

The Effect of Glycopyrrolate on Induction Dose of Propofol during General Anesthesia

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ABSTRACT

Background: Preinduction cardiac output (CO) is a small but significant predictor of induction dose of propofol. We hypothesized that glycopyrrolate, by inducing tachycardia (although to a small extent) would increase CO, and hence the induction dose of propofol. Aim of the study was to find out the dose of propofol required to induce anesthesia in patients receiving glycopyrrolate as compared to those not receiving it.

Materials and methods: Eighty female patients (25-60 years, ASA-1, 2) undergoing elective procedures under general anesthesia were randomized into group G (glycopyrrolate) and group C (control). Patients received 1 ml (0.2 mg) glycopyrrolate (group G) or 1 ml normal saline (group C) intravenously 5 minutes before induction. Anesthesia was induced with propofol at a rate of 0.8 mg/kg/min titrated to achieve a target BIS = 40. Dose of propofol required for induction of anesthesia (loss of consciousness) and to reach the target BIS, heart rate (HR) and mean arterial pressure (MAP) at various intervals were compared. Correlation between the dose of propofol required to reach target BIS = 40 and heart rate after giving the test drug was performed by regression analysis.

Results: The dose of propofol required for achieving target BIS was significantly higher ($p < 0.001$) in group G (2.08 ± 0.42 mg/kg) (mean \pm SD) as compared to group C (1.66 ± 0.23 mg/kg). There was a significant positive correlation between the preinduction HR (3 minutes after giving the test drug) and the propofol dose required to reach target BIS = 40 ($r = 0.356$, $p < 0.01$).

Conclusion: Administration of 0.2 mg of glycopyrrolate intravenously before induction of general anesthesia significantly increased the dose of propofol required for induction of anesthesia.

Keywords: Glycopyrrolate, Propofol, General anesthesia.

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INTRODUCTION

Many factors including age, lean body mass, anxiety, coadministration of other drugs and infusion rate influence the induction dose of propofol. Adachi et al¹ in an observational study in humans showed that preinduction cardiac output (CO) measured noninvasively is a small but significant predictor of induction dose of propofol. Esmolol is known to reduce cardiac output and pre dosing with esmolol has been shown to reduce induction dose of propofol by 25%.²

Antisialogogue action of anticholinergics has been used to decrease secretions from airway during anesthesia. Peripherally acting anticholinergics like glycopyrrolate are preferred as they lack unwanted central actions, such as tachycardia. We hypothesized that glycopyrrolate, by inducing tachycardia (although to a small extent),³⁻⁵ would increase CO, and hence the induction dose of propofol. The aim of the study was to find out the dose of propofol required to induce anesthesia in patients receiving glycopyrrolate as compared to those not receiving it.

MATERIALS AND METHODS

After obtaining approval from our institutional ethical committee and written informed consent from the patients, 80 females (25-60 years) of American Society of Anesthesiologists (ASA) class 1 and 2 scheduled for elective minor radiotherapy and gynecological procedure under general anesthesia were randomized either to receive (group G) or not to receive (group C, control) glycopyrrolate. Exclusion criteria were diabetes mellitus, gastro-esophageal reflux disease, obesity, pregnancy, anticipated difficult airway, allergy to anesthetic agents being used and patients taking β -blockers.

All patients received oral diazepam 0.15 mg/kg and ranitidine 150 mg the night before and on the morning of surgery. In the operating room, after securing intravenous access, electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse-oximeter (SpO₂) and Bispectral index (BISTM, version 3.0 rev 0.5, Aspect Medical Systems, Inc, Newton, MA, USA) were attached and baseline values were recorded.

All patients received fentanyl 1.5 μ g/kg along with 1 ml (0.2 mg) glycopyrrolate (group G) or 1 ml normal

saline (group C) 5 minutes before the induction of anesthesia. Windows excel was used to generate random numbers. Author GDP generated the random numbers which were put into serially numbered envelopes and opened in the operating room just before administration of glycopyrrolate/saline (1 ml each) prepared in identical syringes. The patients and the investigators involved in the anesthetic management were blinded to the group allocation. Heart rate and mean arterial pressure (MAP) were recorded 3 minutes after giving glycopyrrolate (group G) or normal saline (group C) as the peak effect on HR is achieved at 3.7 minutes with glycopyrrolate.⁶ After preoxygenation with 100% oxygen for 3 minutes, anesthesia was induced with propofol infusion using an infusion pump (Pilote-C, Fresenius, France) at a rate of 0.8 mg/kg/min titrated to achieve a target BIS of 40. Once the target BIS was achieved, airway was secured with appropriate sized laryngeal mask airway (LMA) and bilateral air entry was confirmed by auscultation. Patients were allowed to breathe spontaneously. Heart rate, SpO₂, MAP, BIS and end-tidal CO₂ were recorded every minute until 5 minutes after induction and every 5 minutes thereafter till the end of anesthesia. Dose of propofol required for achieving clinical end-point (CEP) [loss of eyelash reflex] and objective end-point (OEP) [target BIS = 40] were extracted for analysis. It was found from the cumulative dose given from the syringe pump display by the time the specific endpoint was achieved.

