A comparative study of the haemodynamic effects of atropine and glycopyrrolate at induction of anaesthesia in Children

*I. Desalu1, O. T. Kushimo1and C. O. Bode2

Department of Anaesthesia1 and *Surgery2
Lagos University Teaching Hospital
PMB, 12003, Lagos, Nigeria

Summary

Background: Bradycardia following administration of halothane and suxamethonium in children leads to reduced cardiac output, which can be prevented with prophylactic anticholinergics. Anticholinergics may result in tachycardia and arrhythmias. This study was designed to compare haemodynamic changes and incidence of cardiac arrhythmias following intravenous atropine and glycopyrrolate.

Study design: Ninety ASA I and II children between one month and twelve years were studied. Premedication was with oral promethazine 1mg/kg. Anaesthesia was achieved with 3% halothane in 33% oxygen and nitrous oxide. Patients were randomly allocated to receive atropine 0.01mg/kg (Group I) or glycopyrrolate 0.005mg/kg (Group II). Tracheal intubation was facilitated with suxamethonium 1.5mg/kg.

Results: Patients in Group I had a 35.7% rise in heart rate from baseline, compared to 22.5% in Group II two minutes after anticholinergic administration (p=0.001). Following intubation, heart rate rose by 9.7% and 13.2% (p<0.05) in Groups I and II respectively, MAP rose similarly in both groups. Arrhythmia occurred in 44.4% of patients in Group I and 11.1% in Group II (p=0.001) and were mainly sinus tachycardia. 2.2% of patients in Group I exhibited bigemini. No patient experienced bradycardia. Hypoxia occurred in 2.2%, hypotension in 13.3% and mild laryngeal spasm in 0% of Group I and 11.1%, 4.4% and 4.4% of Group II respectively.

Conclusion: The use of glycopyrrolate compared to atropine, offered better cardiovascular stability in Nigerian children. Arrhythmias occurred more in patients who had atropine and occurred most frequently after tracheal intubation.

Key-words: Anaesthesia, Anticholinergics, Haemodynamic response, Paediatric

Résumé

Introduction: La bradycardie a la suite de l’administration de l’halothane et du suxamethonium chez des enfants amène a une baisse en ce qui concerne les résultats cardiaques qu’on pourrait éviter avec les anticholinergiques prophylactiques. L’anticholinergique pourrait provoquer la tachycardie et l’arythmie. Cette étude est destinée à comparer des changements hémodynamiques et la fréquence de l’arythmie cardiaque

Key-words: Anaesthesia, Anticholinergics, Haemodynamic response, Paediatric

Correspondence

WAJM VOL. 34 NO. 2. APRIL – JUNE: 2007
surgery. Halothane slows down sinoatrial node conduction, while Suxamethonium stimulates postsynaptic muscarinic receptors in the sinoatrial node, resulting in junctional rhythm and bradycardia. These effects can be prevented by the use of anticholinergics. Anticholinergics are also known to induce serious arrhythmias that may sometimes require anti-arrhythmic therapy.

Atropine can cross the blood brain barrier, resulting in restlessness and drowsiness. Glycopyrrolate exerts its actions mainly on peripheral muscarinic receptors. Advantages over atropine include less tachycardia, better cardiovascular stability, better antisialogogue activity, less central nervous system excitement and earlier postoperative recovery.

Ethnic differences in response to atropine have been identified in adults, but have not been studied in pediatrics. The objective of this study was to compare haemodynamic changes and incidence of cardiac arrhythmias after atropine and glycopyrrolate and identify which anticholinergic is better suited for prophylaxis in Nigerian children.

Materials and methods

Ninety ASA I-II children aged 1 month to 12 years undergoing elective surgery with endotracheal intubation at the Lagos University Teaching Hospital were studied. Exclusion criteria included history of masster spasm, malignant hyperthermia, neurological or neuromuscular disease, mental handicap, cardiac disease, burns of less than six months duration, hyperkalaemia, or any medication known to influence neuromuscular function e.g. aminoglycoside antibiotics or haemodynamic status e.g. cough syrups containing phenylephrine, orivine nasal drops. Institutional approval was attained and verbal parental consent obtained after due explanation. Patients were randomly allocated by blind billing to one of two groups (Group I - i.v. atropine 0.01 mg/kg, Group II - i.v. glycopyrrolate 0.005mg/kg). Routine preoperative fasting was instituted. Premedication with oral promethazine 1mg/kg was given to patients above the age of one year on the morning of surgery.

Baseline heart rate and rhythm, blood pressure, and oxygen saturation were recorded with precordial stethoscope, electrocardiograph leads, blood pressure cuff, and digital pulse oximeter probe respectively. Induction was commenced with gradual increment of halothane up to 3% in 33% oxygen and nitrous oxide, using a Mapleson F or coxial D breathing system. Venous cannulation was performed when the depth of anaesthesia was judged to be adequate. The anticholinergic agent was then administered by bolus injection. Two minutes later suxamethonium was administered. After fascication or 45-60 seconds following suxamethonium administration, laryngoscopy and oral intubation was performed with the appropriate-sized nose-cuffed tracheal tube. Anaesthesia was maintained with 1% halothane and ventilation facilitated with atracurium 0.5mg/kg.

