Glycopyrrolate during sevoflurane–remifentanil-based anaesthesia for cardiac catheterization of children with congenital heart disease

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Background. Remifentanil is recommended for use in procedures with painful intraoperative stimuli but minimal postoperative pain. However, bradycardia and hypotension are known side-effects. We evaluated haemodynamic effects of i.v. glycopyrrolate during remifentanil–sevoflurane anaesthesia for cardiac catheterization of children with congenital heart disease.

Methods. Forty-five children undergoing general anaesthesia with remifentanil and sevoflurane were randomly allocated to receive either saline, glycopyrrolate 6 μg kg⁻¹ or glycopyrrolate 12 μg kg⁻¹. After induction of anaesthesia with sevoflurane, i.v. placebo or glycopyrrolate was administered. An infusion of remifentanil at the rate of 0.15 μg kg⁻¹min⁻¹ was started, sevoflurane continued at 0.6 MAC and cisatracurium 0.2 mg kg⁻¹ was given. Heart rate (HR) and non-invasive arterial pressures were monitored and noted every minute for the first 10 min and then every 2.5 min for subsequent maximum of 45 min.

Results. Baseline HR [mean (SD)] of 117 (20) beats min⁻¹ decreased significantly from 12.5 min onwards after starting the remifentanil infusion in the control group [106 (18) at 12.5 min and 99 (16) beats min⁻¹ at 45 min]. In the groups receiving glycopyrrolate, no significant decrease in HR was noticed. Glycopyrrolate at 12 μg kg⁻¹ induced tachycardia between 5 and 9 min after administration. Systolic and diastolic arterial pressures decreased gradually, but there were no significant differences in the pressures between groups.

Conclusion. I.V. glycopyrrolate 6 μg kg⁻¹ prevents bradycardia during general anaesthesia with remifentanil and sevoflurane for cardiac catheterization in children with congenital heart disease. Administering 12 μg kg⁻¹ of glycopyrrolate temporarily induces tachycardia and offers no additional advantage.

Br J Anaesth 2005; 95: 680–4

Keywords: analgesics opioid, remifentanil; children, congenital heart disease; complications, bradycardia; procedure, cardiac catheterization

Accepted for publication: August 31, 2005

Cardiac catheterization in children with congenital heart disease can be performed under general anaesthesia. If a fast and stable recovery is ensured, the benefits of general anaesthesia i.e. better immobilization, and optimal control of haemodynamics and airway outweigh the advantages of monitored sedation. Remifentanil, a short acting μ-receptor opioid agonist, provides good intraoperative analgesia, predictable emergence and minimal risk of postoperative respiratory depression. It has a suitable pharmacological profile for cardiac catheterization, a procedure that is associated with variable and unpredictable procedural times, requirement of deep anaesthesia towards the end of the procedure (balloon dilatation of valvular or vascular stenosis) and minimal need for postoperative analgesia.

Vasodilatation and bradycardia associated with the use of remifentanil are possible drawbacks in a patient population in whom ventricular filling pressure and rate dependency of cardiac output are critical determinants of haemodynamic stability.¹

The aim of this study was to investigate whether previously reported bradycardia during remifentanil–sevoflurane anaesthesia for cardiac catheterization can be prevented by administration of i.v. glycopyrrolate at induction of anaesthesia.²
Methods

After institutional Ethics Committee approval and written informed consent from the parents, 45 children (ASA II or more, aged 1–36 months) with congenital heart disease and undergoing cardiac catheterization under general anaesthesia, were enrolled in a prospective, randomized, placebo-controlled, double-blind study. Using sealed envelopes, the patients were randomly allocated to one of the three groups by an anaesthetic nurse. For patients receiving glycopyrrrolate, the dose was calculated according to body weight; Group G0, received glycopyrrolate 6 μg kg⁻¹ and Group G₁₂ received 12 μg kg⁻¹ diluted to 2 ml with normal saline. In the placebo group (Group G₀) 2 ml of normal saline was used. The anaesthetist was unaware of the group allocation. All children were fasted for at least 4 h before the procedure. Intake of clear fluids was allowed up to 3 h before induction of anaesthesia. Midazolam 0.3 mg kg⁻¹ was administered rectally in the catheterization unit 20 min before induction of anaesthesia. The monitoring included ECG, non-invasive measurement of arterial pressure, capnography and pulse oximetry. In addition, inspiratory and expiratory gas concentrations (Capnomac, Ultima, Datex, Finland) were measured. After baseline measurements of haemodynamic variables, anaesthesia was induced with sevoflurane in decreasing doses (8–6–4–2 % in oxygen 100%) using a facemask. A 22 or 24 G cannula was inserted in a peripheral vein. After having obtained venous access the appropriate glycopyrrolate or placebo solution was administered i.v., and a remifentanil infusion was started at 0.15 μg kg⁻¹ min⁻¹. In addition cisatracurium 0.2 mg kg⁻¹ was given and an i.v. infusion of glucose 5% at 5 ml kg⁻¹ min⁻¹ was started. Patient’s trachea was intubated using an appropriately sized uncuffed tracheal tube (Mallinckrodt, Ireland) 4 min after the beginning of the remifentanil infusion, and the lungs were mechanically ventilated with oxygen-air, F₁ₒ₂ of 0.4, to maintain end-tidal carbon dioxide concentration between 4.5 and 5.5 kPa. Paracetamol 20 mg kg⁻¹ was then given rectally and anaesthesia was maintained with sevoflurane (0.6 MAC, age adjusted, in oxygen-air) and remifentanil at 0.15 μg kg⁻¹ min⁻¹. For the first 10 min of the procedure heart rate (HR) and arterial pressure were monitored every minute. Thereafter, these parameters were measured every 2.5 min. Hypertension and hypotension were considered significant if systolic arterial pressure (SAP) differed by more than 20% from the baseline value for more than 1 min. Hypertension was planned to be treated with remifentanil bolus 0.2 μg kg⁻¹, and hypotension with phenylephrine bolus 1 μg kg⁻¹.

