THE INFLUENCE OF THREE ANTACIDS ON THE ABSORPTION AND CLINICAL ACTION OF ORAL DIAZEPAM

S. G. NAIH, J. A. S. GAMBLE, J. W. DUNDEE AND P. J. HOWARD

SUMMARY
Diazepam 10 mg given orally alone or with one of the three antacids (aluminium hydroxide 40 ml, magnesium trisilicate 30 ml, sodium citrate 30 ml) was given in a single dose at random to 200 women undergoing minor gynaecological procedures. The concomitant use of aluminium hydroxide or sodium citrate hastened the onset of the soporific effect of diazepam marginally, while magnesium trisilicate tended to delay it. The estimation of plasma diazepam concentrations over 90 min in a similar series of 67 patients showed that the absorption of diazepam was increased significantly by the use of aluminium hydroxide, but there were no striking differences in the four groups. The clinical implications of these findings are discussed.

The case for oral premedication has been reinforced considerably since the introduction of the benzodiazepines. The low water- and high lipid-solubility characteristics of the majority of these compounds result in good absorption when given by mouth. Thus, Gamble, Dundee and Assaf (1975) showed that oral diazepam was absorbed better than diazepam administered by i.m. injection. This finding was confirmed by studies of the plasma concentrations of diazepam.

Further studies in this department have been concerned with those factors which influence diazepam uptake (Gamble et al., 1976), such as the use of atropine and opiates which delay absorption and aluminium hydroxide which enhances it (Gamble, 1975). This paper presents a study in which diazepam was given either alone or with three antacids and reports on the clinical effects and plasma concentrations of diazepam which resulted. Such studies are important in view of the fact that antacids influence the gastrointestinal uptake of a number of drugs (Harvey, 1975).

METHODS
Sedation study. This was carried out in four groups each of 50 women of reproductive years, weighing 40–89 kg and scheduled for minor gynaecological operations in the morning. The patients fasted overnight and received diazepam 10 mg by mouth alone or with one of the three antacids as premedication in random fashion. Those known to be taking hypnotics or tranquillizers were excluded, except where medication had been discontinued for at least 4 weeks.

The premedication consisted of commercially available diazepam 10 mg tablets (Valium, Roche) given alone or with one of the following antacids in a single dose: mist, magnesium trisilicate BPC 30 ml (10 ml contains magnesium trisilicate 0.5 g, magnesium carbonate 0.5 g and sodium carbonate 0.5 g); aluminium hydroxide gel BP 40 ml (contains approximately 4% w/w aluminium oxide); sodium citrate 0.3 mol/litre solution 30 ml (made up in 10% syrup and chloroform water, as described by Lahiri, Thomas and Hodgson, 1973).

The doses employed were larger than those used commonly, and the volumes of antacids were unequal. The larger volume of aluminium hydroxide was given to compensate for its reported ineffectiveness as an antacid in vivo (Morrissey and Barreras, 1974; Harvey, 1975). The patients were observed at 20, 40, 60 and 90 min after the drug administration or once only between 60 and 90 min. On these occasions the degree of drowsiness, apprehension, restlessness or excitement and the incidence of dizziness, emetic effects, tachycardia and arterial hypotension were noted as described by Dundee, Moore and Nicholl (1962a). On the basis of these observations, an efficacy score ranging from 5 (excellent sedation) to 1 (patient very upset, with no sedation) was allocated each time the patient was seen.

The patients were anaesthetized using a standard technique of 2% methohexitone (initial dose 1.6 mg/kg) with 75% nitrous oxide in oxygen (total flow 8 litre/min) with additional small increments of the barbiturate as required. Induction complications were noted and recorded as described by Dundee, Moore and Nicholl (1962b).
The patients were seen again 1 and 6 h after operation and the occurrence of vomiting (including retching) or nausea were noted. Where both nausea and vomiting occurred this was classified as vomiting.

Plasma concentration. This was measured concurrently with the sedation studies on similar patients who had consented to venous cannulation. Patients in whom diazepam or its metabolite were present in the blood sample before the drug administration were excluded. In all, 67 patients who were similar with respect to age and weight were studied.

