EFFECT OF VOLUME OF WATER TAKEN WITH DIAZEPAM TABLETS ON ABSORPTION

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In certain individuals, tablets and capsules are prone to lodge in the oesophagus, particularly if taken with minimal quantities of water or when the subject is in a recumbent position (Evans and Roberts, 1976, 1981; Channer and Virjee, 1982; Hey et al., 1982). Therefore, drugs administered by mouth as premedication, and taken with a small quantity of water, may be held up in the oesophagus and their absorption delayed. Obviously, the sedative effect of such premedication would be delayed also.

Previous studies which have demonstrated delay of tablets in the oesophagus have utilized barium-containing tablets and fluoroscopic screening. However, these have not assessed the probable delay in therapeutic effect. As the elimination half-life of diazepam is long ($T_1/2 24-48$ h) and absorption from the upper small intestine is both rapid and complete (Mandelli, Tognoni and Garattini, 1978), a delay in the attainment of the peak plasma concentration would be an indication of delayed transit proximal to the small intestine.

SUMMARY

Thirty-three patients received either 10 ml (group A) or 50 ml (group B) of water with diazepam tablets as premedication while in the supine position. Plasma diazepam concentrations were measured, a delay in the attainment of the peak plasma concentration being taken as an indication of delayed absorption and oesophageal hold-up. There was no difference between the two groups, although in an important minority (16.7% (group A) and 20% (group B)), absorption was delayed to beyond 60 min. There was a wide scatter of plasma diazepam concentrations in both groups. Dysphagia during swallowing did not appear to delay absorption.

PATIENTS AND METHODS

Patients between the ages of 20 and 80 yr, weighing 50–80 kg and scheduled for elective surgery or arteriography were allocated randomly to one of two groups, having given informed consent. Patients taking benzodiazepines at the time of the study or within the previous month were excluded. Patients in group A received two 5-mg tablets of diazepam (Regent Laboratories Ltd) with 10 ml of water; those in group B received two 5-mg tablets of diazepam, with 50 ml of water. These quantities of water were used as they are representative of the small volumes usually given with oral premedication. The tablet preparation was a disc approximately 7 mm in diameter and 2 mm thick. All patients had fasted for 6 h or more. A wide-bore cannula was inserted, under local anaesthesia, to a large forearm vein for blood sampling. The cannula was flushed periodically with heparinized saline (heparin sodium 10 u. ml$^{-1}$ in normal saline).

The diazepam tablets were taken with the water while the patient was in a semi-recumbent position and the patient immediately rested supine in bed for the duration of the investigation. Each patient was asked whether dysphagia had occurred while taking the tablets or subsequently. Venous samples were collected at 0, 10, 30, 45, 60, 90 and 120 min following administration. In the first few samples analysed, peak plasma concentrations occurred early; therefore, subsequently the timing of the samples was altered to 0, 10, 20, 30, 45, 60 and 90 min. Samples were collected into heparinized tubes and, following separation, the plasma was stored at $-20$ °C for later analysis.

Plasma diazepam was estimated by benzene
TABLE I. Details of patients

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>M:F</td>
<td>10:8</td>
<td>10:5</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>59.9</td>
<td>58.7</td>
</tr>
<tr>
<td>(range)</td>
<td>(20-78)</td>
<td>(36-79)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>67.4</td>
<td>69.2</td>
</tr>
<tr>
<td>(range)</td>
<td>(51-83)</td>
<td>(57.5-80)</td>
</tr>
</tbody>
</table>

The results were analysed using Student's paired t test.

RESULTS

The groups (table I) were comparable. Plasma diazepam concentrations were not extraction and gas–liquid chromatography with griseofulvin as the internal standard (Gamble et al., 1975).

Plasma diazepam concentrations were not

![Graph of mean plasma diazepam concentration against time](image1)

**Fig. 1.** Mean plasma diazepam concentration (± SEM) against time for 10-ml (open circle) and 50-ml (closed circle) groups.

