BIOCHEMICAL ASSESSMENT OF PREOPERATIVE STRESS: A STUDY WITH DIAZEPAM AND MEASUREMENT OF MONOAMINE METABOLITES AND CATECHOLAMINES IN CEREBROSPINAL FLUID AND PLASMA

J. KANTO AND M. SCHEININ

SUMMARY

Diazepam 5 mg or an inert placebo tablet was given as preoperative hypnotic on the night before operation to two groups (n = 18 in each) of healthy women having elective Caesarean section under spinal analgesia. A third group (n = 18) received no hypnotic. The quality of the preoperative night’s sleep assessed subjectively was significantly better in the diazepam-treated patients compared with those receiving no drug. The diazepam-treated patients had also smaller CSF concentrations of noradrenaline (NA) and of the dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC). In comparison with the two other patient groups, in the diazepam group there was no correlation between demographic, physiological or subjectively estimated variables and CSF or plasma measurements of monoamine transmitters and their metabolites. Preoperative fear and apprehension correlated most strongly with preoperative heart rate and with the increase in heart rate from the previous day. The monoamine neurotransmitters or their metabolites were of limited use in monitoring the intensity of preoperative fear and anxiety.

KEY WORDS

Anxiety before anaesthesia and surgery is associated with increased secretion of stress-related hormones, for example adrenaline and cortisol [1, 2]. We have investigated previously the relationship between situational anxiety before surgery and monoamine turnover in the central nervous system (CNS) by measuring monoamine metabolite concentrations in samples of cerebrospinal fluid (CSF) and plasma in healthy patients undergoing Caesarean section under spinal analgesia without premedication [3]. Contrary to our expectations, self-perceived anxiety was clearly associated only with circulatory changes, and catecholamine and monoamine metabolite concentrations in CSF and plasma were poor indicators of preoperative anxiety [3]. However, the subjectively estimated poor quality of the preoperative night’s sleep correlated with biochemical plasma and CSF measures of increased sympathoadrenal activity [3]. In the present study we have evaluated these associations further, with special reference to the effects of diazepam or an inert placebo tablet taken on the night before surgery.

MATERIALS AND METHODS

Subjects and procedure

Fifty-four healthy pregnant women at or near term (37–41 weeks) gave informed consent to the study, which was approved by the local Ethics Committee. The patients were undergoing elective Caesarean section for obstetric reasons, usually fetopelvic disproportion. The pregnancy was uncomplicated in all cases (apart from the need for surgical delivery) and no patient was receiving any medications (except iron salts and vitamins). Arterial pressure and heart rate were recorded on the ward after at least 30 min rest on
the night before surgery. In group 1 \((n = 18)\) the patients received no premedication; in group 2 \((n = 18)\) a placebo tablet was given at 22:00 (11 (SD 1) h before surgery); in group 3 \((n = 18)\) a 5-mg diazepam tablet was given 11 (1) h before surgery. The patients in groups 2 and 3 were blinded to the medications. The patients were allocated randomly to the three groups on the ward, and the anaesthetist (J.K.) was not aware of the groupings. However, two patients in group 1 reported spontaneously on the lack of premedication.

Surgery was performed with the patient under spinal analgesia. An infusion of Ringer’s lactate was given i.v. via a large vein in the right antecubital fossa. After resting for a minimum of 30 min, just before induction of spinal anaesthesia, the patient was asked to grade the quality of the previous night’s sleep and the feelings of preoperative fear and apprehension, on 100-mm visual analogue scales (VAS) (without ticks). The extremes on the scale for quality of sleep were “very poor” (= 0 mm) and “very good” (= 100 mm) and those for fear and apprehension “none at all” (= 0 mm) and “worst possible” (= 100 mm).

Arterial pressure (AP) and heart rate (HR) were measured at 5-min intervals using an oscillotonometer (Cardiocap, Datex, Finland). The greatest preoperative values were used for comparison with the previous night’s recordings. Immediately before subarachnoid block was induced, a sample of venous blood was obtained from the i.v. cannula. A 25-gauge needle was then inserted at L2—3 into the subarachnoid space, with the patient in the lateral decubitus position, and 1.8—2.3 ml of CSF aspirated slowly into a pre-cooled polypropylene syringe and replaced with bupivacaine. The CSF was transferred rapidly to polycarbonate tubes, chilled on ice, centrifuged briefly at +4 °C and stored at —70 °C together with the plasma samples.

Biochemical methods

The concentrations in CSF of the major CNS metabolites of the monoamine neurotransmitters noradrenaline (NA), serotonin (5-HT), and dopamine (DA)—that is, 3-methoxy-4-hydroxyphenylglycol (MHPG; metabolite of NA), 5-hydroxyindoleacetic acid (5-HIAA; metabolite of 5-HT) and homovanillic acid (HVA; metabolite of DA) were measured using high pressure liquid chromatography (HPLC) with electrochemical detection [4]. Concentrations of NA and adrenaline, the NA metabolite 3,4-dihydroxyphenylglycol (DHPG) and the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in plasma and CSF were measured also using HPLC, after extraction on activated alumina [5].