The blood sampling technique was identical to that described by Gamble and others (1975). A 10-ml sample was obtained before drug administration (control sample) and subsequently at 15, 30, 45, 60 and 90 min. These were transferred to heparinized tubes and centrifuged, as soon as possible, at 3000 rev/min for 15 min, those samples awaiting centrifugation being stored in a refrigerator. The supernatant plasma was transferred into 5-ml polystyrene containers and stored at — 20 °C until analysed. Particular care was exercised to avoid haemolysis and contamination with heparinized saline during sampling.

After benzene extraction, plasma diazepam was estimated by gas-liquid chromatography using an electron capture detector with griseofulvin as the internal standard, as described by Gamble and others (1975). Duplicate analyses were carried out on each sample. Plasma diazepam concentrations were expressed in ng/ml.

RESULTS

Table I shows that the patients in each of the four sedation studies were broadly comparable with regard to average age and weight.

<table>
<thead>
<tr>
<th>Diazepam 10 mg with</th>
<th>No. of patients</th>
<th>Average age (yr)</th>
<th>Average weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>50</td>
<td>29</td>
<td>57</td>
</tr>
<tr>
<td>Aluminium hydroxide gel (BP) 40 ml</td>
<td>50</td>
<td>33</td>
<td>60</td>
</tr>
<tr>
<td>Mist. magnesium trisilicate (BPC) 30 ml</td>
<td>50</td>
<td>34</td>
<td>61</td>
</tr>
<tr>
<td>0.3 mol/litre sodium citrate 30 ml</td>
<td>50</td>
<td>29</td>
<td>58</td>
</tr>
</tbody>
</table>

Patient acceptability was satisfactory for all three antacids, although aluminium hydroxide gel appeared to be the least palatable. A few patients thought that the preparation of sodium citrate used in this study was too sweet.

The incidence of drowsiness and apprehension in the various series is displayed in table II. In general, the concomitant use of either aluminium hydroxide or sodium citrate enhanced the early soporific effect of diazepam, but the difference (when "good" and "fair" degrees of drowsiness are considered together) was only significant with aluminium hydroxide at 20 min \( (\chi^2 = 6.184; P<0.025) \) and with sodium citrate at 90 min \( (\chi^2 = 3.858; P<0.05) \). In contrast, magnesium trisilicate tended to decrease the efficacy of diazepam and at 60 min the incidence of notable drowsiness with diazepam-magnesium trisilicate was significantly less than with diazepam alone \( (\chi^2 = 5.876; P<0.025) \).

In general, the anxiolytic action of diazepam paralleled its soporific effect in all series, particularly when given with antacids.

<table>
<thead>
<tr>
<th>Preanaesthetic medication—diazepam 10 mg with:</th>
<th>—</th>
<th>Aluminium hydroxide gel 40 ml</th>
<th>Mist. magnesium trisilicate 30 ml</th>
<th>Sodium citrate 0.3 mol/litre 30 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min: 20 40 60 90</td>
<td>20 40 60 90</td>
<td>20 40 60 90</td>
<td>20 40 60 90</td>
<td>20 40 60 90</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>good</td>
<td>4 20 46 40</td>
<td>8 44 64 60</td>
<td>8 24 40 36</td>
</tr>
<tr>
<td>fair</td>
<td>8 26 24 30</td>
<td>32 20 16 28</td>
<td>20 8 4 20</td>
<td>12 16 24 24</td>
</tr>
<tr>
<td>slight</td>
<td>28 36 18 10</td>
<td>28 16 16 8</td>
<td>16 36 28 28</td>
<td>28 20 16 8</td>
</tr>
<tr>
<td>Apprehension</td>
<td>slight</td>
<td>36 22 4 10</td>
<td>36 16 8 12</td>
<td>24 16 8 0</td>
</tr>
<tr>
<td>moderate</td>
<td>18 6 6 6</td>
<td>4 4 0 0</td>
<td>0 0 0 0</td>
<td>8 4 0 0</td>
</tr>
</tbody>
</table>

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TABLE III. Significance of difference of the frequency of notable (good and fair) drowsiness in patients receiving diazepam 10 mg by mouth with three antacids. In all cases the series with the greater drowsiness appears first.

