Effect of pre-treatment with intravenous atropine or glycopyrrolate on cardiac arrhythmias during halothane anaesthesia for adenoidectomy in children

P. ANNILA, M. RORARIUS, P. REINIKAINEN, M. OIKKONEN, G. BAER

Summary
We studied the effect of anticholinergics on the incidence of cardiac arrhythmias during paediatric anaesthesia. ASA I–II children (n=77) undergoing adenoidectomy were randomly allocated to three groups. Intravenous atropine 0.02 mg kg\(^{-1}\) was given in group A (n=25), glycopyrrolate 0.004 mg kg\(^{-1}\) in group G (n=27) and physiological saline in group P (n=25) 3 min before the induction of anaesthesia. The children breathed spontaneously under halothane anaesthesia with 66% nitrous oxide in oxygen after induction with thiopentone and succinylcholine. Perioperative monitoring of the ECG (Holter recordings) and oxygen saturation was carried out. Ventricular tachycardia occurred in 16.0%, 18.5% and 12.0% of the children in groups A, G and P respectively (ns). The incidence of ventricular arrhythmias (ventricular tachycardia, ventricular bigeminy, ventricular premature beats >10) was 20.0% in group A, 44.4% in group G and 36.0% in group P (ns). Bradycardia (<70 beats min\(^{-1}\)) was observed in 0.0%, 14.8% and 24.0% of patients in groups A, G and P respectively (A vs P, P<0.05). The use of anticholinergics did not influence the incidence of ventricular arrhythmias during halothane anaesthesia in children. Bradycardia was more common in the placebo group than in the atropine group. (Br. J. Anaesth. 1998; 80: 756–760)

Keywords: anaesthesia paediatric; anaesthetics volatile halothane; arrhythmias cardiac; premedication atropine glycopyrrolate

In paediatric anaesthesia, the use of halothane and succinylcholine can cause bradycardia.\(^{13}\) Anticholinergics are given to such patients to prevent vagal reflexes and salivation.\(^{14}\) In addition, atropine attenuates the halothane-associated reduction of cardiac output in children.\(^{9}\) However, the routine use of anticholinergic agents in paediatric anaesthesia remains controversial. In some studies, atropine and glycopyrrolate produced ventricular arrhythmias in children and adults.\(^{6,8}\) Badgwell and colleagues demonstrated that junctional rhythms occurring in children over 1 yr old anaesthetized with halothane usually resolve spontaneously.\(^{9}\) They suggested that anticholinergics are not required in these children for the purpose of preventing junctional arrhythmias. In adults, the use of anticholinergics as premedicants is declining.\(^{10}\) Experimental studies have shown that vagal activation protects the heart against ventricular fibrillation and atropine or vagotomy abolishes this protective effect.\(^{11,12}\)

The incidence of cardiac arrhythmias is high during oral surgery.\(^{13,14}\) However, the arrhythmogenic or antiarrhythmogenic properties of atropine or glycopyrrolate have not been compared in a placebo-controlled study in children anaesthetized with halothane for adenoidectomy. Because of the controversy in the literature, the aim of our study was to clarify the role of anticholinergics in paediatric anaesthesia with particular regard to the incidence of cardiac arrhythmias. To ensure complete data collection, Holter monitoring of the ECG was performed. In this double-blind, randomized study, we chose a dose of atropine that would have a definite cardiac effect, and compared it with a small dose of glycopyrrolate to find out the minimum effective dose of glycopyrrolate to prevent bradycardia.

Patients and methods
The study was approved by the Ethics Committee of Tampere University Hospital and written informed consent was obtained from the parents of each child investigated. Seventy-seven ASA I–II children undergoing adenoidectomy were randomly assigned into three groups, using a list of numbers 1 to 90 randomized to the three groups. Patients were listed in order of recruitment. Atropine (0.02 mg kg\(^{-1}\)) was given intravenously in group A (n=25), glycopyrrolate (0.004 mg kg\(^{-1}\)) in group G (n=27) and physiological saline (same volume, 0.02 ml kg\(^{-1}\)) in group P (n=25). Syringes were prepared and labelled with the patients’ identification numbers by nurses not involved in the study. Only children weighing 10–20 kg were included. Patient characteristics are shown in table 1. The children were premedicated with rectal diazepam 0.5 mg kg\(^{-1}\) and paracetamol 10 mg kg\(^{-1}\), 30 min before anaesthesia. EMLA (Astra, Sweden) cream was applied to the dorsum of the

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Table 1 Patient characteristics (mean (SD)). No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 25)</th>
<th>Group G (n = 27)</th>
<th>Group P (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>30.4 (14.4)</td>
<td>38.4 (18.7)</td>
<td>37.4 (22.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>13.1 (2.8)</td>
<td>14.6 (3.6)</td>
<td>14.0 (3.6)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>90.8 (9.8)</td>
<td>95.1 (3.1)</td>
<td>94.0 (13.1)</td>
</tr>
</tbody>
</table>

Anticholinergic pretreatment and halothane anaesthesia

Analyses were performed with a BMDP statistical software package. Statistical comparison between the groups was performed using a two-way analysis of variance (ANOVA) with Bonferroni’s correction and a paired t-test. The chi-square test was used to test the significance of the frequency of cardiac arrhythmias between the groups. Non-parametric data were analysed by Kruskal-Wallis and Mann-Whitney tests. Data are reported as mean (SD). P < 0.05 was considered statistically significant.