Statistical analysis

Data were analysed using Amstat One and Two programs (GJ & SC Coleman, 1985 and 1986, U.K.) run on an Amstrad 128-K microcomputer. Student’s \(t\) test, analysis of variance (ANOVA), and linear regression analysis were used for parametric variables; non-parametric data were evaluated with the Kruskal–Wallis test, Mann–Whitney \(U\) test, and Spearman’s rank order correlations.

RESULTS

There were no significant differences between the three patient groups in age, weight or height (one-way ANOVA) (table I). The patients in the diazepam group estimated their quality of sleep as significantly better than did those patients who did not receive tablets (Kruskal–Wallis test, \(P = 0.034\); Mann–Whitney \(U\) test, \(P = 0.014\)). However, there was no significant difference between the placebo and diazepam groups. There was no significant difference between the three patient groups with respect to preoperative fear and apprehension, and no significant difference between the groups in HR, in the increase of HR from the previous night, or in arterial pressure. However, fear and apprehension were correlated significantly with preoperative HR (Spearman’s rank order correlations: no hypnotic agent \(r = 0.58, P = 0.011\); placebo \(r = 0.57, P = 0.012\); diazepam \(r = 0.46, P = 0.050\)), and with increase in HR \((r = 0.63, P = 0.005; r = 0.58, P = 0.027; r = 0.61, P = 0.007\), respectively).

The CSF concentrations of NA and DOPAC were significantly smaller in the group receiving diazepam than in the non-premedicated group (ANOVA, followed by Student’s \(t\) test: \(P = 0.027\) and \(P = 0.0075\)) (table II). DOPAC concentration was also smaller in the placebo group than in the non-premedicated group \((P = 0.050)\). MHPG concentrations in CSF were greater in group 2, compared with both group 1 \((P = 0.015)\) and group 3 \((P = 0.034)\). Plasma concentrations did not differ significantly between groups.

In groups 1 and 2, there were several significant (although often relatively low) correlations be-
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TABLE I. Patient characteristics, the patients' subjective estimates of the quality of sleep on the night before surgery and feelings of preoperative fear and apprehension (visual analogue scales), preoperative heart rate (HR) and its increase from the previous day's value (mean (sd)). Significant difference between groups 1 and 3 in quality of sleep (P = 0.014)

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Score on VAS 0–100</th>
<th>HR (beat min⁻¹)</th>
<th>Increase in HR (beat min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication (group 1)</td>
<td>29.8</td>
<td>72.6</td>
<td>162.2</td>
<td>47.2</td>
<td>49.4</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td>(4.2)</td>
<td>(8.3)</td>
<td>(3.3)</td>
<td>(27.8)</td>
<td>(24.4)</td>
<td>(13.6)</td>
</tr>
<tr>
<td>Placebo (group 2)</td>
<td>30.9</td>
<td>73.6</td>
<td>163.5</td>
<td>61.1</td>
<td>53.3</td>
<td>102.7</td>
</tr>
<tr>
<td></td>
<td>(4.6)</td>
<td>(9.4)</td>
<td>(5.6)</td>
<td>(21.1)</td>
<td>(20.0)</td>
<td>(14.2)</td>
</tr>
<tr>
<td>Diazepam 5 mg (group 3)</td>
<td>28.1</td>
<td>73.8</td>
<td>162.4</td>
<td>69.4</td>
<td>58.3</td>
<td>98.7</td>
</tr>
<tr>
<td></td>
<td>(4.0)</td>
<td>(9.4)</td>
<td>(6.1)</td>
<td>(24.8)</td>
<td>(24.8)</td>
<td>(12.7)</td>
</tr>
</tbody>
</table>

TABLE II. Concentrations (mean (sd)) of noradrenaline (NA) and its metabolites, 3,4-dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG), the dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and the main metabolite of serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA) in CSF; concentrations of NA, DHPG, adrenaline (A) and DOPAC in plasma. Significant differences: CSF NA—group 1 vs group 3 (P = 0.027); CSF DOPAC—group 1 vs group 3 (P = 0.007); CSF DOPAC—group 1 vs group 2 (P = 0.050); CSF MHPG—group 1 vs group 2 (P = 0.015); group 2 vs group 3 (P = 0.034)