Statistical analysis was performed using repeated measures analysis of variance (ANOVA) with a Dunnett multiple comparisons post-hoc test for within-group evaluation. Differences between groups were analysed with a one-way ANOVA and a Bonferroni multiple comparisons test. P<0.05 was considered significant.

Results

Forty-five patients were enrolled in the study; 15 received placebo (Group G₀), 15 received glycopyrrorolate 6 μg kg⁻¹ (Group G₆), and the remaining 15 received glycopyrrolate 12 μg kg⁻¹ (Group G₁₂). Four procedures in Group G₀, one in Group G₆, and three in Group G₁₂ lasted not longer than 45 min; consequently, the statistical analysis was limited to data until 45 min after induction of anaesthesia.

The groups were matched for patient characteristics and duration of procedure (Table 1). Induction of anaesthesia and tracheal intubation did not alter HR and mean arterial pressure (MAP) during the first 10 min of starting remifentanil infusion in the three groups, except for an increase in HR starting between 1 and 5 min following tracheal intubation in Group G₁₂ (Table 2). In Group G₀, HR decreased significantly from the baseline value from between 12.5 and 45 min. In contrast to the placebo group, HR was preserved in both the glycopyrrolate groups (Fig. 1); HR was significantly lower in Group G₆ compared with Group G₆ or Group G₁₂ from 3 min after starting the remifentanil infusion (Fig. 1 and Table 2). No significant difference in HR between Group G₀ and Group G₁₂ was seen.

The MAP decreased significantly from 12.5 min after starting remifentanil in Group G₁₂, and from 17.5 min in Group G₀ and Group G₆ (Fig. 2). There were no significant differences in systolic, diastolic, or MAP between any of the groups. Five patients needed treatment for hypotension (one in Group G₀, two in Group G₆, and two in Group G₁₂). None of the patients was treated for hypertension. One patient in Group G₁₂ needed anti-emetic treatment. We encountered no incidents of postoperative respiratory depression or hypoxia.

Discussion

General anaesthesia for cardiac catheterization in children with congenital heart disease decreases the risk of respiratory depression, hypercapnia, and acidosis; these conditions can be detrimental in this patient population and can complicate interpretation of haemodynamic measurements.
Fig 1  Heart rate (HR) during remifentanil infusion in the three groups: Group G0, placebo; Group G6, glycopyrrolate 6 μg kg⁻¹; Group G12, glycopyrrolate 12 μg kg⁻¹. T₀ is time period before starting remifentanil infusion, T₁₂.₅–T₄₅ relate to 12.5–45 min after starting the infusion. Data are mean (SD). *P<0.05 vs T₀; †P<0.05 vs both Group G₆ and Group G₁₂.

Fig 2  Changes in MAP during remifentanil infusion. Group G₀, placebo; Group G₆, glycopyrrolate 6 μg kg⁻¹; Group G₁₂, glycopyrrolate 12 μg kg⁻¹. T₀ is time period before starting remifentanil infusion, T₁₂.₅–T₄₅ relate to 12.₅–45 min after starting the infusion. Data are mean (SD) *P<0.05 vs T₀; †P<0.05 vs T₀; ‡P<0.05 vs T₀, within each group.