Results

The distribution of weight, height and ages of children was similar in all three groups (table 1). Ninety children were recruited but, because of technical difficulties, only 77 Holter recordings (table 1). Ninety children were recruited but, because of technical difficulties, only 77 Holter recordings were faultless and acceptable for the study. There were no between-group differences in the baseline values of heart rate or systolic arterial pressure (SAP). After tracheal intubation, heart rate had increased in all groups. In patients receiving atropine, heart rate increased significantly more than in the other patients (P < 0.001 between group A and group P and between group A and group G). Furthermore, heart rate remained elevated throughout the study at every time point after atropine, but decreased after intubation in the other groups (fig. 1).

Bradycardia (<70 beats min⁻¹) was observed in none, four (14.8%) or six (24.0%) patients in groups A, G and P respectively (P < 0.05 between A and P) (table 2). In patients receiving glycopyrrolate, all bradycardic events occurred during anaesthetic induction or tracheal intubation. In patients receiving saline, bradycardia occurred during surgery except for one patient, who also had a bradycardic event during induction of anaesthesia. All bradycardic episodes were short — of less than 5 s duration — so no medication was needed. The events were not.

In the recovery room, all the children were observed by the same nurse. Estimation of salivation was on an open scale scoring from 1 (no salivation) to 9 (excessive salivation), recorded at 5, 10, 20, 40 and 60 min after the end of surgery. In addition, any complications during the 60-min period were noted.

Figure 1 Mean heart rates during the study in groups of children who received pretreatment before halothane anaesthesia with intravenous atropine (Group A), glycopyrrolate (Group G) or placebo (Group P). Timepoints: I = before the study drug; II = after intubation; III = 2 min after intubation; IV = 5 min after intubation; V = after extubation. **P < 0.001 between group A and group P and between group A and group G. *P < 0.01 between group G and group P. *P < 0.05 between group G and group P.
associated with a low $\text{SpO}_2$. Tachycardia (>$170$ beats min$^{-1}$) was more common in the atropine group than in the saline or glycopyrrolate groups (table 2).

Systolic arterial blood pressures changed in a similar way in all patients, although the pressures were higher in group A than in group P (fig. 2). Arterial pressures increased after intubation and decreased afterwards (fig. 2).

Ventricular tachycardia, that is, three or more consecutive ventricular complexes, was seen in four, five and three patients in groups A, G and P respectively (ns) (table 2). The total number of ventricular arrhythmic episodes (more than $10$ ventricular premature beats in $5$ min, ventricular bigemina or ventricular tachycardia) was five in group A, 12 in group G and $9$ in group P (ns). These episodes occurred mainly during surgery or during tracheal extubation after surgery. Only one child in group A (ventricular tachycardia), one in group G (VPBs) and one in group P (ventricular bigemina) had arrhythmias during anaesthetic induction or tracheal intubation. One child in group G and two children in group P had more than $10$ supraventricular extrasystolic beats (SVEs) in $5$ min (table 2); the patient in group G already had SVEs before receiving the study drug. Ventricular premature beats were seen in one patient (group G) before glycopyrrolate; this child also had ventricular bigemina during tracheal intubation. All episodes of ventricular arrhythmia were short and no treatment was needed. Examples of arrhythmias are shown in fig. 3.

The $\text{PaO}_2$ values ranged between $6.5$ and $8.5$ kPa during the study. During recovery from anaesthesia, salivation was more severe in the patients who had received saline ($P<0.001$) than in those receiving atropine or glycopyrrolate; no difference was seen between group A and group G. Minor complications were seen in three of the $77$ patients: one child in the atropine group and one in the glycopyrrolate group had laryngospasm. One child in the atropine group had laryngitis after operation.

### Discussion

Our results show that there is no difference in the incidence of ventricular arrhythmias during adenoidectomy in children pretreated with atropine, glycopyrrolate or saline. The accuracy of the data were verified by perioperative Holter recording of the ECG. To our knowledge, the present study is the first to compare the effect of glycopyrrolate with that of atropine and saline.

Warran and co-workers found that the incidence of ventricular arrhythmias after i.v. atropine and i.v. glycopyrrolate is identical. Our results were similar to that study. Sigurdsson and colleagues reported that in children, the incidence of ventricular arrhythmias is increased after diazepam—atropine premedication, compared with that after diazepam—morphine—hyoscine. Johannesson and colleagues showed similar results with diazepam—atropine vs diazepam—morphine—scopolamine during adenoidectomy in children.

