GASTROINTESTINAL MOTILITY AND GASTRIC pH AND EMPTYING FOLLOWING INGESTION OF DIAZEPAM

B. A. SCHURIZEK, K. KRAGLUND, F. ANDREASEN, L. V. JENSEN AND B. JUHL

Premedication with benzodiazepines by mouth is used widely and is not usually associated with an increased risk of pulmonary aspiration [1]. Previous studies have shown a decrease in the volume and acidity of the stomach contents after ingestion of diazepam [2, 3]. Several factors influence the absorption of drugs administered by mouth, including gastrointestinal activity [4-6].

This study was undertaken to investigate the effects of diazepam on antroduodenal motility, gastric pH and gastric emptying rate.

**SUBJECTS AND METHODS**

Ten healthy volunteers (seven men and three women, aged 22-30 yr) without gastrointestinal symptoms participated in the study. None was a regular user of any drugs and no medication was taken in the week preceding each of the two study days, which were 8-14 days apart. All subjects fasted overnight before and during the investigations.

Informed consent was obtained from all individuals before the studies, which were approved by the local Ethics Committee.

Antroduodenal motility was recorded using a six-lumen polyvinylchloride tube with an external diameter of 4.7 mm (GIMK-14R7-250 A, William Cook Europe A/S) [7]. Each lumen had an internal diameter of 0.7 mm and a side-hole opening sited at various distances from the tip. The manometric assembly, complete with pH electrode, was passed through a nostril and placed, under fluoroscopic control, so that the tip of the tube was near to the ligament of Treitz.

Side openings at 2, 18, 26, 34 and 42 cm from the tip of the tube were arranged so that two were placed in the gastric antrum (A1 proximal, and A2 distal) and three in the duodenum (D1, D2 and D3). The lumina were perfused continuously with distilled water at a rate of 0.2 ml min⁻¹ per channel, utilizing a pressure infusor. Intraluminal pressure was measured by strain gauge transducers (Gould-Statham) and recorded on a multichannel paper chart recorder (Mingograf 805, Siemens Elema).

Copenhagen) was passed through one lumen and attached to the side of the manometric catheter between the two antral recording sites. The pH electrode was calibrated with commercial buffer solutions (pH 4.01 and 1.09). Gastric antral pH was displayed continuously on a pH-meter (Radiometer, Copenhagen) and recorded on the paper chart recorder. All measurements were recorded also via an interface on a multichannel tape recorder (TEAC xR-510), for later data compression and analysis.

The rate of gastric emptying was assessed by paracetamol absorption after oral ingestion [8-10]. All the investigations commenced at 7 a.m. and the subjects remained supine throughout the investigations. Paracetamol was administered after one complete interdigestive motility complex (IDMC) immediately after the second phase III on the first study day. An IDMC was defined as the motility pattern from the beginning of one phase III to the beginning of the next (fig. 1) [11]. Each individual received diazepam 0.25 mg kg\(^{-1}\) (0.23-0.27 mg kg\(^{-1}\)) as Stesolid tablets, given as whole and half 5- or 10-mg tablets with 40 ml of water. One IDMC later, paracetamol 20 mg kg\(^{-1}\) was administered after the second phase III. Blood samples were taken at 15, 30, 60, 90, 120 and 180 min after ingestion of paracetamol on both study days. Antrudodenal motility and gastric pH were measured continuously until the last blood sample had been taken.

**Data analysis**

The recordings of motility were assessed manually and each phase of the IDMC was identified and assessed separately [11].

The duration of the quiescent phase I was noted. Phase II, which is characterized by persistent irregular contractions, was assessed for duration, frequency and amplitude of contractions and the motility index (frequency × amplitude) calculated. Each phase II was divided into 5-min intervals for assessment of frequency and average amplitude of contraction at each recording site. Phase III of the IDMC was defined as a coordinated burst of activity propagated caudad. Each phase III was assessed for its duration at each site, frequency, velocity of propagation...
(cm min⁻¹) and amplitude of contraction. "Incomplete" phase III periods, defined as those with only antral or duodenal components, were also noted.

