duration of impaired performance of any psychomotor test after the administration of diazepam. Similarly, there was no difference in the changes in visual analogue scoring of the two groups. However, among the cirrhotic patients those with a recent history of encephalopathy showed a significantly impaired performance in the Reitan trail and card sorting tests compared with control subjects (Table 2). The impairment in performance of the card sorting test after diazepam was also significantly greater in cirrhotic patients who had a recent history of encephalopathy than in those who did not.

In the cirrhotic patient group the maximum deterioration in performance in the Reitan trail test after diazepam correlated significantly with the basal Reitan trail test time (P < 0.005); control subjects alone and patient and control groups combined showed a similar relationship (r = 0.753, P < 0.001; Fig. 2). The impairment of Reitan trail test performance also correlated, although less strongly, with serum albumin (r = -0.557, P < 0.005) and with the prothrombin time (r = 0.558, P < 0.005).

The impairment of performance of the psycho-
TABLE 2. Comparison of age, liver function and psychomotor test results in cirrhotic patients with and without a history of encephalopathy and in control subjects

Mean results ± 1 SD are shown. Significance of differences between the two subgroups of cirrhotic patients and control subjects: * P < 0.05; ** P < 0.01; *** P < 0.001.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 11)</th>
<th>Cirrhotic patients</th>
<th>History of recent encephalopathy (n = 5)</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Non-encephalopathic</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>40.6 ± 13.3</td>
<td>44.7 ± 14.3</td>
<td>40.8 ± 6.2</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42.5 ± 7.2</td>
<td>29.6 ± 7.0***</td>
<td>25.6 ± 3.2***</td>
</tr>
<tr>
<td>Prolongation in</td>
<td>0.2 ± 0.6</td>
<td>6.9 ± 3.5***</td>
<td>8.6 ± 4.7***</td>
</tr>
<tr>
<td>prothrombin time (s)</td>
<td></td>
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</tr>
<tr>
<td>Initial Reitan trail</td>
<td>91.1 ± 31.3</td>
<td>98.8 ± 39.7</td>
<td>177.4 ± 73.5**</td>
</tr>
<tr>
<td>test time (s)</td>
<td></td>
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<tr>
<td>Max. deterioration in</td>
<td>18.7 ± 24.6</td>
<td>35.1 ± 47.0</td>
<td>113.8 ± 100.0**</td>
</tr>
<tr>
<td>Reitan trail time (s)</td>
<td></td>
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</tr>
<tr>
<td>Initial card sorting</td>
<td>61.7 ± 10.5</td>
<td>67.8 ± 19.6</td>
<td>90.4 ± 25.2**</td>
</tr>
<tr>
<td>test time (s)</td>
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<tr>
<td>Max. deterioration in</td>
<td>12.7 ± 8.4</td>
<td>6.6 ± 10.9</td>
<td>25.0 ± 12.3*</td>
</tr>
<tr>
<td>card sorting test time (s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial digit symbol</td>
<td>36.4 ± 9.7</td>
<td>33.8 ± 9.2</td>
<td>21.6 ± 8.7*</td>
</tr>
<tr>
<td>substitution test (no.)</td>
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<tr>
<td>Max. deterioration in</td>
<td>2.27 ± 4.39</td>
<td>0.22 ± 2.26</td>
<td>2.60 ± 4.39</td>
</tr>
<tr>
<td>digit symbol substitution test (no.)</td>
<td></td>
<td></td>
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<tr>
<td>Max. delayed memory</td>
<td>3.87 ± 1.76</td>
<td>3.00 ± 0.63</td>
<td>2.67 ± 2.51</td>
</tr>
<tr>
<td>deterioration (no.)</td>
<td></td>
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</table>

FIG. 1. Mean plasma diazepam concentrations (±SE) after intravenous injection of diazepam (0.25 mg/kg) for 11 cirrhotic patients (●) and their age and sex matched controls (○). *Significantly different values at P < 0.05.

Discussion

In this study the effect of diazepam in cirrhotic patients has been compared with that in age and sex matched controls because the disposition of diazepam alters with age [6] and because we have shown that performance of several psychomotor tests changes with age in control subjects. While the study of Branch et al. [5] demonstrated enhanced cerebral sensitivity to an injected dose of diazepam in patients with liver disease compared with normal controls, the two groups were of unequal size and poorly matched for age.

