Atropine and Glycopyrrolate Effects on Lung Mechanics in Normal Man

Thomas J. Gal, MD,* and Paul M. Suratt, MD†

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To assess the comparative bronchomotor effects of large systemic doses of glycopyrrolate and atropine intravenous glycopyrrolate (10 µg/kg), atropine (20 µg/kg), or a placebo was administered to six healthy male volunteers in double-blind fashion. Both drugs produced bronchodilation reflected by significant decreases in airway resistance and increases in specific airway conductance (sGAW) compared to placebo. Glycopyrrolate increased sGAW to a maximal level of 100% ± 7% above control; bronchodilation persisted at this level for more than 4 hours after drug administration. Atropine increased sGAW to a maximum of 88% ± 5% above control 30 minutes after administration, but sGAW returned to control levels between 3 and 4 hours after the drug was given. Both drugs increased maximum expiratory flow rates over the same time course as sGAW, but the percent increases in flow were significantly less than changes in sGAW. Lung elastic recoil was decreased by both drugs over the full range of lung volume. The 32% maximum increase in heart rate after glycopyrrolate was significantly less ($p < 0.01$) than the 60% increase after atropine. It was concluded that vagal blockade with glycopyrrolate dilates large and small airways to the same extent as atropine, but that the effect is more sustained and associated with less cardiac vagal blockade. Lower doses of glycopyrrolate were also studied and the findings showed that maximal bronchodilation is achieved with lower doses (3.2 µg/kg), which are commonly used in routine premedication.

Key Words: AIRWAY: resistance; LUNG: compliance, function; PARASYMPATHETIC nervous system: glycopyrrolate, atropine; PREMEDICATION: anticholinergic, glycopyrrolate, atropine.

ATROPINE, the classic anticholinergic drug, has recognized bronchodilating actions that lower airway resistance (1) and increase dead space (2). The bronchodilation is clinically significant, however, only when large systemic doses (>1.2 mg) are administered. Such doses effectively block reflex bronchoconstriction due to airway irritation (3, 4), but produce undesirable side effects including tachycardia and central nervous system symptoms (5). These adverse effects, in addition to the relatively short-lived effects of atropine on airways (6), have limited the drug's clinical usefulness as a bronchodilator.

Glycopyrrolate, a quaternary ammonium compound with a similar spectrum of activity, was originally introduced as an anticholinergic drug to control gastric acidity (7). Recently the drug has enjoyed widespread use as an adjunct to anesthetic practice. Its potency is about twice that of parenteral atropine both as an antisialagogue (8) and as an antimuscarinic during reversal of neuromuscular blockade (9). Glycopyrrolate may possess bronchodilating properties, but its bronchomotor effects have not been examined. The purpose of this study was to compare the bronchodilating actions of glycopyrrolate to atropine, noting their peak response, duration of action, and side effects when given systemically in doses likely to produce significant vagal blockade. In addition, to determine the dose-response characteristics of glycopyrrolate, airway function was measured after four decreased doses of the drug.

Methods

Six healthy men, 21 to 34 years of age, with normal pulmonary function participated in the study. All were nonsmokers with no history or symptoms of respiratory disease. They gave informed consent after approval of the protocol by the Human Studies Com-

mittee of the University of Virginia. Using a double-blind, randomized crossover technique we administered intravenous injections of either glycopyrrolate (10 μg/kg), atropine (20 μg/kg), or placebo to subjects on separate days. The atropine dose was chosen to achieve significant vagal blockade of the airways (4, 5). The glycopyrrolate dose was based on its 2-fold potency compared to atropine (8, 9).

Pulmonary function studies were performed with subjects in the seated position before each treatment (control) and were repeated $\frac{1}{2}$, 1, 2, 3, and 4 hours after treatment. We also recorded pulse rates and the subjects' subjective symptoms at these times. In addition, airway resistance and flow-volume curves were measured 7 hours after each treatment in four of the six subjects.

Airway resistance (Raw) and functional residual capacity (FRC) were measured by the method of DuBois and co-workers (10, 11) using a variable pressure constant volume body plethysmograph. Raw measured at FRC was converted to its reciprocal airway conductance (Gaw). To eliminate changes produced by variations in lung volume, Gaw was expressed as specific conductance (sGaw) by dividing Gaw by FRC (12). The mean values from 10 satisfactory measurements were used in the results.