Serum paracetamol concentrations were measured by high pressure liquid chromatography [12]. Paracetamol absorption was assessed from serum concentrations at each sampling time, the peak paracetamol concentration (Cmax), the time to reach the peak (tmax) and the area under the serum concentration curves (AUC) for each of the study days and correlated with the pattern of motility.

The motility data for each phase of the IDMC and pH with and without diazepam were pooled and compared for each of the study days.

The median of the highest and lowest antral pH was calculated for each 5-min epoch.

Statistical analysis

Statistical analysis was carried out with the Mann–Whitney, Kruskall–Wallis, Fisher's exact and Spearman rank sum tests. Values are given as medians with range or quartile spans, or both. P < 0.05 was considered significant.

RESULTS

Twenty-five IDMC (two to four in each subject) were observed on the first study day during the recording period, which was a median of 279 (216–464) min. Thirty IDMC (two to four in each subject) were observed on the second study day following ingestion of diazepam. Recording time was a median of 250 (220–342) min.

The cycle duration varied considerably both between and within subjects and with and without diazepam. Table I shows the duration of IDMC and the duration of the phases I, II and III after ingestion of paracetamol on the first and second study days. No significant difference was found between the study periods.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Diazepam</th>
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</thead>
<tbody>
<tr>
<td><strong>IDMC (min)</strong></td>
<td>90 (47–161)</td>
<td>68 (37–113)</td>
</tr>
<tr>
<td><strong>Phase I (min)</strong></td>
<td>20 (7–53)</td>
<td>19 (5–45)</td>
</tr>
<tr>
<td><strong>Phase II (min)</strong></td>
<td>49 (20–133)</td>
<td>38 (3–135)</td>
</tr>
<tr>
<td><strong>Phase III (min)</strong></td>
<td>6.5 (4–13)</td>
<td>7.5 (3–15.5)</td>
</tr>
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</table>

**Phase II motility and pH**

Diazepam did not alter the frequency of antral or duodenal contractions (fig. 2), but increased the amplitude of contraction in the gastric antrum and the proximal duodenum (fig. 3). The motility index increased in both antrum and duodenum (fig. 4). A narrow range of pH values was observed in the control study following paracetamol, the median (range) of the lowest and highest values being 1.4 (0.9–1.7) and 2.4 (1.3–2.8), respectively. Diazepam reduced the secretion of acid by the
stomach, the median (range) values being 2.1 (1.2–3.5) and 2.9 (1.5–4.6), respectively (P < 0.01).

**Phase III motility and pH**

Diazepam did not affect the frequency of occurrence of phase III of the IDMC. After ingestion of paracetamol, 19 phase III periods were recorded on the first study day and 23 on the second. Twenty-three per cent of the phase III periods were complete with antral activity on the control day, compared with 43.8% following diazepam. The median duration of phase III at all measuring sites was longer both with and without diazepam when an antral component was present (table II) (P < 0.01). The duration increased at the distal measurement sites. The frequency and amplitude of contraction did not differ between the two study days (table III).

The velocity of propagation following diazepam

<table>
<thead>
<tr>
<th>TABLE II. Duration (min) of phase III (with (+) and without (−) antral activity) in control measurements and following diazepam. Median values (range). *P &lt; 0.01 compared with phases without antral activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antral activity</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>A1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>A2</td>
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<td></td>
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<tr>
<td>Duodenal phase III</td>
</tr>
<tr>
<td>D1</td>
</tr>
<tr>
<td></td>
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<td>D2</td>
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<td>D3</td>
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</tbody>
</table>
Table III. Frequency of contractions (min⁻¹) and amplitudes (mm Hg) of contractions during phase III at antral (A1, A2) and duodenal (D1, D2, D3) sites. Median values (range)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Amplitude</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Antral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>(3.3–3.7)</td>
<td>(3.2–3.6)</td>
</tr>
<tr>
<td>A2</td>
<td>3.5</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>(3.0–4.0)</td>
<td>(3.1–3.9)</td>
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<tr>
<td>Duodenal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>9.1</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>(7.5–12.1)</td>
<td>(6.6–11.1)</td>
</tr>
<tr>
<td>D2</td>
<td>11.6</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>(9.8–12.9)</td>
<td>(9.7–12.1)</td>
</tr>
<tr>
<td>D3</td>
<td>11.6</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>(10.6–13.3)</td>
<td>(10.1–12.8)</td>
</tr>
</tbody>
</table>

