INFLUENCE OF PREMEDICATION ON THE SYMPATHETIC AND ENDOCRINE RESPONSES AND CARDIAC ARRHYTMIAS DURING HALOTHANE ANAESTHESIA IN CHILDREN UNDERGOING ADENOIDECTION

G. H. SIGURDSSON, S. LINDAHL AND N. NORDÉN

SUMMARY

The occurrence of cardiac arrhythmia was investigated in 80 children during halothane anaesthesia for adenoidectomy. Two different premedication were studied. Forty children (group A) were premedicated with diazepam 5 mg rectally and atropine 0.3–0.4 mg sublingually and 40 (group B) received a rectal solution including diazepam 0.5 mg kg\(^{-1}\), morphine 0.15 mg kg\(^{-1}\) and hyoscine 0.01 mg kg\(^{-1}\). In 17 of these children (nine in group A and eight in group B) plasma concentrations of catecholamines, ACTH and corticosteroids were measured. In group A the mean plasma concentration of catecholamines increased more than 300% during surgery, while it was virtually unchanged in group B (P<0.01). Plasma concentrations of ACTH, cortisol and 17-a-hydroxyprogesterone were also greater in group A than in group B. The occurrence of ventricular arrhythmia in group A was significantly more frequent (20.0%) than in group B (2.5%) (P<0.05). It was concluded that in these two comparable groups of patients ventricular arrhythmia during halothane anaesthesia was almost eliminated by the use of more effective premedication, as a result of decreases in the sympathetic and endocrine responses to surgery.

Ventricular arrhythmias occur commonly, particularly during surgical stimulation, when halothane is administered during oral surgery (Tuohy, 1968; Miller et al., 1970; Ryder, 1970; Ryder and Townsend, 1974; Lindgren, 1981; Sigurdsson et al., 1983). These arrhythmias can be prevented by beta-blockade or by blocking the afferent impulses from the surgical field with local anaesthetic agents (Tolas and Allen, 1970; Rollason and Hall, 1973; Plowman, Thomas and Thurlow, 1974). This suggests that the common pathway for the development of such arrhythmias is sympathetic stimulation of the myocardium sensitized by halothane (Katz and Bigger, 1970; Thurlow, 1972).

The influence of different anaesthetic techniques on the endocrine response to surgical stress has been the subject of many recent investigations (Engquist et al., 1980; Glisson and Balasaraswathi, 1981; Kono et al., 1981; Roizen, Horrigan and Frazer, 1981) including a study, on children undergoing adenoidectomy during halothane anaesthesia, in which effective premedication was shown to modify the stress response as reflected by plasma concentrations of ACTH and cortisol (Sigurdsson, Lindahl and Nordén, 1982). The aim of the present study was to investigate if this more efficient premedication (a rectal solution of diazepam 0.5 mg kg\(^{-1}\), morphine 0.15 mg kg\(^{-1}\) and hyoscine 0.01 mg kg\(^{-1}\)) also decreased the catecholamine response and, with this, the occurrence of ventricular arrhythmias in children undergoing adenoidectomy under halothane anaesthesia.

PATIENTS AND METHODS

Eighty children undergoing adenoidectomy were studied. No child had evidence of acute infection, or cardiopulmonary disease. The children were divided into two equal groups. In group A the mean age was 5.1 yr (range 2–12 yr) and in group B 5.4 yr (range 1–12 yr). In 17 children (nine in group A and eight in group B), the plasma concentrations of the catecholamines, ACTH, cortisol and 17-a-hydroxyprogesterone were measured. The mean age of the children in group A, in whom these hormones were measured, was 4.9 yr (range 2–7 yr) with a mean body weight of 19.8 ± 3.4 (SD) kg. The corresponding mean age in group B was 4.6 yr (range 3–7 yr) and the mean body weight was 17.9 ± 3.1 (SD) kg.