![Graph of percentage of patients reaching peak plasma concentration](image2)

**Fig. 2.** Percentage of patients reaching their peak plasma concentration by a given time. Open histograms = 10-ml group; hatched histograms = 50-ml group.
FIG. 3. Individual peak plasma concentrations for patients in groups A and B. —— = Mean value.

significantly different between the two groups (fig. 1). Mean plasma concentrations of approximately 215 ng ml\(^{-1}\) at 45 min were attained in both groups. Similarly, there was no significant difference in the extent of absorption (as measured by area-under-curve 0–90 min) or in the first-order absorption rate constant between the groups.

The peak plasma concentration was attained by 45 min in the majority of subjects (fig. 2). However, there was a substantial number of patients (16.7% in group A and 20% in group B) in whom the peak plasma concentration was delayed until 90 min or longer. Age and sex had no effect on the time at which the plasma concentration peaked. Individual peak plasma concentrations showed a wide scatter around mean values of 305 and 292 ng ml\(^{-1}\) for groups A and B, respectively (fig. 3). However, there was no statistically significant difference between groups.

No patient was taking cimetidine or drugs known to effect upper gastrointestinal motility. Similarly, none of the patients was known to have upper gastrointestinal pathology (e.g. peptic ulceration), although one patient, in group A, had undergone a partial gastrectomy 30 yr previously.

Nine patients complained of dysphagia while swallowing the tablets. However, in all of these the peak plasma concentrations had been reached by 45 min, eight having concentrations greater than 215 ng ml\(^{-1}\) at that time.

DISCUSSION

We have shown no significant difference in the pattern of absorption of diazepam when taken by mouth with 10 ml or 50 ml of water. For the majority of subjects these small volumes allowed tablets to pass into the stomach and small intestine without pharmacokinetic delay. The fact that both the timing of the peak plasma concentration and its value corresponded to previously reported values in the majority of our subjects supports this view (Gamble, Dundee and Assaf, 1975).

However, there was a significant minority of subjects (16.7% in group A and 20% in group B) in whom the peak plasma concentration was attained after 60 min. Evans and Roberts (1976) found that 14% of aspirin-sized tablets were delayed in the oesophagus for longer than 10 min, when taken in the supine position with 15 ml of water; and other studies noted similar delays (Hey et al., 1982). It seems reasonable to assume that the subjects in this trial in whom there was a delay in attaining the peak plasma concentration experienced a similar hold-up of tablets in the oesophagus.

Most tablets contain a swelling agent to facilitate rapid disintegration and the preparation of diazepam used in this study contains starch. When a tablet is swallowed with minimal quantities of water the hygroscopic properties of the swelling agent may cause it to adhere to the oesophageal mucosa, and this is the presumed mechanism of delay.

The wide scatter of peak plasma concentrations which occurred in our study has been noted by other workers. Gamble, Dundee and Assaf (1975) attributed this to variable absorption. On the other hand, Mandelli, Tognoni and Garattini (1978)
claimed that absorption after oral administration was rapid and complete.

Tablets passing directly into the stomach should rapidly absorb water and disintegrate, giving rise to a high peak plasma concentration. However, tablets adhering to the oesophageal mucosa would disintegrate slowly, thus producing lower peak plasma concentrations. Hey and colleagues (1982) have shown that tablets and capsules of various shapes and sizes, which adhere to the oesophageal mucosa, start to disintegrate at the site of hold up.

None of the subjects with delayed or low peak plasma concentrations complained of dysphagia. This is not surprising, however, as the majority of subjects noted to have hold-up of tablets in the oesophagus at fluoroscopy were not aware of this (Evans and Roberts, 1976; Hey et al., 1982). Indeed, all subjects in our study who noted dysphagia did not have a delayed or low peak plasma concentration.

Certain pathological processes and drugs having a pharmacological effect on the upper gastrointestinal tract are known to affect intestinal absorption. However, no such pathological or pharmacological cause for the delay in peak plasma concentration could be implicated in our patients.

In conclusion, only a small volume of water is needed for most patients to ensure a rapid transit of diazepam tablets through the oesophagus. However, in a minority of subjects some delay is likely. These cannot be predicted from a history of dysphagia at the time of swallowing. It might be advisable to encourage swallowing premedication while sitting or standing, and a larger volume of water would reduce, although probably not eliminate, hold-up of tablets in the oesophagus.

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REFERENCES