Statistical Analysis

Parametric data were analyzed using the independent t-test and count data were compared using the Chi-square test. Hemodynamic data (HR, MAP) were analyzed using one-way ANOVA test for comparison within the group and independent t-test for comparison between the two groups. Results are expressed as mean \pm SD and $p < 0.05$ was considered significant. Correlation between the dose of propofol required to reach target BIS = 40 and preinduction HR (3 minutes after giving the test drug) was performed by regression analysis. Statistical analysis was performed with SPSS, version 13.0 for Windows.

RESULTS

Eighty female patients were studied and all of them successfully completed the study. The two groups were comparable (Table 1) with respect to age, weight, height, body mass index (BMI) and ASA status. The dose of propofol required to achieve CEP were similar in the two groups. The dose of propofol required for achieving target BIS (Table 1) was significantly higher ($p < 0.001$)

in group G (2.08 ± 0.42 mg/kg) as compared to group C (1.66 ± 0.23 mg/kg). Hemodynamic values are shown in Table 2. Though the baseline HR and MAP were higher in group G, the difference between the two groups were not significant. Although the HR increased after giving glycopyrrolate (group G), the rise was not significant compared to the baseline value. There was a significant positive correlation, even though very weak, (Fig. 1) between the preinduction HR (3 min after giving the test drug) and the propofol dose required to reach target BIS = 40, with the following equation showing the relationship: $y = 0.0085x + 1.072$ ($r = 0.356$, $p < 0.01$).

DISCUSSION

The study evaluated the effect of glycopyrrolate on induction dose of propofol and found that use of intravenous glycopyrrolate in the antisialogogue dose (0.2 mg) increased the dose of propofol required to achieve the target BIS of 40. The possible mechanisms for this increase in dose may be increase in the CO secondary to increase in HR by glycopyrrolate. Glycopyrrolate increases the HR in a dose dependent manner. The peak effect on HR is achieved at 3.7 minutes in comparison to 2.6 minutes with atropine.⁶ Upton et al⁷ demonstrated an inverse relationship between peak concentration of propofol and cardiac output. This means a high concentration of propofol is expected when a normal dose is injected in a patient with low cardiac output and clinically, many anesthesiologists approve this finding, as critically ill patients with low cardiac output usually require very small doses of propofol. These observations suggest that the coadministration of drug that alters cardiac output can affect the initial kinetics of propofol. Reduction in the CO may be the additional reason for decrease in propofol requirement when used with midazolam, fentanyl and esmolol.^{8,9} The use of continuous infusion of esmolol, a β_1 adrenergic receptor antagonist, have shown a 26% reduction in

Table 1: Patient characteristics and propofol dose (mean \pm SD)

Variable	Group G (n = 40)	Group C (n = 40)	p-value
Age (yrs)	48.7 \pm 8.2	45.1 \pm 9.6	0.079
Height (cm)	158 \pm 4.7	159.6 \pm 6.5	0.204
Weight (kg)	53.2 \pm 10.8	52.7 \pm 10.9	0.829
BMI (kg/m ²)	21.4 \pm 4.4	20.3 \pm 3.8	0.243
ASA			
1	34	32	0.556
2	6	8	
Dose of propofol (mg/kg)			
CEP	1.26 \pm 0.27	1.17 \pm 0.24	0.099
OEP	2.08 \pm 0.42	1.66 \pm 0.23	<0.001

ASA: American society of anesthesiologists; BMI: Body mass index; CEP: Clinical end-point (loss of eyelash reflex); OEP: Objective end-point (target BIS = 40)

Table 2: Hemodynamic variables (mean \pm SD)