The children in group A were premedicated with diazepam 5 mg rectally (about 0.25 mg kg\(^{-1}\)) and atropine 0.3–0.4 mg sublingually. Patients in group B were premedicated with a rectal solution of
diazepam 0.5 mg kg$^{-1}$, morphine 0.15 mg kg$^{-1}$ and hyoscine 0.01 mg kg$^{-1}$. The premedication was scheduled for 20–40 min before the induction of anaesthesia.

ECG electrodes were applied while the child was still awake and in the presence of one of its parents. An arterial pressure cuff of appropriate size was placed around the left arm. All children 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) (Sigurdsson, Lindahl and Nordén, 1982).

Inhalation anaesthesia with nitrous oxide in oxygen (F$\text{O}_2$ 0.5) and halothane (maximum concentration 2.5\%) was used. An oral endotracheal tube was passed in all children without the use of neuromuscular blocking drugs. Respiration was spontaneous. Rotameters for oxygen and nitrous oxide and a Mark III halothane vaporizer were calibrated. A Mapleson D circuit with fresh gas flows of three times the estimated minute ventilation of the child was used to avoid rebreathing. At the induction of anaesthesia an infra-red carbon dioxide analyser (Siemens–Elema, Stockholm, 130) (Olsson et al., 1980) was incorporated in the anaesthetic circuit. It was calibrated with two test gases of known carbon dioxide concentrations within the measuring range. Because of dispersion of the infra-red spectrum by nitrous oxide, carbon dioxide values were corrected by a factor of 0.95. ECG and end-tidal carbon dioxide tensions (PE'CO$_2$) were recorded continuously (Siemens–Elema, EM 81). Heart rate (HR) and respiratory rate (f) (b.p.m.) were calculated from the ECG record and the end-tidal carbon dioxide record, respectively. Systolic and diastolic arterial pressures were measured intermittently and the mean arterial pressure (MAP) calculated.

**Biochemical methods**

After the induction of anaesthesia a peripheral vein was cannulated for the sampling of blood. Samples for the measurement of ACTH and cortisol concentrations were collected in test tubes containing EDTA (10.5 mg/7 ml blood) and aprotinin (Trasylol, Bayer, West Germany, 3000 KIE/7 ml blood) which had been prechilled in ice-water. The samples were kept at 0°C until centrifuged in a refrigerated centrifuge. The resulting plasma was stored at −20°C. ACTH was determined by radioimmunoassay (ACTHK, Sorin Biomedica, Italy) using rabbit antiserum raised against porcine ACTH coupled to bovine serum albumin. Human ACTH was used as standard and $^{125}$I-ACTH as tracer (Sigurdsson, Lindahl and Nordén, 1982). Cortisol concentration was determined using a solid phase radioimmunoassay (Gammacoat, Clinical Assays, Mass., USA) with rabbit anti-cortisol serum attached to the test tubes as binding protein and $^{125}$I-cortisol as tracer. A radioimmunochemical method was also used for the assay of 17-α-hydroxyprogesterone (OHPK, Sorin Biomedica, Italy). The method was based on rabbit antibodies against the 3-conjugate to bovine serum albumin. The tracer was tritiated and dextran-coated charcoal was used for separation. Samples for measuring the total catecholamine concentration were drawn in tubes with 20 μ litre of anticoagulant and antioxidant (EGTA 90 mg ml$^{-1}$, glutathione 60 mg ml$^{-1}$ and pH 6.0–7.4) per ml of blood. A modification of the radioenzymatic method of Passon and Peuler (1973) (Upjohn Diagnostics, U.S.A.) based on rat liver catechol-O-methyltransferase and S-adenosyl-L-methionine-$^3$H-methyl) was used. After periodate oxidation the resulting $^3$H-vanillin was extracted and measured by liquid scintillation. Between-runs coefficient of variation for the assay was from 4% to 10%, depending on concentration. Normal values for adults were 0.8–2.4 nmol litre$^{-1}$.