As Sigurdsson and co-workers concluded, more effective sedative premedication reduces the sympathetic and endocrine response to surgery, altering the incidence of arrhythmias. This was probably the case in both of those studies. Anticholinergic agents alter the balance between sympathetic and parasympathetic activity in the autonomic nervous system by blocking the parasym-
pathetic muscarinic receptors. In adults, sympathetic predominance may cause arrhythmias. Furthermore, cardiac vagal activity is an important protector against sudden cardiac death. Our results do not support the suggestion that anticholinergics are arrhythmogenic. The autonomic nervous system of children may react differently compared with that of adults.

Bradycardia (< 70 beats min⁻¹) was more common in children receiving saline than in those to whom atropine was given. However, in all the children, even those in the saline group, the events were short and resolved spontaneously. Persisting sinus tachycardia (> 170 beats min⁻¹), occurred in 23 of the 25 patients in the atropine group. This hyperdynamic state, together with the well known effects of atropine on the central nervous system, may contribute to the discomfort (flushing, irritability) that children experience in the recovery room. Our results strongly suggest that atropine, rather than being used routinely, could well be kept as a drug only for unresolved bradycardias during adenoidectomy.

The effect of glycopyrrolate in preventing bradyarrhythmias is dose related. We used a relatively small dose of glycopyrrolate (0.004 mg kg⁻¹) to study its effectiveness in preventing bradycardia. The effect of glycopyrrolate on haemodynamic variables was moderate compared with that of atropine. However, the doses used in this study (glycopyrrolate 0.004 mg kg⁻¹ vs atropine 0.02 mg kg⁻¹) were not equipotent; Lerman and Chinyanga concluded that atropine 0.02 mg kg⁻¹ is equipotent with glycopyrrolate 0.01 mg kg⁻¹.

Probably in part because of the small dose of glycopyrrolate used in the present study, bradyarrhythmic events were seen four times in group G compared with six times in group P. Bradycardias tended to occur during induction in patients receiving glycopyrrolate but during surgery in patients receiving saline. The effect of glycopyrrolate, however, starts within 2 min and reaches its maximum by 3–7 min. Therefore, it is possible that the 3-min waiting time before anaesthetic induction was too short to prevent bradyarrhythmic episodes in some of our patients. Lavis and colleagues have shown that heart rate does not change as rapidly after i.v. glycopyrrolate (0.005 mg kg⁻¹) as it does after i.v. atropine (0.01 mg kg⁻¹). Thereafter heart rate remained at the same level after both drugs. In our patients, the antialogue effect of glycopyrrolate was obvious, proving the anticholinergic properties of this drug.

We used a relatively high dose of atropine to study the arrhythmogenic properties, if any, of atropine in this analysis, which was verified by Holter recording of the ECG. Palmsano and colleagues recommended at least atropine 0.01 mg kg⁻¹ with halothane and nitrous oxide in children. The dose of atropine 0.01 mg kg⁻¹ is suggested to be as effective as 0.02 mg kg⁻¹ in preventing bradycardia, with fewer side effects. Our placebo-controlled study suggests that a high dose of atropine does not cause ventricular arrhythmias during halothane anaesthesia and that a small dose of glycopyrrolate, given early enough, is probably as effective in preventing bradycardia.

During spontaneous breathing under halothane, \( P_{\text{ET}} \text{O}_2 \) tensions are higher than in controlled ventilation, sometimes exceeding the physiological limit. Hypercarbia is known to produce arrhythmias. During halothane—nitrous oxide anaesthesia, the median arrhythmic threshold is greater than 10.7 kPa. This was not reached in our patients. Therefore, raised \( P_{\text{ET}} \text{O}_2 \) does not explain the incidence of arrhythmias in this study. Hypoxia was prevented by manual ventilation, if necessary, and therefore arrhythmic episodes should not stem from a hypoxic origin.

The incidence of ventricular arrhythmias is related to the inhalation agent used. With halothane, the incidence of arrhythmias is higher than with enflurane or isoflurane. It has also been shown by Sigurdsson and colleagues that arrhythmias were significantly fewer in children who received halothane anaesthesia for myringotomies compared with adenoidectomy. In their study, there were almost no dysrhythmias in children receiving enflurane.

In conclusion, the incidence of ventricular arrhythmias during halothane anaesthesia in children was similar after pretreatment with atropine, glycopyrrolate or saline. Atropine prevented bradyarrhythmic events but caused persisting sinus tachycardia in most patients. Bradyarrhythmic events were short and recovered spontaneously in patients receiving glycopyrrolate or saline. This study suggests that routine pretreatment with anticholinergic agents is unnecessary in children undergoing adenoidectomy during halothane anaesthesia.

References

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