INFLUENCE OF PREMEDICATION ON PLASMA ACTH AND CORTISOL CONCENTRATIONS IN CHILDREN DURING ADENOIDECTOMY

G. SIGURDSSON, S. LINDAHL AND N. NORDEN

SUMMARY
The endocrine response to stress, as reflected by the plasma concentrations of ACTH and cortisol, was investigated in 14 children receiving two different premedications during halothane anaesthesia for adenoidectomy. Seven children (group A) were premedicated with diazepam 5 mg rectally and atropine 0.3-0.4 mg sublingually and seven (group B) received a rectal combination of diazepam 0.5 mg kg⁻¹, morphine 0.15 mg kg⁻¹ and hyoscine 0.01 mg kg⁻¹. Before and after surgery plasma concentrations of ACTH and cortisol were lower in group B than in group A. In group A mean values for ACTH increased from 40.7 ng litre⁻¹ before adenoidectomy to 352.9 ng litre⁻¹ (P<0.001) after adenoidectomy. The corresponding increase in group B was from 12.1 ng litre⁻¹ to 82.1 ng litre⁻¹ (P<0.01). In group A mean cortisol concentrations increased from 235.7 nmol litre⁻¹ to 655.7 nmol litre⁻¹ after adenoidectomy (P<0.001) and in group B from 121.4 nmol litre⁻¹ to 427.9 nmol litre⁻¹ (P<0.01). End-tidal carbon dioxide tension was approximately the same in both groups. It was concluded that the combination of diazepam, morphine and hyoscine decreased the endocrine response to stress.

Although the plasma concentrations of ACTH and cortisol are increased during surgery (Sandberg, Eik-Nes and Samuels, 1954; Hume, Bell and Barter, 1962; Ichikawa et al., 1971) this response can be obtunded by high doses of morphine and fentanyl, and by extradural anaesthesia (George et al., 1974; Engqvist et al., 1977; Hall et al., 1978; Brandt et al., 1978). Since the influence of premedication on the endocrine response to preoperative anxiety and to surgical stimuli, as reflected by plasma concentrations of ACTH and cortisol, has not been reported previously, this study compared the plasma concentrations of ACTH and cortisol following the administration of two different premedications to children undergoing adenoidectomy.

PATIENTS AND METHODS
Fourteen children scheduled for adenoidectomy were studied, none of whom had any evidence of acute infection, cardiac failure or pulmonary disease. All the children were fasted overnight and were randomly divided into two equal groups, A and B. In group A the mean age was 5 (range 3-7) yr with a mean body weight of 20.4 ± 3.2 (SD) kg and in group B, mean age was 4 (range 3-6) yr with a mean body weight of 17.1 ± 2.5 (SD) kg. The children in group A were premedicated with diazepam 5 mg (Stesolid) rectally, that is about 0.25 mg kg⁻¹, and atropine 0.3-0.4 mg sublingually 20-40 min before the induction of anaesthesia. In group B was from 12.1 ng litre⁻¹ to 82.1 ng litre⁻¹ (P<0.01). Group A mean cortisol concentrations increased from 235.7 nmol litre⁻¹ to 655.7 nmol litre⁻¹ after adenoidectomy (P<0.001) and in group B from 121.4 nmol litre⁻¹ to 427.9 nmol litre⁻¹ (P<0.01). End-tidal carbon dioxide tension was approximately the same in both groups. It was concluded that the combination of diazepam, morphine and hyoscine decreased the endocrine response to stress.

Both groups were anaesthetized by the same anaesthetist, who was not informed of the premedication used. Before induction of anaesthesia the anaesthetist evaluated the sedative effect of the premedication according to a modification of the method described by Barker and Nisbet (1973) (table I). During induction the anaesthetist also evaluated the antisialagogue effect as adequate (0) or inadequate (-). Inhalation anaesthesia with nitrous oxide in oxygen (FIO₂, 0.5) and halothane (maximum concentration 2.5%) was used. An oral endotracheal tube was inserted in all of the children without the
Table I. Evaluation of premedication

