EFFECT OF DIAZEPAM ON DRUG ABSORPTION AND GASTRIC EMPTYING IN MAN

B. ADELHØJ, O. U. PETRING, J. BRYNNUM, M. IBSEN AND H. E. POULSEN

Diazepam decreases apprehension, excitement and autonomic responses (Dundee and Haslett, 1970), and remains one of the most widely used benzodiazepines. Although diazepam is a safe drug (Kanto, 1981), the effect on gastric emptying in man is not clear.

In the present study we determined the effect, if any, of diazepam on gastric emptying in man, using paracetamol absorption as an index of the rate of gastric emptying. Paracetamol is not absorbed to any appreciable extent from the stomach, but is readily absorbed from the upper small intestine. In this way the rate of absorption of paracetamol following oral administration is dependent on the rate of gastric emptying (Heading et al., 1973). Simultaneous measurements of paracetamol absorption and gastric emptying have confirmed that measurement of the rate of paracetamol absorption is a dependable expression of gastric emptying (Clements et al., 1978).

SUBJECTS AND METHODS

Informed consent was obtained from each subject and the experimental study was approved by the local Ethics Committee.

Seven healthy volunteers (four women) (age 23–36 yr, body weight 45–75 kg, height 155–183 cm) were each studied on two occasions in random order with an interval of at least 2 weeks between studies. Diazepam (5 mg ml\(^{-1}\)) or physiological saline 0.04 ml kg\(^{-1}\) i.v. was given double-blind to each volunteer. On each occasion they were investigated after an overnight fast. Fasting was continued until the end of the investigation.

The subjects remained at rest in bed in a semi-recumbent position and a slow i.v. infusion of physiological saline was established. Immediately after the injection of the test solution (over 2 min) the subjects ingested paracetamol 20 mg kg\(^{-1}\) dissolved in 200 ml of water. Venous blood samples were taken from an indwelling cannula before and 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min after the administration of the paracetamol. Serum was separated and stored at \(-20^\circ\text{C}\) until measurement of serum paracetamol concentration by high pressure liquid chromatography was performed (Lo and Bye, 1979).

Paracetamol absorption was assessed from the plasma concentrations at each sampling time, the peak paracetamol concentration (C\(_{\text{max}}\)), the time to reach peak concentration (t\(_{\text{max}}\)) and the area under the plasma concentration–time curve from 0 to 120 min (AUC).

A paired Student's \(t\) test was used; \(P\) values less than 0.05 were considered statistically significant.

RESULTS

Mean plasma paracetamol concentrations at each sampling time are given in table I; the individual
TABLE I. Mean plasma paracetamol concentrations (± SEM) and \( P \) values (Student's \( t \) test) at each sampling time with and without diazepam. Patients received paracetamol 20 mg kg\(^{-1}\) body weight dissolved in 200 ml water.

<table>
<thead>
<tr>
<th></th>
<th>Mean plasma paracetamol concentrations (µg ml(^{-1}))</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Saline</td>
<td>6.2±6.2</td>
<td>14.9±8.0</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>4.3±5.2</td>
<td>9.5±6.5</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( P )</td>
<td>0.39</td>
<td>0.24</td>
</tr>
</tbody>
</table>

TABLE II. The individual values of the peak serum paracetamol concentration (\( C_{\text{max}} \)), the time from administration of paracetamol to its peak concentration (\( t_{\text{max}} \)), the area under the plasma concentration–time curve from 0 to 120 min (AUC) and \( P \) values with and without diazepam.

<table>
<thead>
<tr>
<th>Subject</th>
<th>( C_{\text{max}} ) (µg ml(^{-1}))</th>
<th>( t_{\text{max}} ) (min)</th>
<th>AUC (µg min(^{-1}) ml(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>Diazepam</td>
<td>Saline</td>
</tr>
<tr>
<td>1</td>
<td>14.9</td>
<td>17.8</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>16.0</td>
<td>20.7</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>16.5</td>
<td>15.9</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>18.6</td>
<td>20.3</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>28.3</td>
<td>17.9</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>12.0</td>
<td>10.3</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>20.5</td>
<td>18.9</td>
<td>20</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>18.1±2.0</td>
<td>16.5±1.5</td>
<td>34.3±5.7</td>
</tr>
<tr>
<td>( P )</td>
<td>0.57</td>
<td>0.30</td>
<td>0.56</td>
</tr>
</tbody>
</table>

values of \( C_{\text{max}} \), \( t_{\text{max}} \) and AUC are presented in table II.