**Measurements**

ECG, MAP, $f$ and PE'CO$_2$ were measured at the following stages:

1. before induction of anaesthesia;
2. after induction of anaesthesia (approximately 2.5 min after start of induction);
3. during undisturbed anaesthesia (3.5–4.5 min after start of induction);
4. before intubation of the trachea;
5. after intubation of the trachea;
6. during adenoidectomy;
7. after adenoidectomy;
8. after extubation, when the child was breathing normally and was judged to control its airways adequately, swallowing and reacting in a lively way to painful stimuli, but still not awake, “partial recovery”;
9. 15 min after operation, when the child was awake.

Blood samples were taken at stages 3, 7 and 9.
ECG criteria

Sinus tachycardia (ST) was not classified as an arrhythmia. HR less than 60 beat min⁻¹ during 5 s or more was used as a criterion for sinus bradycardia (SB). Isolated ectopic beats were reported only when at least three were seen in the same child. Beats with bizarre QRS configurations were considered to be of the ventricular origin (VES), unless there was positive evidence for a supraventricular origin. Three or more consecutive beats of ventricular origin were regarded as ventricular tachycardia (VT).

Statistical methods

The two-tailed F-test and Student’s t-test were used to compare the variances and mean values in the two groups. When there was no significant difference in variance the pooled variance estimate was used in the t-test (Afifi and Azen, 1979). Otherwise the separate variance estimate of the level of significance was used. Stepwise linear discriminant analysis (Afifi and Azen, 1979) was used to find all variables that contributed significantly to the discrimination between the children in groups A and B. The Chi-square test was used to test significance in frequency of ventricular arrhythmias between the two groups.

RESULTS

All children in group A and 38 children in group B received their premedication between 25 and 50 min before induction of anaesthesia. One child in group B had its premedication 90 min and another 130 min before induction of anaesthesia. Mean sedative score (± SEM) for the premedication was significantly greater in group B (4.1 ± 0.2, good) than in group A (3.0 ± 0.2, fair) (P<0.001). The mean induction time (that is the time until intubation) and the time until “partial recovery” (defined above) were comparable in the two groups (table I). Slight airways obstruction (stridor) was noted in three children in each group during the induction of anaesthesia (excitation stage). One child in group A had slight airway obstruction immediately after extubation of the trachea. These airway problems were always short lived and laryngospasm with cyanosis was not observed in any child. No airway problems were noted in the period after operation. Reactions to intubation, such as coughing and closure of vocal cords, occurred in 10 children in group A and in nine children in group B.

Arrhythmias

Only those children who had a normal ECG before anaesthesia were included in the study. The frequency and classification of arrhythmias are shown in table II. Arrhythmias were observed in 26 children in group A (65%) and in 18 children in group B (45%). Junctional rhythm was the most common arrhythmia in both groups. Eight children in group A (20%) and one child in group B (2.5%) developed ventricular arrhythmia (P<0.05). Two of the children in group A had multifocal ventricular ectopic beats and four developed episodes of ventricular tachycardia with heart rates of 140–200 beat min⁻¹ (fig. 1). The child in group B who developed ventricular arrhythmia had isolated unifocal ventricular ectopic beats for 40 s during surgery. Supraventricular arrhythmias were mostly seen during undisturbed anaesthesia, while ventricular arrhythmias occurred during or shortly after surgery.

The mean arterial pressure increased by almost 10% and the heart rate by 25–30% in both groups during surgery. No significant differences were found between the groups in mean arterial pressure, but heart rates at stages 1, 2, 6, 7 and 8 were among