<table>
<thead>
<tr>
<th>Score</th>
<th>Behaviour of the child</th>
<th>Reaction to induction of anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Crying or struggling</td>
<td>Crying or struggling</td>
</tr>
<tr>
<td>1</td>
<td>Calm</td>
<td>Wincing or vocalizing</td>
</tr>
<tr>
<td>2</td>
<td>Sedated</td>
<td>Moving the hands or head</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Sleeping but arousable</td>
<td>Estimation of sedation (I + II)</td>
</tr>
</tbody>
</table>

- 0–1.9 = poor
- 2–3.9 = fair
- 4–5.9 = good
- 6–7.9 = excellent

Use of neuromuscular blocking drugs. Respiration was spontaneous. Retameters for oxygen and nitrous oxide, and the Mark III halothane vaporizer, were calibrated. A Mapleson D circuit with fresh gas flows of three times the minute ventilation of the child was used to avoid rebreathing. During the induction of anaesthesia an infra-red carbon dioxide analyser (Siemens-Elema, Stockholm, 130) (Olsson et al., 1980) was incorporated in the anaesthetic circuit.

E.g., capillary perfusion (CP) and end-tidal carbon dioxide tension (PE'CO₂) were recorded continuously (Siemens–Elema, EM81). Heart rate (HR) and breathing frequency were calculated from e.g. recordings and end-tidal carbon dioxide curves, respectively. Systolic and diastolic arterial pressures were measured intermittently and the mean arterial pressure (m.a.p.) calculated. The carbon dioxide analyser was calibrated using two test gases of known carbon dioxide concentration. Because of dispersion of the infra-red spectrum by nitrous oxide, all carbon dioxide values were corrected by a factor of 0.95 which referred to 50% nitrous oxide.

After the induction of anaesthesia a vein on the extensor side of the hand was cannulated to allow blood sampling. Samples for the measurement of ACTH and cortisol concentrations were collected in test tubes containing EDTA (10.5 mg/7 ml blood) and aprotinin (Trasylool, Bayer, Germany, 3000 KIE/7 ml blood) which had been pre-chilled on ice-water. The samples were kept at 0°C until centrifugation in a refrigerated centrifuge. The supernatants were then stored at −20°C. The concentration of ACTH was determined by radioimmunoassay (ACTHK, Sorin Biomedica, Italy) using rabbit antiserum raised against porcine ACTH coupled to bovine albumin. Human ACTH was used as standard and ¹²⁵I–ACTH as tracer. The coefficient of variation in duplicate determinations was 17% for values less than 50 ng litre⁻¹ and 10% for values greater than 50 ng litre⁻¹ (Hedner, Nordén and Valdemarsson, 1981). Cortisol concentration was determined using a solid phase radioimmunoassay (Gammacoat, Clinical Assays, Mass., U.S.A.) with rabbit anti-cortisol serum attached to the test tubes as binding protein and ¹²⁵I-cortisol as tracer. The coefficient of variation was less than 7%. The cross reactivity was 88% for prednisolone and insignificant for other steroids tested.

Blood samples for analysis of venous oxygen (PVO₂) and carbon dioxide (PvCO₂) tension were taken in syringes and kept on ice until the analyses were performed 10 min later (IL413, Instrumentation Laboratories, Italy).

Measurements

For the evaluation of relative changes in capillary perfusion the amplitude obtained during undisturbed anaesthesia and before intubation of the trachea (An, see below) was chosen as reference.

E.g., CP, MAP and PE'CO₂ were measured at the following stages of anaesthesia and adenoidectomy: B = Before induction of anaesthesia; S = after induction of Sleep; An = during undisturbed Anaesthesia before intubation; Int = 1 min after Intubation; Ad = during Adenoidectomy; aAd = after Adenoidectomy; Ext = after Extubation; P = 15 min Post-op.

Blood samples were taken at stages An (sample 1), aAd (sample 2) and P (sample 3).

Statistics

Comparisons between the groups were carried out with paired Student's t test and the Chi-square test.

