Lack of anxiolytic effect of diazepam in pre-anaesthetic medication

S. WIKINSKI, M. LOMBARDO, J. H. MEDINA AND M. C. RUBIO

SUMMARY

In 30 female patients undergoing elective cholecystectomy, we have compared the anxiolytic effect of diazepam 10 mg with placebo, using measurements of cardiovascular (arterial pressure and heart rate), biochemical (plasma concentrations of noradrenaline, adrenaline, cortisol and dopamine β-hydroxylase), subjective (visual analogue scale) and behavioural (Hamilton anxiety test) variables. Pretreatment evaluation was carried out the day before surgery and post-treatment examination was performed 1.5-2 h after oral administration of premedication, immediately before transfer of patients to the operating room. We found that diazepam 10 mg had no significant effect on any of the measured variables. (Br. J. Anaesth. 1994; 72: 694-696)

KEY WORDS

Premedication: diazepam.

Benzodiazepines are prescribed widely as anxiolytics before surgery but several investigators have found little difference in their anxiolytic effects compared with placebo [1-3]. The aim of our study was to examine the anxiolytic effect of diazepam in a homogeneous group of patients, using cardiovascular, biochemical, behavioural and subjective variables and measuring plasma concentrations of the drug and its principal active metabolites.

METHODS AND RESULTS

We studied 30 female patients, ASA I or II, undergoing elective cholecystectomy. Women with a psychiatric history, those who received benzodiazepines on admission or those with a history of alcohol abuse were excluded. All patients gave informed consent and the study was approved by the hospital Ethics Committee.

Pretreatment evaluation was performed on the day before surgery and patients were allocated randomly, in a double-blind fashion, to two groups. Subjects received either diazepam 10 mg or identical placebo tablets orally, 1.5-2 h before surgery. Post-treatment evaluation was performed on the ward immediately before transfer of the patient to the operating room.

Pre- and post-treatment measurements consisted of the following: systolic (SAP) and diastolic (DAP) arterial pressures, heart rate (HR), plasma concentrations of adrenaline, noradrenaline, cortisol and dopamine β-hydroxylase and the Hamilton test for anxiety (HAT) and a visual analogue scale (VAS) (0-10 cm, "totally calm–extremely anxious").

For pretreatment evaluation, we applied also the state-trait anxiety inventory (IDARE) to classify patients into low- or high-trait anxiety groups, as subjects with high basal levels of anxiety may be more sensitive to the anxiolytic properties of benzodiazepines.

Plasma concentration of diazepam, N-desmethyldiazepam and oxazepam were measured by high pressure liquid chromatography with ultraviolet detection in samples obtained during post-treatment evaluation (1.5–2 h after administration of the drug). The detection limit of the assay for all compounds was 100 ng ml⁻¹.

Comparison of the mean of the differences between post- and pretreatment values was by the student's t test and VAS and HAT were compared using the Wilcoxon test. P < 0.05 was considered statistically significant. The power of the observations, evaluated by t test, was 70–80%.

The diazepam group comprised 17 patients (mean age 43.8 (range 20-61) yr, weight 63.9 (SD 2.0) kg, height 1.60 (0.08) m) and the placebo group comprised 13 patients (age 40.8 (21-60) yr, weight 67.0 (3.3) kg, height 1.59 (0.02) m). However, some of the comparisons were performed using a smaller number of patients (table I).

When post-treatment values were compared with pretreatment values, SAP was the only variable which showed a statistically significant change; this was increased in the placebo group (P < 0.05). Comparison between the placebo and diazepam groups for SAP was almost significant (P = 0.053).

Cardiovascular, biochemical subjective and behavioural measurements are shown in table I.

Plasma concentrations of benzodiazepines were measured in 11 patients in the diazepam group. Baseline values were always below the limit of detection of the assay, as were two of the samples. Values ranged from 0.11 to 2.2 μg ml⁻¹ (mean 0.88 μg ml⁻¹).