Fig. 5. Absorption curves for paracetamol with and without diazepam. ○ = Control measurements; • = after diazepam. Values are medians with range.

was unchanged in the gastric antrum and proximal duodenum, but decreased in the distal duodenum (table IV) (P < 0.05).

The pH values during phase III were increased following diazepam, the median lowest and highest values (range) in the control period being 1.4 (0.9–6.8) and 3.4 (1.6–7.2), respectively, and 2.5 (0.9–6.8) and 3.4 (1.6–7.2), respectively (P < 0.01) following diazepam.

Gastric emptying

Paracetamol was given a median of 95 (58–175) min after diazepam. The absorption curves for the two study days are shown in figure 5. The rate of
gastric emptying did not differ significantly between the two study days, but gastric emptying tended to increase following diazepam \( (P = 0.052 \) at 15 min and \( P = 0.062 \) at 30 min for serum concentrations of paracetamol).

No paracetamol was absorbed during phase I. Three patterns of absorption were seen on both study days. One group were fast absorbers, another medium and the third slow. \( C_{\text{max}} \) and \( t_{\text{max}} \) for the three groups are shown in table V. Only two of the volunteers had the same pattern of absorption during the two study days. The number of fast, medium and slow absorbers did not change following diazepam.

The patterns of absorption correlated with the patterns of motility on both study days (fig. 6) \( (P < 0.03 \) and \( P < 0.02 \)). The characteristics of the motility pattern during phase II are shown in table VI. The duration of phase II was longer in the group of medium absorbers than in the group of fast absorbers \( (P < 0.01) \).

### DISCUSSION

Many drugs alter the rate of gastric emptying, either by an effect on smooth muscle or by influencing the release of gastrointestinal hormones which modulate gastrointestinal activity. There are few studies in man that demonstrate the magnitude and significance of these effects [6, 13].

Diazepam is used widely as a tranquillizer and as a premedicant before anaesthesia, and is absorbed better after oral than after i.m. administration, the same dose giving higher peak concentrations [14, 15]. Paracetamol was administered approximately 1.5 h after the diazepam, when the plasma concentration should have been close to its peak value [16]. The treatments were not given in random order, so that the presence of normal antroduodenal motility could be ensured in each volunteer before proceeding to the study proper. There is no reason to presume that this would have influenced the results.

The actions of diazepam on antroduodenal motility are probably mediated by its actions on higher regulatory structures in the central nervous system through the cholinergic vagal fibres which enhance contractions [7, 17]. The acidity of the stomach contents was reduced following diazepam, probably through a similar mechanism.

Serum paracetamol concentrations were used in this study as an index of gastric emptying rate. Paracetamol has often been used as a model for absorption studies as it is a weak acid \( (pK_a = 9.5) \) and is largely un-ionized in the stomach. It is not absorbed from the stomach, but is absorbed rapidly from the small intestine and its rate of absorption is an indirect measure of gastric emptying [8].
tended to accelerate the rate of gastric emptying, probably by increasing the strength of contrac-
tions during phase II. The rapidity of paracetamol absorption depended partly upon the occurrence
of antral activity and partly upon the duration of phase II. The occurrence of antral contractions
increased towards the end of phase II and the rate of absorption increased accordingly.

It was noted that some volunteers were fast
absorbers on the first study day and slow on the
second. It would appear that the pattern of
absorption is not constant, but varies in parallel
with the pattern of antroduodenal motility.

We conclude that diazepam increases the ampi-
tude of contractions and the motility index during
phase II of the IDMC and reduces the acidity of
the stomach contents.

ACKNOWLEDGEMENTS

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parenteral morphine/scopolamine with regard to gastric
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