Results

Sedative effects

The evaluation of the sedative effects showed that the scores (table I) were greater in group B than in group A (table II). However, these differences were not significant.
PREMEDICATION AND HORMONAL RESPONSE

![Graph of MAP](image)

**Fig. 1.** Upper panel: Mean values ± SEM for mean arterial pressure (MAP). Lower panel: Mean values ± SEM for capillary perfusion during anaesthesia and adenoidectomy as related to the values at undisturbed anaesthesia (An). Group A (O—O), group B (●—●).

**TABLE II. Evaluation of sedation**

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Antisialagogue effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3 4 4 3 3 3 3 3 4</td>
<td>3.4</td>
</tr>
<tr>
<td>B</td>
<td>4 3 5 5 2 5 4</td>
<td>4.1</td>
</tr>
</tbody>
</table>

**Heart rate, mean arterial pressure, capillary perfusion and cardiac arrhythmias**

In both groups HR increased by about 30% during the procedure. MAP and CP were somewhat lower in group B after anaesthesia than in group A (fig. 1). At Ad capillary perfusion was significantly greater in group A than in group B (P<0.05). Four children in each group had supraventricular cardiac arrhythmia. In group A, three children also developed ventricular arrhythmia, while none was seen in group B.

**ACTH**

Plasma concentrations of ACTH at An and P were significantly less in group B than in group A (P<0.01 and P<0.001, respectively, fig. 2). The

**Fig. 2.** Mean values ± SEM for plasma concentrations of ACTH at An, aAd and P for group A (white columns) and for group B (stippled columns). **P<0.01, ***P<0.001.
values (mean ± SEM) in group A increased from 40.7 ± 6.5 ng litre⁻¹ at An to 352.9 ± 46.5 ng litre⁻¹ at P (P < 0.001). The corresponding increase in group B was from 12.1 ± 2.0 ng litre⁻¹ to 82.1 ± 17.3 ng litre⁻¹ (P < 0.01).

Cortisol

Plasma cortisol concentrations were significantly lower in group B compared with group A (P < 0.01, P < 0.001 and P < 0.01, respectively, fig. 3). The values (mean ± SEM) in group A increased from 235.7 ± 36.1 nmol litre⁻¹ at An to 655.7 ± 18.4 nmol litre⁻¹ at P (P < 0.001). In group B the corresponding increase was from 121.4 ± 15.2 nmol litre⁻¹ to 427.9 ± 63.3 nmol litre⁻¹ (P < 0.01).

Gas exchange

There was a statistically significant increase in respiratory rate and $P_{E}CO_{2}$ in both groups during anaesthesia and surgery, but there were no significant differences between the groups (fig. 4). Venous oxygen and carbon dioxide tensions were normal in both groups.

DISCUSSION

To avoid the diurnal variations in ACTH and plasma cortisol concentrations (Nilsson, Arner and Hedner, 1963) all children were investigated between 8.30 and 10.30 am. In both groups premedication was administered between 20 and 40 min before the induction of anaesthesia. Standardized methods for anaesthesia and surgery were used. Mean age, body weight and preoperative fasting were comparable in the two groups.

The anaesthetist judged the sedative and antaialagogue effect of the premedication used in group B to be somewhat better than in group A. The material is, however, too small for any conclusions to be drawn on sedative effects, but the results confirm earlier reports that the combination of diazepam, morphine and hyoscine is advantageous (Lindahl, Olsson and Thomson, 1981).

Surgical procedures result in an increase in plasma cortisol concentration (Sandberg, Eik-Nes and Samuels, 1954; Cooper and Nelson, 1962; Hume, Bell and Barter, 1962; Nilsson, Arner and Hedner, 1963) and the secretion of ACTH increases rapidly after the skin incision (Ichikawa et al., 1971), which is relevant in this study since the time between the first and second blood samples was only 5–10 min. In other words, ACTH and cortisol are suitable indices of the endocrine stress response during short
PREMEDICATION AND HORMONE RESPONSE

procedures like adenoidectomy. The method used for the analysis of ACTH is known to give spurious values outside the normal range in about 2% of measurements (Hedner, Nordén and Valdemarsson, 1981). Obviously increased values were not observed in the unstressed state in the present clinical material.