Although there is no established theoretical base for performance evaluation after sedating drugs [16], the tests were chosen to measure different aspects of psychomotor function. These tests have been shown to be sensitive to the effects of benzodiazepines [17], or in the case of the Reitan trail test to be a sensitive index of hepatic encephalopathy [7]. They were expected to detect changes in alertness, concentration, perception, manual dexterity, co-ordination and performances tended to last longer in the patient group for the Reitan trail test and card sorting test, whereas delayed memory testing was impaired longer in control subjects.
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memory. The visual analogue scale testing was used to show changes in subject-awareness of deficit.

The data obtained were not suitable for detailed pharmacokinetic analysis because of the fluctuations in plasma total diazepam concentrations, which have also been noted in other studies [18]. These fluctuations in total drug levels are now known to be associated with reciprocal changes in the free fraction of diazepam [18]. Because of this our data cannot be used for calculations of free drug kinetics or volume of distribution, since such calculations require constancy in factors controlling plasma concentrations. The cause of these variations remains to be elucidated, but possible factors include changes in plasma concentration of free fatty acids [19] and tryptophan [20], both of which can compete with diazepam for binding sites on plasma protein. Variations in the levels of these and other endogenous compounds may explain the decrease in the free fraction of diazepam observed postprandially [21]. However, we found no relationship in our patients between fluctuations in plasma total levels of the drug and mealtimes.

This study has shown that after a fixed dose of diazepam by weight, plasma total diazepam concentrations were significantly lower in cirrhotic patients than in controls during the distribution phase of the drug concentration curve, but not during the later post-equilibrium phase. Plasma samples for investigating protein binding were collected at a fixed time (4 h) after diazepam administration, when previous studies had shown binding to be minimal [22]. A significantly greater proportion of the drug was in the free form in the cirrhotic patients compared with controls, in agreement with other workers [23] who found that impaired protein binding of the drug in chronic alcoholic patients was associated with low levels of serum albumin. Taken together, our data show that the non-bound concentration of diazepam in plasma was not significantly different in cirrhotic and control groups. Since there is no reason to expect differences in brain-to-plasma water distribution this probably indicates similar brain diazepam concentrations in the two groups. This may explain the lack of significant differences between the effect of diazepam on cerebral function in cirrhotic patients as a group and their matched controls, as judged by the degree of change in the psychomotor tests. There was no difference in the duration of impairment of performance between the two groups. With the exception of the delayed word memory test, psychomotor function usually returned to baseline values by 8 h after diazepam. Since peak concentrations of the metabolite N-desmethyldiazepam were not reached until 24 h after diazepam injection, we consider that this metabolite contributed little to the changes in psychomotor testing.

Diazepam metabolism is certainly impaired in patients with chronic liver disease [5, 10, 24, 25] and patients with low levels of serum albumin suffer more toxic effects from the drug on chronic dosing, possibly as a result of decreased protein binding [26]. However, these factors appear to play little part in determining patient response to a single dose of the drug, as used for procedures such as endoscopy. In this study, cirrhotic patients with normal cerebral function as judged by psychomotor tests did not have increased cerebral sensitivity to diazepam, although their liver function (serum albumin and prothrombin time) was significantly impaired. The effect of diazepam was only exaggerated in those cirrhotic patients who already showed impairment in performance of psychomotor tests, and the Reitan trail test seemed the most sensitive of the tests. These patients often had a previous history of encephalopathy, and this implies that patients currently encephalopathic would experience excessive and possibly dangerous sedation after receiving diazepam, although for ethical reasons such patients were not included in this study. The effect of diazepam in patients with a recent history of encephalopathy tended to be prolonged compared with both the other cirrhotic patients.
and controls, but the differences between the groups were not significant. Diazepam may interact with some of the neurotropic substances circulating in encephalopathic patients, since it is known that benzodiazepines affect metabolism of brain catecholamines in rats [27].

Thus cirrhotic patients with an increased cerebral sensitivity to diazepam can be identified before administration of the drug by means of psychomotor tests, particularly the Reitan trail test, and these are more useful than tests of liver function or drug metabolism. Care is also required in patients with a past history of encephalopathy.

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References