<table>
<thead>
<tr>
<th>Series compared</th>
<th>Minutes after drug administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Aluminium hydroxide gel v. mist. magnesium trisilicate</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>$P$</td>
</tr>
<tr>
<td>Sodium citrate v. mist. magnesium trisilicate</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td></td>
<td>$P$</td>
</tr>
</tbody>
</table>

TABLE IV. Average (± SEM) plasma diazepam concentrations (ng/ml) following diazepam 10 mg given by mouth alone or with three antacids as shown.

<table>
<thead>
<tr>
<th>Diazepam 10 mg with</th>
<th>No. of patients</th>
<th>Average wt (kg)</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium hydroxide gel (BP) 40 ml</td>
<td>17</td>
<td>59.0 ± 3.34</td>
<td>65 ± 22</td>
<td>122 ± 18</td>
<td>—</td>
<td>199 ± 24</td>
<td>194 ± 23</td>
</tr>
<tr>
<td>Sodium citrate 0.3 mol/litre 30 ml</td>
<td>20</td>
<td>59.2 ± 1.67</td>
<td>69 ± 24</td>
<td>177 ± 24</td>
<td>199 ± 20</td>
<td>188 ± 14</td>
<td>172 ± 12</td>
</tr>
<tr>
<td>Mist. magnesium trisilicate (BPC) 30 ml</td>
<td>15</td>
<td>59.9 ± 2.01</td>
<td>45 ± 16</td>
<td>107 ± 27</td>
<td>154 ± 25</td>
<td>181 ± 22</td>
<td>172 ± 15</td>
</tr>
<tr>
<td>Mist. magnesium trisilicate (BPC) 30 ml</td>
<td>15</td>
<td>57.0 ± 1.94</td>
<td>66 ± 20</td>
<td>101 ± 25</td>
<td>122 ± 14</td>
<td>153 ± 19</td>
<td>156 ± 17</td>
</tr>
</tbody>
</table>

— no sample analysed.

AVERAGE EFFICACY SCORE

AVERAGE PLASMA DIAZEPAM CONCENTRATION (ng/ml)

FIG. 1. Average efficacy scores and plasma concentrations before operation in two comparable groups of patients over 90 min after the administration of diazepam 10 mg alone or with three antacids.
Table III summarizes the comparable significance values when diazepam was given with the various antacids. This table is based on the incidence of "good" and "fair" drowsiness and probability values greater than the accepted 5% are not included. It can be seen that sedation was best when aluminium hydroxide was used.

Before operation there were no toxic effects attributable to diazepam or its combination with antacids.

The four series were comparable as regards the average duration of anaesthesia and the incidence of excitatory phenomena, and respiratory upset during induction was similar in each, as was the frequency of emetic sequelae after operation.

Table IV shows the average plasma diazepam concentrations following diazepam 10 mg alone or with the three antacids. There were no striking differences in the four series, except that the concomitant use of aluminium hydroxide resulted in a significantly higher concentration at 30 min \((t = 2.033; \text{ d.f.} = 35; P < 0.05)\), suggesting earlier absorption.

Figure 1 is a comparison of the time-course of the sedative effect (as indicated by the mean efficacy score) of diazepam 10 mg and the mean plasma concentrations in comparable groups of patients. It can be seen that these follow a similar pattern for the first hour, but sedation does not decrease with the decrease in plasma concentrations.

**DISCUSSION**

It would have been helpful to attempt to correlate the degree of sedation with the plasma concentrations in individual patients. However, this was not possible since blood sampling interferes with the clinical assessment of sedation. A plot of mean efficacy scores against mean plasma concentrations in similar groups of patients gives a sigmoid curve, since there is a minimum plasma diazepam concentration below which there would be no drug-induced soporific effect and once diazepam has induced sleep there is no increase in the efficacy score with increasing plasma concentrations. This is overcome in figure 2 by the use of logarithms. The plasma concentration-
response relationship of all series is parallel except for the 60-min reading with aluminium hydroxide, and this is explained by the earlier onset of action and the more rapid increase in plasma concentration when this antacid is used.