Heart rate, rhythm and arterial oxygen saturation were continuously monitored from two minutes before induction of anaesthesia to two minutes after intubation, while the blood pressure was monitored every two minutes using Cardiocap 5® (Datex, Ohmeda, Helsinki).

For the purpose of this study, the following definitions were used:
- Bradycardia: 20% reduction from baseline heart rate.
- Tachycardia: heart rate > 160 beats/minutes
- Hypotension: >30% reduction from baseline systolic blood pressure.
- Hypoxia: oxygen saturation < 94%.
- Arrhythmia: any disorder of rhythm or rate observed.

Data was analysed using SPSS® (10 Inc. Chicago Illinois). A p value of <0.05 was accepted as statistically significant.

Results

Table 1 shows the clinical and demographic data of subjects. There was no significant difference in the demographic, clinical and induction characteristics of the two groups.

| Table 1 Demographic and clinical characteristics of patients |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                             | Atropine (n=45)             | Glycopyrrolate (n=45)        | P value                     |
|                             | (Mean ± SD)                 | (mean ± SD)                 |                             |
| Mean age (years)            | 4.1 ± 2.7                   | 4.1 ± 2.4                   | 0.951                       |
| Mean weight (kg)            | 14.8 ± 6.3                  | 15.1 ± 5.4                  | 0.784                       |
| Gender ratio (M:F)          | 31: 14                      | 33:12                       | 0.816                       |
| ASA classification ratio    | 36.9                        | 38.7                        | 0.783                       |
| ASA I/II                    |                             |                             |                             |
| Mean PCV (%)                | 34.4 ± 3.2                  | 34.5 ± 2.7                  | 0.930                       |
| Mean temperature (°C)       | 36.8 ± 0.2                  | 36.6 ± 0.3                  | 0.075                       |
| Premedication - Induction time (mins) | 20± 85.2                   | 192 ± 90.4                  | 0.431                       |
| Mean duration of induction (mins) | 6.7 ± 2.3                   | 5.9 ± 2.0                   | 0.089                       |
| Mean intubation attempts    | 1.3 ± 0.6                   | 1.2 ± 0.4                   | 0.529                       |
Fig. 1 shows the mean heart rate and MAP trends of both groups. Both groups had similar preinduction heart rate and MAP which decreased similarly as induction progressed.

Following administration of anticholinergic, mean heart rate rose significantly within both groups with patients given atropine having a greater rate of increase compared to those given glycopyrrolate. Thirty seconds after anticholinergic administration, mean heart rate rose in the atropine group by 15.7% (14.9 beats) compared to 5.4% (4.7 beats) in the glycopyrrolate group (p<0.001) while MAP rose by 6.5% (3.6mmHg) and by 1.4% (1mmHg) respectively (p<0.001). At one minute, there was an additional rise in mean heart rate of 10.2% (11.5 beats) and 9.2% (9 beats) in the atropine and glycopyrrolate group respectively. By two minutes, the additional mean increase was similar in both groups, 7.0% (7.7 beats), and 6.5% (7.1 beats). At one and two minutes, additional increase in MAP was comparable in both groups. The total rise in mean heart rate was 35.7% in the patients given atropine and 22.5% in those given glycopyrrolate (p<0.001).

The administration of suxamethonium resulted in insignificant differences in heart rate and MAP of both groups. Following intubation, there was a mean heart rate rise of 9.7% (15.3 beats) in the patients given atropine and 13.2% (19.6 beats) in those given glycopyrrolate (p<0.05). MAP rose to approximately the same extent in both groups.

Arrhythmias occurred in 25 patients (27.7%). 20 patients in the atropine group (44.4%) and 5 patients in the glycopyrrolate group (11.1%) exhibited sinus tachycardia (ST) while 1 patient from the atropine group (2.2%) exhibited bigemini. This occurred after the administration of suxamethonium, but resolved before intubation was attempted. No patient developed sinus bradycardia.

Intubation resulted in the highest frequency of arrhythmias. Fourteen patients (31.1%) given atropine compared with 5 (11.1%) of those given glycopyrrolate developed arrhythmia post-intubation (p<0.05).

Complications were similar in both groups. 2.2% of patients given atropine developed hypoxia, 0% mild laryngeal spasm and 13.3% hypotension compared with 11.1% hypoxia, 4.4% mild laryngeal spasm and 4.4% hypotension in glycopyrrolate group.

The only significant factors for development of arrhythmias were patient group (p value<0.001) and phase of induction (p<0.05) in the post-intubation phase). Patients given atropine were 4 times more likely to develop arrhythmia.