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV$_1$) were measured with a model 840 waterless rolling seal spirometer (Ohio Medical Products, Madison, WI). All volumes were corrected to body temperature and pressure saturated with water vapor. The best effort defined by the curve with the largest FVC and FEV$_1$ was used for analysis. During the forced expiration flow derived by electronic differentiation of the spirometer's volume signal was also plotted against volume on a fast response X-Y recorder (model 7041A, Hewlett-Packard Co, Waltham, MA) to obtain maximum expiratory flow volume (MEFV) curves from which peak expiratory flow (PEFR) and expiratory flow at midvital capacity (Vmax 50) were quantitated. To obtain a partial expiratory flow-volume (PEFV) curve, subjects, after a quiet exhalation to FRC, inspired to about 60% of vital capacity and then forcefully exhaled to residual volume (RV) and expiratory flow vs lung volume was recorded. Immediately after recording the PEFV curve, subjects inspired maximally to total lung capacity (TLC) and then expired forcefully to RV to obtain a reference MEFV curve. Flow was quantitated at 40% of FVC above RV (Vmax 40) or more specifically at TLC minus 60% of FVC (13). Curves were

only used in the results if RV for PEFV and reference MEFV curve coincided.

Lung elastic recoil was measured from expiratory pressure volume curves by a quasistatic method. Transpulmonary pressure was estimated as the difference between the pressure at the mouth and esophageal pressure (13). A 10-cm long balloon containing 0.5 ml of air was placed in the midesophagus and connected to a Validyne MP-45 differential pressure transducer (range $\pm$ 50 cm H_2O) (Validyne Engineering Corp, Northridge, CA); the opposite side of the transducer was connected to a pressure tap in the mouthpiece. Transpulmonary pressure was simultaneously plotted against lung volume on the X-Y recorder while subjects inspired to TLC and then expired slowly (approximately 0.2 L/sec) to RV. A line of best fit was drawn by eye through at least three sets of pressure volume data that agreed $\pm$ 1 cm H_2O. The static recoil pressure of the lung (PstL) was estimated from transpulmonary pressure measured at 10% intervals of TLC calculated by adding the mean inspiratory capacity to FRC during the recording of pressure volume curves.

Finally, the dose-response characteristics of glycopyrrolate were assessed by administering four decreased doses of the drug (1 μg/kg, 1.9 μg/kg, 3.2 μg/kg, and 6.1 μg/kg) in random sequence to each of the six subjects on separate days. In this experiment measurements of Raw and FRC were made 2 hours after drug administration.

Statistical significance of the changes after each drug compared to placebo was analyzed with the paired t-test; $p < 0.05$ was considered statistically significant. Values are expressed as means $\pm$ SEM.

Results

Mean Raw decreased and sGaw increased significantly after both atropine and glycopyrrolate (Fig 1, A and B). Inasmuch as FRC did not change significantly with either drug ($p > 0.05$), the changes in Raw and sGaw appeared to be mirror images of each other. The maximum increase in sGaw with glycopyrrolate (100% $\pm$ 7% above control) occurred 2 hours after the drug was administered and remained at this level for more than 4 hours. Seven hours after administration of glycopyrrolate sGaw in four subjects was still 56% above control levels. The peak increase in sGaw with atropine (88% $\pm$ 5% above control) did not differ significantly from that with glycopyrrolate ($p < 0.01$, paired t-test). In contrast to glycopyrrolate,
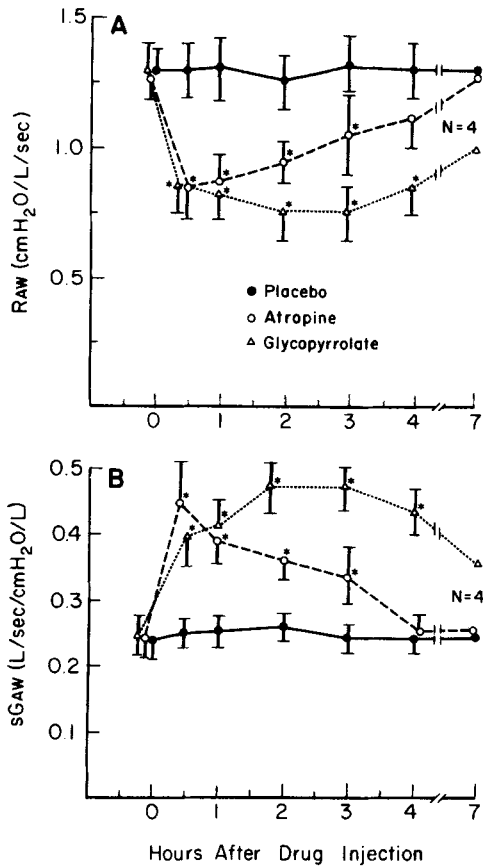

FIG 1. Time-related changes in airway resistance (RAW) after drug administration (A) and changes in specific airway conductance (sGAW) (B). Values are means ± SEM for six subjects; * $p < 0.01$ denotes significant difference from placebo (paired t-test).