<table>
<thead>
<tr>
<th></th>
<th>Concentration (nmol litre⁻¹)</th>
<th>CSF</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA  DHPG  MHPG  DOPAC  HVA  5-HIAA</td>
<td>NA  DHPG  A  DOPAC</td>
<td></td>
</tr>
<tr>
<td>No medication (group 1)</td>
<td>1.55  13.4  42.0  5.8  206  128</td>
<td>1.23  5.3  0.15  15.5</td>
<td></td>
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<tr>
<td></td>
<td>(0.54) (5.0) (7.8) (2.6) (43) (31)</td>
<td>(0.50) (1.6) (0.10) (5.6)</td>
<td></td>
</tr>
<tr>
<td>Placebo (group 2)</td>
<td>1.50  12.0  47.8  3.6  226  178</td>
<td>1.27  6.2  0.15  16.4</td>
<td></td>
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<tr>
<td></td>
<td>(0.54) (2.1) (6.7) (1.3) (88) (69)</td>
<td>(0.50) (1.1) (0.11) (7.1)</td>
<td></td>
</tr>
<tr>
<td>Diazepam 5 mg (group 3)</td>
<td>1.09  10.4  41.6  3.3  206  149</td>
<td>1.34  5.9  0.24  17.9</td>
<td></td>
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<tr>
<td></td>
<td>(0.56) (4.5) (9.9) (1.2) (60) (64)</td>
<td>(0.04) (1.4) (0.18) (6.9)</td>
<td></td>
</tr>
</tbody>
</table>

tween patient characteristics, physiological and subjectively estimated variables and different CSF or plasma measurements. For example, body weight correlated negatively in groups 1 and 2 with the concentrations of the acidic monoamine metabolites DOPAC, HVA and 5-HIAA in CSF. Similar relationships were not detected in the diazepam-treated patients. The most consistent of these associations appeared to be a negative correlation between quality of sleep and CSF concentrations of NA and its metabolites in the non-premedicated group (NA: \( r = -0.61 \), \( P = 0.007 \); DHPG: \( r = -0.54 \), \( P = 0.04 \); MHPG: \( r = -0.57 \), \( P = 0.03 \)). In contrast, these correlations were not significant in groups 2 and 3.

There were also many significant interrelationships between the CSF and plasma measurements in groups 1 and 2, but not as many in group 3. For example, the CSF and plasma concentrations of NA and its metabolites showed significant positive intercorrelations in groups 1 and 2; the greatest correlations were between NA and DHPG in CSF (\( r = 0.84 \) and \( r = 0.73 \)). NA and adrenaline concentrations in plasma were significantly correlated only in group 1 (\( r = 0.60 \), \( P = 0.02 \)). All acidic monoamine metabolite concentrations in CSF were positively intercorrelated, but again only in groups 1 and 2.

DISCUSSION

The patients receiving diazepam 5 mg orally on the night preceding surgery slept significantly better than those who did not receive medication. This difference was associated with significantly smaller CSF concentrations of NA and the dopamine metabolite DOPAC in the diazepam group. However, the use of diazepam as a hypnotic had no effect on subjective perception of preoperative anxiety or circulatory variables. Poor quality of sleep was associated with biochemical signs of increased noradrenergic activity in the
group receiving no hypnotic, which corroborates our earlier results [3]. Interestingly, in both the diazepam and the placebo groups there was no negative association between quality of sleep and the CSF concentrations of NA and its metabolites DHPG and MHPG. On the whole, diazepam appeared to perturb many of the associations observed between the patient characteristics, physiological or subjectively estimated variables and the different CSF or plasma measurements; this was not the case with placebo treatment. Similarly, administration of diazepam was not associated with many of the normal intercorrelations between the CSF and plasma concentrations of the different monoamine neurotransmitters and their metabolites. In our opinion, reduced sympathoadrenal activation in the diazepam-treated patients is the most likely explanation for the three phenomena. This is supported by previous findings of positive correlations between anxiety and CSF NA and MHPG concentrations in depressed patients [6, 7].

The negative association of body height with the concentration of 5-HIAA in lumbar CSF and the positive correlations between the acidic monoamine metabolites, 5-HIAA, DOPAC and HVA in CSF have been reported previously [8, 9]. Interestingly, diazepam treatment appeared to abolish these associations.

In our previous study, we found that poor quality of sleep during the preoperative night was associated with increased NA and MHPG concentrations in CSF and NA and adrenaline in plasma in patients without any drug treatment [3]. This may lead to disturbances of cardiac rhythm and suggests, therefore, that benzodiazepines are useful for the treatment of situational preoperative insomnia [10, 11].

The limited usefulness of hormones and monoamines and their metabolites as outcome measures has been observed in earlier clinical premedication studies with anxiolytic agents [3, 5, 12-14]. In spite of many statistically significant correlations between preoperative anxiety and CSF or plasma concentrations, few clinically useful associations have been observed. Thus subjective VAS assessments or simple measurements of HR or the increase in HR or arterial pressure from the previous day [3] appear to be more useful and reliable indicators of the severity of preoperative anxiety than the biochemical measurements undertaken here.

REFERENCES