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Glycopyrrolate Compared with Atropine in Prevention of the Oculocardiac Reflex during Eye-muscle Surgery

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The oculocardiac reflex, a trigeminal–vagal reflex, characterized by bradycardia, dysrhythmias, sinoatrial arrest, or even cardiac arrest, may be initiated by traction on eye muscles during surgical correction of strabismus. Previous studies using atropine for prevention and treatment of this reflex found its efficacy to be dependent upon the dose, mode, and time of administration.[1-3]

The anticholinergic drug, glycopyrrolate, offers theoretic advantages over atropine in operations for strabismus: purely peripheral anticholinergic effect, long action, and few associated dysrhythmias.[4]

Venugopal *et al.*[6] performed an unmasked study comparing atropine and glycopyrrolate given im preoperatively to patients undergoing various extraocular procedures. Mean age was not stated. Glycopyrrolate was superior to atropine in prevention of bradycardia, but made no difference in the incidences of other dysrhythmias. Possibly, the vagolytic effect of the intramuscularly administered drugs was dissipated preoperatively. Traction on eye muscles, the stimulus most often associated with the oculocardiac reflex, may not occur in all extraocular surgical procedures.

The present study, comparing glycopyrrolate with atropine with respect to incidences of bradycardia, dysrhythmias, and postoperative vomiting, was controlled, masked to eliminate bias, and utilized only anticholinergic drugs given intravenously to patients who needed surgical correction of strabismus with general anesthesia.

METHODS

Sixty patients between the ages of 1 and 53 years, with a mean age of 10.1 years, who needed surgical correction of strabismus with general anesthesia were studied. None received atropine or scopolamine eye drops preoperatively. Each patient was evaluated preoperatively by one of the authors. Premedication consisted of droperidol, 0.1 mg/kg, with a maximal dose of 5 mg, im, one and a half to two hours preoperatively.

TABLE 1. Distribution

Agent	Number of Subjects	Mean Age (Years) ±SD	Sex	
			Male	Female
Glycopyrrolate	20	10.7 ± 10.89	8	12
Atropine	20	7.1 ± 6.73	12	8
Saline solution	20	12.5 ± 14.43	6	14

For patients 8 years of age or less, anesthesia was induced by administration of N_2O–O_2–halothane by mask, after which an intravenous infusion was established. Endotracheal intubation was performed during deep halothane anesthesia. For patients more than 8 years old, an intravenous infusion was started prior to induction of anesthesia. Following pretreatment with pancuronium, 0.5–1.0 mg, iv, N_2O–O_2–halothane was administered and endotracheal intubation facilitated with succinylcholine, 1 mg/kg, iv.

After the intravenous infusion was begun, a baseline pulse rate was recorded and the anticholinergic drug, the identity of which was unknown to the anesthesiologist, was given iv. Atropine, .02 mg/kg, maximum dose 0.6 mg, or glycopyrrolate, .01 mg/kg, maximum dose 0.3 mg, or saline solution, .05 ml/kg, maximum dose 1.5 ml, was administered in a randomized fashion. Pulse rate a minute after injection was recorded. A 30 per cent decrease in baseline pulse rate was considered bradycardia.

Maintenance of anesthesia for all patients was with N_2O–O_2, 60:40, vaporizing halothane 1–1. per cent. A nonrebreathing system with a fresh gas flow 2.5 times the estimated minute volume was used for patients weighing less than 30 kg. For patients weighing 30 kg or more, circle system with soda lime absorber was used.

Blood pressure, electrocardiogram, pulse rate, and body temperature were monitored frequently. Respiration was controlled until return of spontaneous breathing, then assisted. If the pulse rate decreased to 30 per cent less than baseline, atropine, .02 mg/kg,

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to as much as 0.4 mg, was given by intravenous injection and the surgeon was asked to discontinue muscle traction until the pulse rate returned to at least the baseline level.

The data were analyzed by analysis of variance with three groups. Only P values are reported; $P < 0.05$ was considered significant.

Results

The 60 patients comprised three groups of 20 each, similar with regard to sex and age distributions (table 1).

The baseline mean pulse rates were similar in all groups (table 2). A minute after drug administration, the mean pulse rate of patients receiving saline solution remained unchanged, *i.e.*, −3.6, SD = 8.46 beats/min. The mean pulse rate increase after glycopyrrolate administration was 26.75, SD = 4.78 beats/min, and that after atropine administration, 44.8, SD = 4.81 beats/min. The pulse rate increase in patients receiving anticholinergic drugs was significant, $P < 0.02$. The pulse rate increase with atropine was greater than that with glycopyrrolate ($P < 0.05$; table 2).

There was no bradycardia intraoperatively in patients receiving glycopyrrolate or atropine. The single patient in whom bradycardia developed after administration of atropine had bradycardia after completion of the surgical procedure and arrival in the recovery room. There was, however, a greater incidence of bradycardia in patients who received saline solution, *i.e.*, eight patients (40 per cent) became bradycardiac ($P = 0.01$). There was no difference among glycopyrrolate, atropine, and saline solution with respect to other dysrhythmias or postoperative vomiting ($P > 0.02$, table 3). All patients in whom bradycardia developed were effectively treated with a single dose of atropine, iv. These patients were then completely protected against the oculocardiac reflex when traction was reapplied to the muscle. Patients receiving the two types of induction were similar with respect to age and sex distributions. There was no difference between the incidences of bradycardia associated with mask induction and with intravenous induction (table 4). Three children who experienced bradycardia during mask induction of anesthesia were treated with atropine, iv, and eliminated from the study.