Hours After Drug Injection

FIG 2. Time-related changes in V̇max 40 (A) and changes in lung elastic recoil pressure (PsTL) at 60% of total lung capacity (TLC) (B). Values are mean ± SEM for six subjects. V̇max 40 = expiratory flow at TLC—60% of forced vital capacity (FVC), i.e., 40% of FVC above residual volume; * $p < 0.01$ denotes significant difference from placebo (paired t-test).

sGAW after atropine reached its maximum 30 minutes after the drug and declined progressively, reaching control levels between 3 and 4 hours after the drug.

Maximum increases in V̇max 40 after glycopyrrolate and atropine were 72% and 60% above control levels, respectively; these statistically significant time-related changes paralleled those of sGAW (Fig 2, A). PsTL decreased after both glycopyrrolate and atropine. The changes were significantly different from placebo ($p < 0.01$) at all lung volumes 1 hour after the drugs were given (Fig 3). The time-related changes in PsTL at 60% of TLC (a lung volume near normal inspiration) indicate that the maximal decrease in PsTL occurred at this time interval (Fig 2, B).

Maximum expiratory flow rates were related to PsTL at the same lung volumes to plot maximum flow-static recoil curves (Fig 4). At any level of PsTL the expiratory flow rates were increased significantly after atropine and glycopyrrolate compared to placebo ($p < 0.01$).
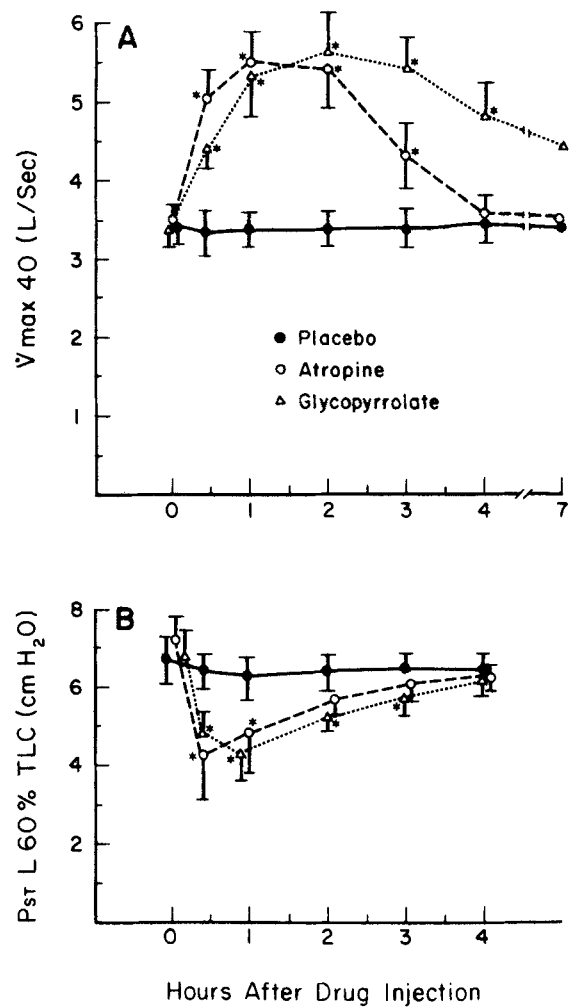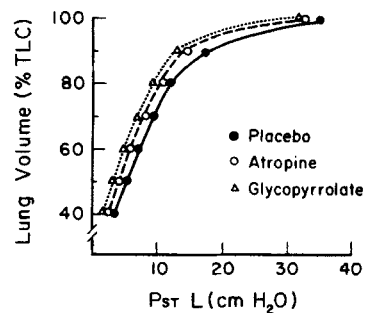

FIG 3. PsTL plotted vs lung volume expressed as percent of TLC 1 hour after drug administration. Values of PsTL are means for six subjects after placebo, atropine, or glycopyrrolate.

FVC did not change significantly, but other parameters such as FEV_1, PEFR, and $\dot{V}max$ 50 increased significantly above control ($p < 0.01$) after both drugs and their time course paralleled changes in sGaw. However, the maximal changes PEFR (11% above control), FEV_1 (3%), and $\dot{V}max$ 50 (19%) were considerably less than changes in sGaw.