It is also known that ACTH often reaches plasma concentrations above the concentration required for maximal corticosteroid output from the adrenals (Ganong, Alpert and Lee, 1974). Simultaneous analyses of plasma concentrations of ACTH and cortisol revealed a discrepancy in relative changes of plasma concentrations between ACTH and cortisol. ACTH concentrations increased more than eight times the initial value in group A, while the corresponding cortisol plasma concentrations increased less than three-fold. This supports the findings of Ganong, Alpert and Lee (1974), and demonstrates the inability of the adrenals to respond to the full ACTH stimulus.

Plasma concentrations of ACTH and cortisol were both significantly smaller in group B compared with group A, a result which, to some extent, might be explained by a decrease in anxiety. It was shown that, compared with the initial values of ACTH and cortisol during undisturbed anaesthesia, the increase after surgery was greater in group A than in group B. This cannot be explained by a decrease in anxiety alone. The suppressed ACTH and cortisol responses found in group B (premedicated with diazepam, morphine and hyoscine) might be a result of the morphine. However, the doses of morphine were small compared with those (1 - 4 mg kg⁻¹) described previously to block the ACTH and cortisol responses to surgery and stress (Reier, George and Kilman, 1973; George et al., 1974; Brandt et al., 1978).

The effect of diazepam in decreasing anxiety before operation is well documented (Tornetta, 1965; Dobkin et al., 1970) and Oyama and colleagues (1969) found that diazepam 0.2 mg kg⁻¹ decreased the plasma free cortisol concentration. However, the sedative effect of diazepam is dose-dependent, even though there are great individual variations in the response to the drug (Brown and Dundee, 1968). Therefore, the differences in hormonal stress response between the two groups might to a large extent be explained by the larger dose of diazepam used in group B.

In addition, it has been shown that diazepam increases the effects of pethidine, morphine and hyoscine when used in various combinations (Dundee et al., 1970). We feel that these additive effects were most probably the explanation of the clearcut differences in endocrine stress response demonstrated in this study.

ACKNOWLEDGEMENTS

This investigation was supported by grants from the Medical Faculty, University of Lund. We thank Mrs Gunvor Ekdahl for excellent technical assistance.

REFERENCES


Influence of premedication on plasma ACTH and cortisol concentrations during adenoidectomy in children

Influence de la prémedication sur des concentrations plasmatiques d’ACTH et de cortisol chez des enfants subissant une adénoidectomie

En 14 niños que recibían dos premedicaciones distintas durante la anestesia por halotano a someterse a una adenoidecтомia, se averiguó la respuesta endocrina a la tensión, tal como reflejada por las concentraciones de ACTH y de cortisol en el plasma. A siete niños (grupo A), se les administró como premedicación 5 mg de diazepam rectalmente y 0,3–0,4 mg de atropina sublingual, y a los siete niños del grupo B, una combinación rectal de 0,5 mg kg⁻¹ de diazepam, 0,15 mg kg⁻¹ de morfina y 0,01 mg kg⁻¹ de hiascina. Antes y después de la operación, las concentraciones de ACTH y de cortisol en el plasma eran más bajas en el grupo B que en el grupo A. En el grupo A, los valores medios del ACTH aumentaron desde 3,95 ng litre⁻¹ antes de la adenoidecтомia hasta 12,1 ng litre⁻¹, mientras que en el grupo B, las concentraciones de ACTH después de la adenoidecтомia fueron de 12,1 ng litre⁻¹ (P < 0,01). El aumento correspondiente en el grupo B fue de 3,95 ng litre⁻¹ (P < 0,01). En el grupo A, las concentraciones de cortisol aumentaron después de la adenoidecтомia de 0,03 nmol litre⁻¹ a 0,15 nmol litre⁻¹ (P < 0,01). La CO₂ de fin de expiración fue de 427,9 nmol litre⁻¹ (P < 0,01). La tensión respiratoria terminal de anhidrido carbónico era más o menos igual en ambos grupos. Se concluyó que la combinación de diazepam, morfina y hiascina hace disminuir la respuesta endocrina a la tensión.