**Discussion**

Children are prone to vagally mediated bradycardia that may compromise cardiac output, allow the occurrence of re-entrant excitation arrhythmias and sometimes result in cardiac arrest. Anticholinergics block the parasympathetic muscarinic receptors resulting in tachycardia.11

Most authorities agree that the onset of action and peak effect of atropine occur earlier than glycopyrrolate.13–15. In this study, the administration of atropine led to an earlier onset of tachycardia. The effect of atropine begins about 25 seconds after i.v injection and peaks in 1-3 minutes, while that of glycopyrrolate starts at 2 minutes and peaks in 3-7 minutes.13,15 Overall heart rate rose by 35.7% (34.1 beats) with atropine and by 22.5% (20.8 beats) with glycopyrrolate two minutes after administration. This was statistically significant and compares well with other studies.13,16

It has been suggested that the maximum heart rate obtained with anticholinergics is within normal physiological range for adequate cardiac function in children.10-17. Sinus tachycardia that developed in this study, did not compromise blood pressure or oxygenation.
Since MAP rises with heart rate, blood pressure changes are therefore greater with atropine because of the greater change in heart rate.\textsuperscript{13,16} This was confirmed in this study as MAP rise was greater after atropine (15.3%) compared to glycopyrrolate (11.2%).

The increase in heart rate and blood pressure that occurs after anticholinergic administration, result in an increase in rate-pressure-product and therefore myocardial oxygen consumption which may be detrimental to children with heart disease. Care must therefore be taken when this category of children are considered for general anaesthesia.

We have demonstrated an earlier heart rate and blood pressure change with atropine, and a longer duration of action of glycopyrrolate, which are similar to studies undertaken in other parts of the world. This shows that ethnic differences may not exist in children as demonstrated in adults.\textsuperscript{69}

The effect of atropine on the heart rate depends on the dosage used. In infants and children, cardio-inhibition is seen with doses < 3.6 mcg/kg and is thought to be due to either vagal stimulation or block of peripheral M-1 receptors, which normally modulate the liberation of acetylcholine.\textsuperscript{6} Cardiac acceleration is seen with a minimum dose of 7.2-14.3 mcg/kg due to block of M-2 receptors in the SA node.\textsuperscript{8} We used a dose of 10 mcg/kg of atropine, which is within the cardiac-activating range. Palmisano\textsuperscript{16} observed that a dose of 9 mcg/kg resulted in a 50% rise in heart rate. This greater heart rate response may be because the children in that study were unpremedicated with high levels of circulating catecholamines that resulted in greater heart rate values.

Side effects of atropine include excessive tachycardia, inhibition of sweating, rise in body temperature, dry mouth, blurred vision, drowsiness, and the central anticholinergic syndrome (CACS).\textsuperscript{10,14} Glycopyrrolate has less CNS effects, superior anti-sialogogue activity, less tachycardia and less postoperative restlessness compared with atropine.\textsuperscript{67} These anticholagogue and cardiac differences are due to their different affinities for muscarinic receptor subtypes.

No episodes of bradycardia was observed thus confirming the efficacy of anticholinergics in attenuating bradycardia due to suxamethonium. Some patients did however show a decrease in heart rate of 10 or more beats after suxamethonium (15.5% in atropine group and 6.6% in glycopyrrolate) thus demonstrating that glycopyrrolate may be better at attenuating the drop in heart rate associated with suxamethonium.

Patients given glycopyrrolate had a greater rise in heart rate after intubation. This was probably because its peak effect occurred much later than that of atropine. Therefore during the phase of intubation, the effects of atropine had plateaued while that of glycopyrrolate was just reaching its peak. Lavis\textsuperscript{15} suggested that heart rate change was greater with glycopyrrolate at intubation because patients who received atropine had shown an initial greater rise in heart rate and therefore the subsequent rise after intubation was not as great as in patients who received glycopyrrolate.

Arrhythmias occurring with atropine are more malignant than those with glycopyrrolate.\textsuperscript{5} The only incident of abnormal rhythm in this study occurred in the atropine group. Comparison between studies is hindered by the variety of induction agents used. Some studies found no difference in the incidence or severity of arrhythmia between the two drugs.\textsuperscript{14,15} Other studies have demonstrated junctional tachycardia, nodal rhythm, ventricular ectopic beats and bigemini. The lower incidence of arrhythmia observed in this study may have been due to the use of continuous ECG monitoring which is not as sensitive in detecting rhythm changes as a recorded ECG rhythm strip with subsequent analysis. Most arrhythmias occurred after intubation, which re-emphasises the importance of gentle laryngoscopy, and intubation.

Conclusion

In Sub-Saharan Africa, where newer more cardiotabile drugs are not widely available, the paediatric patient is still being induced with halothane and intubation facilitated by suxamethonium which frequently results in bradycardia that may compromise cardiac output. This necessitates the use of prophylactic anticholinergics. Glycopyrrolate is a safer drug when compared with atropine offering better cardiovascular stability and less incidence of arrhythmias. It is available in this sub-region at an approximate cost of 1 (one) US cent/kg which is ten times the cost of atropine. Notwithstanding, its use should be encouraged as prophylaxis in Nigerian children especially those with cardiac disease as we have demonstrated that it is a safer drug.

References


5. Mirahkhor RK. Premedication with atropine or glycopyrrolate in children. Effect on heart rate and rhythm during induction and maintenance of anaesthesia. Anaesthesia '982; 37: 1032 – 1036.

6. Lerman J, Chinyanga HM. The heart rate response to succinylcholine in children: a comparison of atropine and...