The main site of absorption of most drugs is thought to be the upper small intestine (Smith and Rawlins, 1973). However, the stomach is a potentially important absorption site when the pH is favourable (Travell, 1940; Hogben et al., 1957). Thus several factors could account for the altered absorption of diazepam when combined with antacids, including changes in the rate of gastric emptying and changes in gastric pH.

One would have expected that any antacid which increases the gastric pH to near that of the $pK_a$ of diazepam (3.3) would enhance absorption of the drug from the stomach. It is possible that this was achieved to a greater extent by aluminium hydroxide than any of the other antacids used in this study.

The use of antacids before operation has increased greatly in recent years, particularly in obstetrics (Crawford, 1971; Peskett, 1973). The sequelae of aspiration of gastric contents are lessened by reducing gastric acidity. Magnesium trisilicate is probably the most popular antacid for this purpose, being recommended by Taylor and Pryse-Davies (1966) and Crawford (1970). However, apart from being palatable there seems little else to recommend it (Harvey, 1975). It is not a very effective antacid (Kirsner, 1941; Armstrong and Martin, 1953; Lahiri, Thomas and Hodgson, 1973; Morrissey and Barreras, 1974) and has a potential toxicity (Joekes, Rose and Sutor, 1973) which appears to have been forgotten. Our studies would not support its superiority over aluminium hydroxide or sodium citrate but the present findings apply only to a single dose; the situation may be different with repeated administrations.

The clinical significance of the findings of this study may lie as much in increasing the safety of an oral premedicant as in enhancing its action. Irrespective of whether or not an antacid increases the uptake of an oral premedicant, its use before operation can be recommended. If it does both, as in the case of aluminium hydroxide and diazepam, its use should be encouraged.

ACKNOWLEDGEMENTS

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REFERENCES


INFLUENCE DE TROIS ANTI-ACIDES SUR L'ABSORPTION ET L'ACTION CLINIQUE DU DIAZEPAM ADMINISTRE PAR VOIE ORALE

RESUME
Dix mg de diazépam administrés par voie orale seul ou avec l'un des trois anti-acides: hydrate d'aluminium 40 ml, trisilicate de magnésie 30 ml, citrate de soude 30 ml, ont été donnés au hasard, en une seule dose à 200 femmes subissant des interventions gynécologiques mineures. L'usage concomitant de l'hydrate d'aluminium ou du citrate de soude a activé marginalement le commencement de l'effet soporifique du diazépam, alors que le trisilicate de magnésie a plutôt eu tendance à le retarder. L'estimation des concentrations de diazépam dans le plasma sur 90 min dans une série similaire de 67 patientes montre que l'absorption de diazépam a été augmentée d'une manière significative par l'emploi d'hydrate d'aluminium, mais il n'y a eu aucune différence frappante dans les quatre groupes. On expose dans cette communication les implications cliniques de ces constatations.

LA INFLUENCIA DE TRES ANTACIDOS SOBRE LA ABSORCIÓN Y ACCIÓN CLINICA DE DIAZEPAM POR VIA ORAL

SUMARIO
Diazepam 10 mg en administración oral, solo o con uno de los tres antácidos (hidróxido de aluminio 40 ml, trisilicato magnésico 30 ml, citrato sódico 30 ml), fue dado en dosis única aleatoria a 200 mujeres sometidas a intervenciones menores ginecológicas. El empleo concomitante de hidróxido de aluminio o de citrato sódico aceleró marginalmente el comienzo del efecto soporífico del diazepam, mientras que el trisilicato magnésico tendió a demorarlo. El cálculo de concentraciones plasmáticas de diazepam en 90 min durante una serie similar de 67 pacientes mostró que la absorción de diazepam fue aumentada significativamente por el empleo de hidróxido de aluminio, pero no había diferencias notables en los cuatro grupos. Se comentan las implicaciones clínicas de estos hallazgos.