<table>
<thead>
<tr>
<th>TABLE I. Mean values (SEM) for induction time, operation time and for &quot;partial recovery&quot; (see definition in the text) (s) for the two groups</th>
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</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Induction</td>
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<tr>
<td>Adenoidectomy</td>
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<td>&quot;Partial recovery&quot;</td>
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</tbody>
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<tr>
<th>TABLE II. Classification of arrhythmias. Note that ventricular arrhythmias occurred in eight children in group A compared with one in group B. VES = ventricular extrasystole (ventricular ectopic beat). *P &lt; 0.05 for the difference between group A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Arrhythmias: total</td>
</tr>
<tr>
<td>Supraventricular arrhythmias</td>
</tr>
<tr>
<td>Junctional rhythm</td>
</tr>
<tr>
<td>Ectopic atrial rhythm</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Unifocal VES or bigemini</td>
</tr>
<tr>
<td>Multifocal VES</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
</tr>
</tbody>
</table>
FIG. 1. ECG (lead V5) in a 6-yr-old boy. At the end of surgery he developed irregular ventricular arrhythmia at a rate of 160 beat min⁻¹. During the arrhythmia MAP was 115 mm Hg, plasma catecholamines 14.9 nmol litre⁻¹, \( P_{\text{E}CO_2} \) 6.7 kPa, venous \( P_{CO_2} \) 6.3 kPa and venous PO₂ 26.3 kPa.

the variables which discriminated between the two groups.

**Plasma concentrations of total catecholamines, ACTH, cortisol and 17-α-hydroxyprogesterone**

During undisturbed anaesthesia there was no difference in catecholamine concentrations between the groups (stage 3) (fig. 2), but at stages 7 and 9 the concentrations were significantly greater in group A than in group B (\( P < 0.01 \) and \( P < 0.05 \), respectively) (fig. 2). In group A the mean (± SEM) concentration increased more than three times, from 4.9 ± 0.6 nmol litre⁻¹ at stage 3 to 17.9 ± 2.7 nmol litre⁻¹ at stage 7 (\( P < 0.001 \)). In group B, there was no significant change in mean concentrations of catecholamines during the procedure. The mean plasma concentrations of ACTH, cortisol and 17-α-hydroxyprogesterone were greater on all occasions on which they were measured in group A than in group B (fig. 3A, B and C).

**Gas exchange**

In both groups respiratory rate and \( P_{\text{E}CO_2} \) increased during undisturbed anaesthesia and surgery. The mean \( P_{\text{E}CO_2} \) values were 0.1–0.4 kPa greater in group B than in group A at all stages, but this difference was not statistically significant. The greatest \( P_{\text{E}CO_2} \) values (mean ± SEM) were found after intubation (stage 5) in both groups—6.5 ± 0.1 kPa in group A and 6.8 ± 0.1 kPa in group B.

In the stepwise discriminant analysis the variables

![Graph showing mean values ± SEM for plasma concentrations of total catecholamines at stage 3, 7 and 9 for group A (n = 9; continuous line) and for group B (n = 8; dotted line). *P < 0.05; **P < 0.01.](image-url)
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were entered into a discriminating function, provided that the variable gave a significant contribution at each step to the discrimination between group A and B. Thus 10 of the 20 variables were found to contribute to this discrimination, including catecholamine concentration, the concentration of all the hormones measured, and heart rate at the various stages of the procedure (table III). Using the final discrimination function, it was possible to classify all patients in group A and B to the correct group, that is no miss-classification error occurred (fig. 4).

DISCUSSION

A few decades ago efficient premedication was considered of clinical importance to decrease salivation and laryngeal reflexes and to suppress excitement during induction of anaesthesia. Since the development of newer and more effective inhalation anaesthetics it has been suggested that these advantages are less important and it has been debated whether premedication should be used at all. There are, however, reports pointing out that preoperative anxiety in children might result in psychological disturbances (Eckenhoff, 1953), and even increase peri-operative bleeding (Haq and Dundee, 1968).

Recently, it was shown that premedication with a combination of diazepam 0.5 mg kg$^{-1}$, morphine 0.15 mg kg$^{-1}$ and hyoscine 0.01 mg kg$^{-1}$ administered rectally decreased the endocrine response to surg (Sigurdsson, Lindahl and Nordén, 1982). In the present study, two premedications were used in two comparable groups of children subjected

Fig. 3. Mean values ± SEM for plasma concentrations of ACTH (A), cortisol (B) and 17-$\alpha$-hydroxyprogesterone (C) at stage 3, 7 and 9 for group A ($n=9$; continuous line) and for group B ($n=8$; dotted line). *$P<0.05$; **$P<0.01$; ***$P<0.001$. 