Table 2  Changes in heart rate (HR), systolic and diastolic arterial pressure. Group G₀, placebo; Group G₆, glycopyrrolate 6 μg kg⁻¹; Group G₁₂, glycopyrrolate 12 μg kg⁻¹. SAP, systolic arterial pressure; DAP, diastolic arterial pressure. T₀, sevoflurane 1 MAC, before infusion of remifentanil; T₁–₁₀, 1–10 min after starting remifentanil infusion; T₄ coincides with tracheal intubation. n=15 in each group. Data are given as mean (SD). *P<0.05 vs Group G₀.
that are necessary for decision making.\textsuperscript{5} The use of remifentanil during general anaesthesia for cardiac catheterization is associated with bradycardia.\textsuperscript{2} Although pre-treatment with glycopyrrolate can prevent bradycardia during halothane anaesthesia,\textsuperscript{4} its use in preventing opioid-induced bradycardia had not been studied so far.

The major finding of our study is that glycopyrrolate 6 or 12 \( \mu g \) kg\(^{-1}\) administered as an i.v. bolus after induction of anaesthesia, prevents bradycardia during remifentanil–sevoflurane anaesthesia for catheterization of children with congenital heart disease. In the placebo group, bradycardia occurred from 12.5 min after the start of the remifentanil infusion, whereas in both glycopyrrolate groups no bradycardia was noticed during 45 min of study period. Also, the HR changes were qualitatively similar in both the glycopyrrolate groups in this time course (Fig. 1), suggesting no benefit of using the higher dose. In quantitative terms, the higher dose of glycopyrrolate caused tachycardia 1 min after tracheal intubation and this was significant until 5 min after intubation. The clinical relevance of this tachycardia is uncertain as maximal mean HR was only 140 beats min\(^{-1}\) (Table 2). The time course of this HR increase coincided with the pressor response to tracheal intubation, which typically peaks at 1–2 min after laryngoscopy and usually subsides within 5–6 min, whereas tachycardia may persist for 10 min.\textsuperscript{5} Because the stress response to tracheal intubation was blunted in Group G0 and Group G6, and the anaesthetic regimen was the same in the three groups, the bolus effect of glycopyrrolate is a plausible explanation for the tachycardia seen in Group G12. Whereas a bolus of remifentanil can induce severe bradycardia and hypotension,\textsuperscript{5,6} even our technique of using low concentration–high flow continuous infusion of remifentanil induced bradycardia (Group G0). At the infusion rate set in our study, patients received a total of remifentanil 0.6 \( \mu g \) kg\(^{-1}\) in the time period of 4 min, before tracheal intubation; this dose is sufficient to prevent stress response.\textsuperscript{5} The addition of glycopyrrolate 6 \( \mu g \) kg\(^{-1}\) not only prevented bradycardia during induction of anaesthesia, but also kept HR virtually constant during 45-min study period.

We preferred giving glycopyrrolate by i.v. route as compared with the rectal route because the latter route can be associated with variable and/or incomplete gastrointestinal absorption.\textsuperscript{7} In a previous study in a similar population, rectal glycopyrrolate could not prevent bradycardia, albeit higher doses of remifentanil were used.\textsuperscript{7} After i.v. bolus, the mean distribution phase half-life of glycopyrrolate is 2.22 (1.26) min and mean elimination phase half life is 0.83 (0.27) h.\textsuperscript{7} Nevertheless, in the present study it protected against bradycardia for a prolonged period of time. It should also be noted that there is no linear relationship between the plasma level of glycopyrrolate and the HR response after i.v. administration.\textsuperscript{6} We preferred glycopyrrolate to atropine because the latter has central effects and leads to more prolonged impairment of parasympathetic nervous system control of HR than equipotent doses of glycopyrrolate.\textsuperscript{8}

Although the use of glycopyrrolate efficiently prevented bradycardia, there was a significant, but clinically acceptable decrease in arterial pressure in all study groups. The decrease in MAP (between 15 and 20\%) in this study was consistent with the findings of other studies in paediatric patients.\textsuperscript{29,30} In children undergoing general surgery, Chana\textsuperscript{2}navaz and colleagues studied the effect of atropine during remifentanil–sevoflurane anaesthesia using echocardiography.\textsuperscript{9} They described a reduction in cardiac index related to a decrease in HR in the placebo group and a decrease in stroke volume in atropine-treated patients, without changes in myocardial contractility. Although we did not study myocardial contractility in our study, the effect of remifentanil–sevoflurane on myocardial contractility is likely to be as small in our study as in the study by Chanavaz and colleagues. Because glycopyrrolate kept HR virtually unchanged in our patients, this raises the question whether the decrease in MAP in our patients was related to a decrease in preload and/or a decrease in afterload with this anaesthetic technique.

In conclusion, remifentanil–sevoflurane is a safe and feasible anaesthetic technique for paediatric cardiac catheterization, but is associated with bradycardia and a moderate degree of hypotension. We have shown that i.v. glycopyrrolate 6 \( \mu g \) kg\(^{-1}\) at induction of anaesthesia effectively prevents bradycardia, but not a moderate degree of hypotension.

### Acknowledgement

Support for this study was solely provided by departmental and institutional funding.

### References