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Table I. Effects of diazepam and placebo on visual analogue scale (VAS), Hamilton anxiety test (HAT), systolic (SAP) and diastolic (DAP) arterial pressures, heart rate (HR) and plasma concentrations of adrenaline, noradrenaline, cortisol and dopamine-β-hydroxylase (DBH) (mean (SEM)). n = number of paired (pre and post) comparisons. D values = differences between mean of values before and after treatment for each patient. No significant differences between diazepam and placebo groups

<table>
<thead>
<tr>
<th></th>
<th>Diazepam</th>
<th>Placebo</th>
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<tr>
<td></td>
<td>Pre</td>
<td>n</td>
</tr>
<tr>
<td>VAS (cm)</td>
<td>2.70 (0.6)</td>
<td>17</td>
</tr>
<tr>
<td>HAT (points)</td>
<td>9.70 (2.9)</td>
<td>6</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>125.0 (5.1)</td>
<td>17</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>82.35 (2.5)</td>
<td>17</td>
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<tr>
<td>HR (beat min⁻¹)</td>
<td>72.94 (2.9)</td>
<td>17</td>
</tr>
<tr>
<td>Adrenaline (pg ml⁻¹)</td>
<td>74.33 (9.5)</td>
<td>6</td>
</tr>
<tr>
<td>Noradrenaline (pg ml⁻¹)</td>
<td>430.0 (92.0)</td>
<td>6</td>
</tr>
<tr>
<td>DBH (nmol h⁻¹ ml⁻¹)</td>
<td>9.40 (2.6)</td>
<td>12</td>
</tr>
<tr>
<td>Cortisol (ng dl⁻¹)</td>
<td>9.4 (1.3)</td>
<td>4</td>
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</tbody>
</table>

Although we examined only four patients in the diazepam group and six in the placebo group, we found no changes in plasma cortisol concentrations.

Dopamine β-hydroxylase activity has not been studied previously as an indicator of anxiety, but several authors have proposed that it may reflect catecholamine activity indirectly. In our study, dopamine β-hydroxylase activity had a wide range of values, and although there was a tendency towards a decrease after treatment with diazepam, the difference was not statistically significant.

Total plasma concentrations of benzodiazepines were within the therapeutic range in most patients. The lack of anxiolytic effect of diazepam in our study is unlikely to be explained by differences in plasma drug concentrations, as there was no correlation between anxiolytic efficacy (measured as change in any of the indicators we studied) and plasma concentrations of the drug. Finally, anxious patients were not more sensitive to the anxiolytic effects of diazepam, suggesting that individual personality was not the cause of the absence of anxiolysis.

In conclusion, our results showed that diazepam 10 mg probably prevented increases in systolic arterial pressure but failed to modify subjective anxiety, behaviour variables or concentrations of dopamine β-hydroxylase, adrenaline, noradrenaline and cortisol, or diastolic arterial blood pressure and heart rate.

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REFERENCES

COMMENT
Our data are consistent with previous reports and support the hypothesis that diazepam, at the dose used in this study, is no more effective than placebo in relieving preoperative anxiety. However, other authors, using only some of the indicators we have used, have reported a beneficial anxiolytic effect of benzodiazepines in surgical patients [4, 5].

Reinhart and colleagues [1] found no changes in systolic arterial pressure after administration of diazepam but an improvement in subjective apprehension scores was observed. However, we found an increase in systolic arterial pressure in the placebo group which was not found in the patients treated with diazepam. Forrest, Brown and Brown [2] compared six common preoperative medications and while diazepam 10 and 15 mg produced significantly more sedation than placebo, no drug had a significant effect on apprehension scores.

Fell and colleagues [3] measured plasma concentrations of adrenaline and noradrenaline before and after administration of diazepam or papaveretum with hyoscine for premedication. They reported no changes in subjective perceived anxiety or plasma concentrations of noradrenaline. Furthermore, they found an increase of 40% in plasma concentrations of adrenaline in both groups. Plasma cortisol is known to be raised in various acute stressful situations, but most studies have failed to demonstrate any change with anxiolytic treatment [6].

The lack of anxiolytic effect of diazepam, or the absence of a beneficial effect in our study, is unlikely to be explained by differences in plasma concentrations. An assessment of anxiety.

In conclusion, our results showed that diazepam 10 mg probably prevented increases in systolic arterial pressure but failed to modify subjective anxiety, behaviour variables or concentrations of dopamine β-hydroxylase, adrenaline, noradrenaline and cortisol, or diastolic arterial blood pressure and heart rate.

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