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Table III. The discriminating variables. The variables in the table give a significant contribution to the classification of all patients into group A and B respectively. Notice that plasma catecholamines at stage 9 are not included, although there was a statistically significant difference between the groups at this stage (fig. 2). This is because they did not add further information for discrimination between the groups, since there was even larger difference at stage 7. OHP = 17\(\alpha\)-hydroxyprogesterone.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>9</td>
<td>0.120</td>
<td>-0.00364</td>
</tr>
<tr>
<td>Catecholamine</td>
<td>7</td>
<td>0.848</td>
<td>-4.66</td>
</tr>
<tr>
<td>Heart rate</td>
<td>6</td>
<td>0.973</td>
<td>-1.82</td>
</tr>
<tr>
<td>Heart rate</td>
<td>7</td>
<td>-0.291</td>
<td>2.48</td>
</tr>
<tr>
<td>OHP</td>
<td>3</td>
<td>2.02</td>
<td>-0.655</td>
</tr>
<tr>
<td>Cortisol</td>
<td>7</td>
<td>-0.0174</td>
<td>-0.280</td>
</tr>
<tr>
<td>Cortisol</td>
<td>9</td>
<td>-0.0088</td>
<td>0.189</td>
</tr>
<tr>
<td>Heart rate</td>
<td>8</td>
<td>0.0890</td>
<td>-1.32</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1</td>
<td>0.732</td>
<td>2.15</td>
</tr>
<tr>
<td>Heart rate</td>
<td>2</td>
<td>-0.0243</td>
<td>1.07</td>
</tr>
<tr>
<td>Constant</td>
<td></td>
<td>-99.9</td>
<td>-113.1</td>
</tr>
</tbody>
</table>

...a combination of diazepam 0.5 mg kg\(^{-1}\), morphine 0.15 mg kg\(^{-1}\) and hyoscine 0.01 mg kg\(^{-1}\) adminis-

ted before the induction of anaesthesia, an interval during which peak plasma concentrations of rectally administered diazepam and morphine are known to occur (Lindahl, Olsson and Thomson, 1981; Westerling et al., 1982). That the premedication with diazepam, morphine and hyoscine resulted in a greater mean sedative score, was probably a result of the larger dose of diazepam, combined with the sedative properties of morphine and hyoscine (Conner et al., 1977).

The patients who received the more sedative premedication also had lower plasma concentrations of ACTH, cortisol and 17\(\alpha\)-hydroxyprogesterone during undisturbed anaesthesia. Unexpectedly, however, the catecholamine concentrations were similar in the two groups at this stage of anaesthesia. This may have been a result of an increased catecholamine release during the second stage of anaesthesia, which was unaffected by the premedication used, as has been shown in adults after an inhalation induction with halothane (Joyce et al., 1982). Joyce, Roizen and Eger (1981) have shown that if the excitation stage is circumvented by an i.v. induction (thiopentone), before the addition of halothane, catecholamine release can be prevented.

On the basis of these findings it is evident that the second stage of anaesthesia is still of clinical importance, despite the development of modern inhalation anaesthetics.

Although the more sedative premedication did not prevent increases in plasma catecholamines during the induction of anaesthesia, it effectively decreased the catecholamine and endocrine response during surgery. Since diazepam decreases plasma catecholamines during morphine anaesthesia (Hoar et al., 1981) and since the central sedative effects of diazepam are dose dependent (Brown and Dunce, 1968), and have been attributed to an inhibitory action on cerebral sympathetic neurotransmitter activity (Biswas and Carlsson, 1978; Bertilsson, 1978), it seems likely that the larger dose of diazepam used in the more efficient premedication contributed to the decreased catecholamine response to surgery—in association with the analgesic and sedative effects of the morphine and hyoscine.