At no sampling time did the mean paracetamol concentration after the administration of diazepam differ significantly from the mean concentration after saline (\( P > 0.05 \)).

After the administration of the saline, mean \( C_{\text{max}} \) was 18.1±2.0 µg ml\(^{-1}\) (mean of 7 values ± SEM), mean \( t_{\text{max}} \) was 34.3±5.7 min and mean AUC was 1394±122 µg min\(^{-1}\) ml\(^{-1}\). After diazepam, mean \( C_{\text{max}} \) was 16.5±1.5 µg ml\(^{-1}\), mean \( t_{\text{max}} \) 42.1±7.2 min and mean AUC was 1277±134 µg min\(^{-1}\) ml\(^{-1}\). None of these values was significantly different from control (\( P > 0.05 \)).

The respective 95% confidence limits for the differences between the peak paracetamol concentration and the time to peak paracetamol concentration were —3.0 to 8.0 µg ml\(^{-1}\) and —12.2 to 27.8 min, respectively.

DISCUSSION

In the present study paracetamol absorption was used as an index of gastric emptying. This method has been demonstrated to correlate well with other methods used to estimate gastric emptying (Clements et al., 1978).

The study demonstrated that the absorption of paracetamol was not altered significantly by a single i.v. dose of diazepam 0.2 mg kg\(^{-1}\), and would indicate that gastric emptying was not changed significantly by diazepam.

The patterns of gastric emptying were similar in the seven subjects. After both diazepam and placebo, the absorption of the paracetamol seemed to follow a first-order process and gastric emptying was either type 1 or type 2 as classified by Clements and colleagues (1978). However, gastric emptying was delayed slightly in two subjects (No. 3 and No. 5) after diazepam i.v., and this may reflect small individual variations in the rate of gastric emptying produced by diazepam.

Paracetamol absorption was rapid in seven patients awaiting elective general anaesthesia who received diazepam 10 mg i.m. as premedication (Todd and Nimmo, 1983) and paracetamol concentrations from 15 to 90 min after diazepam administration were almost identical to those obtained in eight healthy volunteers who were not receiving diazepam after the same dose of paracetamol (Nimmo and Prescott, 1978). Paracetamol absorption was used as an index of gastric emptying. This method has been demonstrated to correlate well with other methods used to estimate gastric emptying (Clements et al., 1978).

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Tamol absorption was also rapid 2 weeks after minor surgery on the extremities in patients who had received diazepam 15 mg by mouth (Adelhøj et al., 1984; Petring et al., 1984). However, the present study differs from these studies in a number of ways. First, we gave a larger dose of diazepam than Todd and Nimmo (1983) and, furthermore, we gave the diazepam i.v. Diazepam is fairly rapidly and almost completely absorbed after oral ingestion (Bellatunono et al., 1980), but the absorption depends on gastric emptying (Gamble et al., 1976). After i.m. injection, absorption of diazepam is slow and erratic, possibly because of crystallization at the injection site, resulting in peak plasma concentrations which are lower than after oral administration (Kanto, 1975). Moolenaar and co-workers (1980) showed that a peak concentration of $375 \pm 79 \text{ ng ml}^{-1}$ was reached $95 \pm 39 \text{ min}$ after diazepam 10 mg i.m. in nine volunteers, a peak plasma concentration of $383 \pm 102 \text{ ng ml}^{-1}$ was reached $52 \pm 40 \text{ min}$ after diazepam 10 mg orally and a peak plasma concentration of $650 \pm 104 \text{ ng ml}^{-1}$ was obtained $6 \pm 5 \text{ min}$ after diazepam 10 mg i.v. Finally, our subjects served as their own control and were studied under the same circumstances with and without diazepam.

On the basis of this study and the cited data we conclude that diazepam has no important clinical effect on gastric emptying.

Consequently, diazepam per se does not prolong gastric emptying, and should not increase the likelihood of nausea, vomiting, or delay in the absorption of drugs or fluid, and so increase the risk of aspiration of gastric contents.

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REFERENCES