Table 2. Pulse Rate (Mean ± SD)

Agent	Pulse Rate (Beats/Min)		
	Baseline	1 Min Later*	Increase†
Glycopyrrolate	94.5 ± 23.21	121.2 ± 26.25	26.95 ± 4.78
Atropine	99.5 ± 22.46	144.3 ± 17.94	44.8 ± 4.81
Saline solution	100.9 ± 21.27	97.2 ± 18.75	−3.6 ± 8.46

* Significant difference between glycopyrrolate and atropine *vs.* saline solution, $P < 0.01$.

† Increase for atropine significantly greater than that for glycopyrrolate, $P < 0.05$.

Table 3. Complications

Agent	Bradycardia*	Other Arrhythmias	Postoperative Vomiting
Glycopyrrolate	0	0	1
Atropine	1	0	2
Saline solution	8	2	3

* Significant difference between glycopyrrolate and atropine *vs.* saline solution, $P < 0.01$.

Table 4. Effect of Type of Induction

Agent	Number of Subjects	Mean Age (Years) ±SD	Bradycardia
Glycopyrrolate			
Mask induction	10	3	0
Intravenous induction	10	± 18.5	0
Atropine			
Mask induction	13	2.2	0
Intravenous induction	7	± 15	0
Saline solution			
Mask induction	9	3.3	4
Intravenous induction	11	± 19.6	4

Discussion

This study indicates that young patients undergoing surgical correction of strabismus have a significant incidence of bradycardia, which can be prevented by anticholinergic drugs administered iv prior to surgical stimulation. Both atropine and glycopyrrolate cause sinus tachycardia, the extent of tachycardia being greater after atropine.

These findings differ from those in elderly patients undergoing intraocular procedures with local anesthesia, in whom anticholinergic drugs did not decrease the incidences of bradycardia and dysrhythmias, and in whom tachycardia was not greater after atropine than after glycopyrrolate.[5] Young patients have more active vagal reflexes than the elderly, and surgical correction of strabismus is more conducive to the oculocardiac reflex than intraocular operations. One would expect from Frolkis' study[7] that because the tonic effect of the sympathetic and parasympathetic nerves

on the heart lessens with advancing age, the tachycardia following anticholinergic drugs would lessen in aged patients.

We conclude that the incidence and severity of bradycardia that can develop during surgical correction of strabismus are of sufficient magnitude to warrant use of anticholinergic drugs. Glycopyrrolate appears to be superior to atropine because, in the doses used, it caused less tachycardia. However, both atropine and glycopyrrolate are effective in prevention of the oculocardiac reflex during surgical correcton of strabismus when given intravenously just before the operation is begun.

Data analysis was accompanied in consultation with the Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri.

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Acid-aspiration Prophylaxis by Use of Preoperative Oral Administration of Cimetidine

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With the introduction of cimetidine, an effective gastric histamine H-2 receptor antagonist, preanesthetic prophylaxis against gastric acid aspiration may be reality.[1,2] The risk of severe pulmonary damage with aspiration of gastric acid has been correlated with a gastric-fluid *p*H of less than 2.5, and is further increased with volumes of 25 ml or more.[3–6] In a recent study, the administration of 300 mg cimetidine, iv, 45 to 60 min prior to endotracheal intubation was associated with a higher gastric-fluid *p*H than controls.[2] The number of patients at risk for severe pulmonary damage if aspiration occurs, as defined by gastric-fluid *p*H less than 2.5 and volume of 25 ml or more at endotracheal intubation, was reduced (less than 10 per cent in patients premedicated 45 to 60 min preoperatively).

A randomized double-blind study was undertaken to assess whether a preoperative 300-mg oral dose of cimetidine would significantly increase the gastric-fluid *p*H compared with a similar treatment with a placebo. Also, comparative analyses of post-intubation gastric volumes were performed, since our earlier studies with intravenously administered cimetidine suggested a reduction in volume compared with control conditions.[2]

This investigation was approved by the medical center's committee on human experimentation.

Method

All patients studied were selected from ASA Physical Status I or II patients scheduled for elective orthopedic and gynecologic procedures with general endotracheal anesthesia. Fifty-two patients (ages 18 to 64 years) participated in this study after giving informed consent. Randomization from standard tables was accomplished with the aid of the Pharmacy Department at this institution. Patients were assigned to the random list in sequence by the Pharmacy Department on receipt of the preoperative orders for patient inclusion in the protocol. Each patient received orally either 300 mg cimetidine or dextrose placebo, administered with 30 ml of water. The study medication was ordered for administration one and one half to two hours prior to the anticipated anesthetic induction time. A minimal interval of 60 min between oral premedication and induction of anesthesia was chosen because of its clinical applicability and the known occurrence of peak blood levels 60 to 90 min after oral administration.[7,8] Variation in the operative schedule

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