Adrenergic activation occurs during surgical stress in man and this is not caused by anaesthesia alone (Halter, Pflug and Porte, 1977). It is also known that endogenous catecholamines and sympathomimetic drugs produce cardiac arrhythmias by increasing automaticity and stimulating ectopic
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REFERENCES


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**INFLUENCE DE LA PREMEDICATION SUR LES REPONSES ENDOCRINIENNES ET METABOLIQUES ET SUR LES TROUBLES DU RYTHME AU COURS DE L'ANESTHESIE A L'HALOTHANE CHEZ DES ENFANTS SUBISSANT UNE ADENOIDEKTOMIE**

Nous avons étudié la survenue de troubles du rythme cardiaque chez 80 enfants au cours d'une anesthésie à l'halothane pour adénoidectomie. Deux prémédications différentes ont été utilisées. Quarante enfants (groupe A) ont été prémédiqués par 5 mg de diazepam par voie rectale et 0,3–0,4 mg d'atropine par voie sublinguale et 40 enfants (groupe B) ont reçu une solution intrarectale comportant 0,5 mg kg$^{-1}$ de diazepam, 0,15 mg kg$^{-1}$ de morphine et 0,01 mg kg$^{-1}$ d'hioscine. Chez 17 de ces enfants (neuf du groupe A et huit du groupe B), les concentrations plasmatiques de catécholamines, d'ACTH et de corticostéroïdes ont été mesurées. Dans le groupe A, la concentration plasmatique moyenne de catécholamines augmentait de plus de 300% pendant l'acte chirurgical alors qu'elle n'était pratiquement pas modifiée dans le groupe B ($P<0,01$). Les concentrations plasmatiques d'ACTH, de cortisol et de 17-alpha-hydroxyprogesterone étaient également plus élevées dans le groupe A que dans le groupe B. La survenue de troubles du rythme ventriculaire était significativement plus fréquente dans le groupe A (20%) que dans le groupe B (2,5%) ($P<0,05$); nous en déduisons que dans ces deux groupes comparables de patients les arrhythmies ventriculaires au cours de l'anesthésie à l'halothane étaient pratiquement éliminées par l'usage d'une prémédication plus efficace, du fait d'une diminution des réponses adrénergiques et endocriniennes à la chirurgie.

**EINFLUS DER PRÄMEDIKATION AUF SYMPATHISCHE UND ENDOKRINE REAKTION UND HERZRHYTHMUSTÖRUNGEN WÄHREND HALOTHANANKOSEN BEI KINDERN ZUR ADENOIDEKTOMIE**

**RESUMEN**

Se investigaron los sucesos de arritmias cardiacas en 80 niños durante la anestesia con halotano en niños sometidos a adenoidectomía. Se estudiaron dos prémédicaciones diferentes. Cuarenta niños (grupo A) fueron premedicados rectalmente con 5 mg de diazepam y 0,3–0,4 mg de atropina sublingualmente, y otros 40 (grupo B) recibieron una solución rectal que incluyó 0,5 mg kg$^{-1}$ de diazepam, incluyendo 0,15 mg kg$^{-1}$ de morfina y 0,01 mg kg$^{-1}$ de hioscina. Se midieron las concentraciones de catecolaminas, ACTH y corticosteroides en el plasma de 17 de estos niños (nueve del grupo A y ocho del B). En el grupo A la concentración media de catecolaminas en el plasma aumentó en más del 300% durante la intervención quirúrgica, mientras que en el grupo B permaneció prácticamente inalterada ($P<0,01$). Las concentraciones de ACTH, cortisol y 17α-hidroxiprogesterona en el plasma fueron también superiores en el grupo A que en el B. Los casos de arritmias ventriculares en el grupo A fueron significativamente más frecuentes (20,0%) que en el grupo B (2,5%) ($P<0,05$). Se concluyó que en estos dos grupos de pacientes comparativos, la arritmia ventricular durante la anestesia con halotano se eliminó casi totalmente por el uso de una prémédicación más efectiva, como consecuencia de las disminuciones de las respuestas simpáticas y endocrinas a la intervención quirúrgica.