Heart rate reached its maximum (32% above control) ½ hour after glycopyrrolate (Fig 5). This increase was significantly less ($p < 0.01$) than the 60% increase following atropine. Subjective sensations of dry mouth were more severe and persistent after glycopyrrolate than after atropine. Subjects noted dryness of the mouth up to 10 hours following glycopyrrolate. None of the subjects receiving glycopyrrolate experienced visual blurring, drowsiness, or lightheadedness described by four of the six subjects after atropine.
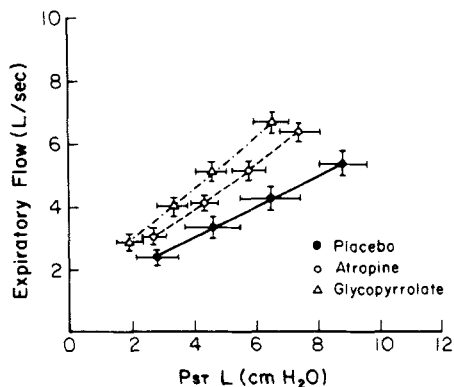

Fig 4. Mean maximum flow-static recoil curves in six subjects 1 hour after placebo, atropine, or glycopyrrolate. Expiratory flows at 10% intervals of TLC between 70% and 40% TLC are plotted against PsTL. Bars indicate means ± SEM for both flow and pressure.
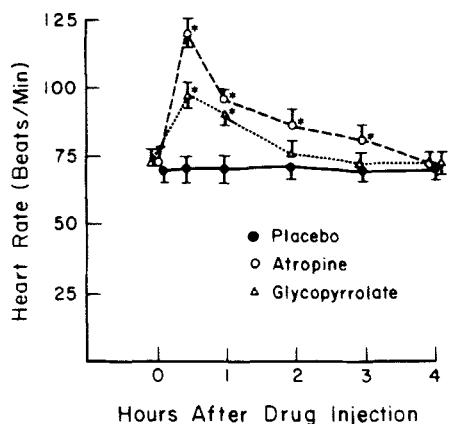

Fig 5. Time-related changes in heart rate following drug administration. Values are means ± SEM for six subjects. * $p < 0.01$ denotes significant difference from placebo (paired t-test).

Maximal increases in sGaw occurred after glycopyrrolate doses of approximately 3.2 mg/kg (Fig 6). These are considerably lower than doses used in the first portion of the study and are similar to those used in routine preanesthetic medication.

Discussion

This study demonstrates that glycopyrrolate administered intravenously is an effective bronchodilating drug in normal subjects. Effects on the airways are qualitatively and quantitatively similar to atropine in large doses, but are associated with less cardiac vagal blockade. Dose-response data (Fig 5) suggest that similar maximal bronchodilation (sGaw 100% above control) occurs with smaller doses of glycopyrrolate (3.2 μg/kg). Such doses are commonly used as preanesthetic medication and are associated with minimal changes in heart rate. In contrast, premedicant doses of atropine (6 to 8 μg/kg) increase sGaw less than 50% above control while significantly increasing heart rate (6, 14).

The measurement of sGaw in normal subjects reflects, for the most part, the dimensions of the larynx and the larger central airways (trachea and major bronchi) (15). The increases in sGaw observed after both drugs imply that a marked increase occurs in the caliber of these airways. Despite this bronchodilation, maximum increases in FEV_1, PEFR, and $\dot{V}max$ 50 were less dramatic. This apparent dichotomy between increases in sGaw and expiratory flow rates has been noted previously (1). After smooth muscle relaxation,
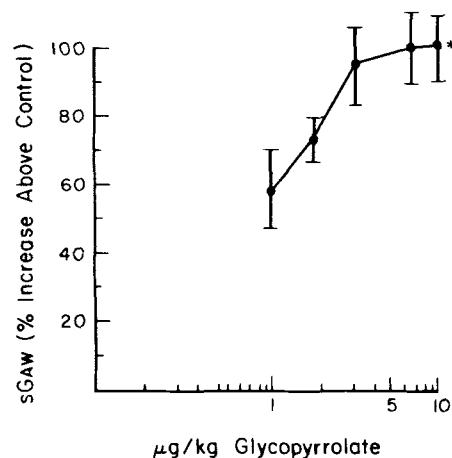

Fig 6. Dose-response curve for bronchodilation after glycopyrrolate. Percent increase in sGaw is plotted as a function of increasing dose on a log scale. Values are means ± SEM for six subjects. * Denotes large systemic dose (10 μg/kg) used in initial phase of study to produce significant vagal blockade in airways.

the large airways become more compressible in the presence of the high transmural pressures associated with forced expiration; this tends to limit increases in expiratory flows (16). During the low flow rates at which sGaw is measured, transmural stress on the airways is small and relaxation of bronchial smooth muscle is more directly reflected by increases in sGaw.