Variables		Group G (n = 40)	Group C (n = 40)	p-value (independent t-test)**
HR (b/min)	Baseline	93.6 \pm 14.6	90.2 \pm 12.6	0.277
	After drug	100.9 \pm 16.9	88 \pm 12.9	0.000 (<0.001)
	CEP	91.5 \pm 18.4	83.2 \pm 12.6	0.024
	OEP	86.3 \pm 11.2	80.5 \pm 13.1*	0.040
	1	86.3 \pm 12.2	80.6 \pm 12.4*	0.044
	2	85.1 \pm 12.4	79.2 \pm 12.3*	0.037
	3	85 \pm 14.5	78.2 \pm 11.3*	0.025
	4	84.7 \pm 11.7	80.9 \pm 14.1	0.207
	5	83.4 \pm 11.2*	78.5 \pm 12.2*	0.071
	MAP (mm Hg)	Baseline	101 \pm 15.4	96.3 \pm 14.9
After drug		100.3 \pm 16.1	98.1 \pm 13.4	0.520
CEP		95.5 \pm 16.2	97.7 \pm 10.8	0.377
OEP*		72.4 \pm 10.9	77.3 \pm 10.4	0.047
1*		83.2 \pm 12.8	77.1 \pm 12.5	0.039
2*		82.3 \pm 15.5	80.4 \pm 15	0.584
3*		82.7 \pm 14.1	80.1 \pm 12.7	0.392
4*		81.7 \pm 13.8	78.5 \pm 12.5	0.288
5*		79 \pm 13.3	78.1 \pm 12.1	0.750

HR: Heart rate; MAP: Mean arterial pressure; CEP: Clinical end-point (loss of eyelash reflex); OEP: Objective end-point (target BIS = 40); 1, 2, 3, 4, 5 minutes after Laryngeal Mask insertion; *Significant ($p < 0.05$) within group compared to baseline value (One-way ANOVA); **Comparison between groups

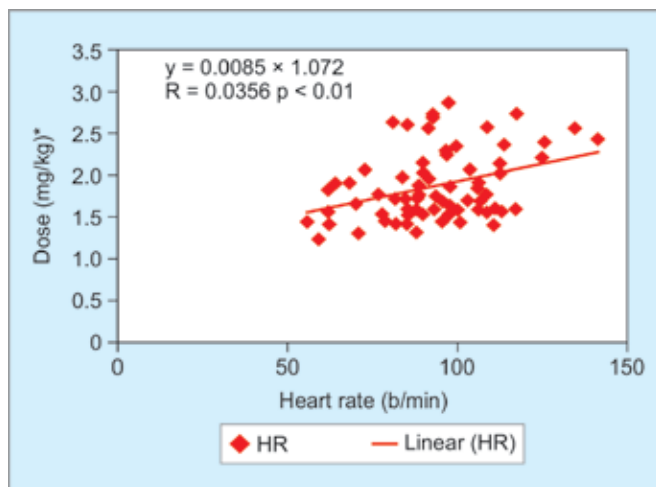


Fig. 1: Relation between the HR after giving the test drug and the propofol dose required to reach target BIS = 40; *Propofol dose to reach target BIS = 40 (bi-spectral index)

the minimum effective plasma concentration (Cp50) of propofol for skin incision during balanced anesthesia with propofol, nitrous oxide and morphine.¹⁰

Adachi et al¹ concluded that in addition to age and weight, CO is an important predictive variable for the hypnotic dose of propofol; as the cardiac output increased, the hypnotic dose of propofol and time for achieving hypnosis is increased. A similar report¹¹ published during our study period demonstrated that after the administration of atropine, CO was significantly increased from 4.28 ± 0.83 to 5.76 ± 1.55 L/min ($p < 0.0001$). The authors concluded that following administration of atropine, the propofol requirements for the induction of anesthesia were increased and propofol concentrations

were decreased during continuous infusion of propofol. A significant difference in the doses of propofol to achieve OEP while they were similar for CEP in the present study could be because of the subjective nature of assessment involved in CEP.

Glycopyrrolate is not routinely used prior to induction of general anesthesia nowadays. However, it is used as an antisialagogue in anticipated difficult airway during diagnostic bronchoscopy, rigid bronchoscopy for retrieval of foreign body, esophagoscopy, double lumen endotracheal tube insertion, nasal intubation, surgical procedures on the upper airway and as vagolytic to treat bradycardia. Results of this study can also be used for understanding the mechanism of altered drug dosage requirement in different HR situation.

Our study has some limitations:

- The sample size was not calculated
- The plasma concentration of propofol were not measured directly
- We did not measure the CO before and after glycopyrrolate
- All the patients were females as these patients underwent minor procedures during which the airway is commonly managed with LMA which is known to cause very little hemodynamic stimulation following its insertion.

CONCLUSION

Administration of 0.2 mg of glycopyrrolate intravenously before induction of general anesthesia significantly

increased the dose of propofol required for induction of anesthesia.

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