Compared to sGaw, the measurements of flow during maximal forced expiratory maneuvers reflect more the properties of the lung and more distal airways (17). Flow measurements during PEFV curves are particularly sensitive to changes in airway tone and possess the distinct advantage of being unaffected by upper airway resistance (18). Both atropine and glycopyrrolate increased flow rates on PEFV curves (V̇max 40). These changes suggest dilation of peripheral airways; however, a fuller explanation of the changes in expiratory flows requires a consideration of the other force responsible for flow, PstL. According to the theory of Mead et al (19), expiratory flow may be increased by a decrease in small airway resistance, but also by an increased PstL. PstL decreased after both atropine and glycopyrrolate. The increased flow in face of the decreased PstL (Fig 4) must result from a decreased resistance or, more specifically, a dilation of smaller peripheral airways.

The decreased PstL observed after glycopyrrolate treatment could represent an artifact due to an increase in esophageal tone as a result of the drug. However, esophageal tone was decreased by glycopyrrolate in this study and by atropine in a previous study (20). This would tend to minimize decreases in PstL and thus could not explain the observed decrease in PstL. The most likely cause for the decreased lung recoil is dilation of peripheral lung units including the alveolar ducts. This may increase alveolar size and in turn reduce lung retractile pressure. Such a loss of lung elastic recoil might be expected to produce an increase in FRC since the latter volume reflects the balance between the outward recoil of the chest wall and the inward recoil of the lung. In this study neither glycopyrrolate nor atropine produced consistent increases in FRC compared to placebo. These results are at variance with the findings of DeTroyer et al (20) who recently noted a consistent increase in FRC shortly after vagal blockade with atropine. The mean increase they noted was small (250 ml) and was similar in magnitude to the variations of FRC in our subjects following treatment with placebo.

The sensitivity of various end organs to effects of anticholinergic drugs differs considerably. However,

the magnitude and duration of the bronchodilating action of glycopyrrolate parallels its activity as an antisialagogue (21). This sustained, profound drying effect renders the use of parenteral glycopyrrolate impractical as a bronchodilator in ambulatory patients. On the other hand, its prolonged effects on the airways may prove useful in patients with bronchial hyperreactivity who must undergo general anesthesia. In these patients a reduction in the resting bronchomotor tone is likely to decrease the bronchoconstrictive response to irritant stimuli such as tracheal intubation (22).

Until recently the clinical use of anticholinergics has been restricted because of concerns that they cause slowing of mucus transport by increasing viscosity of secretions. This in turn could cause mucus inspissation and thus increase airway obstruction. Conflicting reports, however, indicate that intravenous atropine inhibits (23), or increases (24) mucociliary transport. Short- and long-term observations in patients with airway hypersecretion strongly suggest that anticholinergic agents can effectively and safely relieve airway obstruction and aid expectoration (25).

We conclude that in normal subjects intravenous glycopyrrolate produces dilation of large central airways that is reflected by increases in sGaw. Increases in V̇max 40 and decreased PstL suggest that dilation of peripheral airway units occurs as well. This bronchodilation is similar qualitatively and quantitatively to that with large systemic doses of atropine, but is associated with less cardiac vagal blockade and no central nervous system effects. The airway effects of glycopyrrolate are sustained near maximal values following a single intravenous dose in contrast to the relatively short-lived effects of atropine. In addition, maximal bronchodilation is achieved with common premedicant doses of glycopyrrolate, well below those producing significant vagal blockade. Glycopyrrolate thus appears to be a potentially valuable adjunct to anesthesia for patients in whom reflex airway reactivity is likely, particularly for those with concomitant cardiac disease.

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Intracardiac Injections during Cardiopulmonary Resuscitation

Fifty-three patients were observed prospectively for the development of complications resulting from 147 intracardiac injections received during cardiopulmonary resuscitation (CPR). Patients in an intensive care unit were included in the study if they had received intracardiac injections and met one of the following conditions: successful CPR with survival for more than 24 hours; successful CPR with survival for less than 24 hours and a full autopsy secured; CPR not successful and a full autopsy secured. Although pericardial effusion was noted in six of 17 echocardiograms and a hemopericardium was found in eight of 28 autopsies, cardiac tamponade was not observed. A pneumothorax developed in one patient. None of the autopsies disclosed coronary artery or ventricular lacerations. Percutaneous puncture of the heart during CPR seldom results in serious complications. When other sites are not readily available, intracardiac injections are safe and appropriate for the administration of emergency medication. *(Davison R, Barresi V, Parker M, Meyers SN, Talano JV: Intracardiac injections during cardiopulmonary resuscitation: a low risk procedure. JAMA 1980; 244:1110-1).*