The Effects of Glycopyrrolate on the Motor Functions of the Esophagus *•

HIGINO C. LAURETA, M.D.**

INTRODUCTION

ATROPINE decreases the pressure at the high pressure zone (HPZ) at the gastroesophageal junction thereby compromising its physiologic sphincter function.[1,2] Moreover, it inhibits esophageal peristaltic waves.[3] These promote esophageal reflux and produce esophagitis. This is particularly undesirable in a patient who suffers from esophageal reflux and chronic esophagitis.

The effects of atropine on the motor functions of the esophagus are to be expected because the motor nerves of the esophagus, the vagi, are cholinergic nerves. The anticholinergic drugs that are used for the treatment of peptic ulcer can potentially produce the same adverse effects on the motor functions of the esophagus as those by atropine. Whether these anticholinergic drugs actually produce these effects especially in the recommended dose is not known. The purpose of this study was to determine the effects of a potent anticholinergic drug, glycopyrrolate, on the motor functions of the esophagus.

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MATERIALS AND METHODS

Four young and healthy Pilipino volunteers, two men and two women, were tested for this study.

The motor functions of the esophagus were studied by intraluminal pressure measurements. This method has been previously described.[4] The pressure detecting device consisted of three water-filled polyethelene tubes (P.E. 190; inside diameter, 0.047 in., outside diameter, 0.067 in.) 120 cm long, tied together at the dital end so that the side openings at the distal end were in tandem five cm apart. The tubes were attached to pressure transducers (Statham P32Db) and the pressures recorded on Grass polygraph. The apparatus was calibrated so that one mm Hg pressure produced one mm deflection on the polygraph.

The pressure recording tubing assembly was passed through the nose until the side openings of all three tubes at the distal end were in the stomach. Pressure recordings were made with the subject in the recumbent position. The tubing assembly was withdrawn in stepwise fashion at one half to one cm in-

terval. Pressure were recorded at the lower esophageal sphincter, body of the esophagus, and the upper esophageal sphincter. The responses to swallows of two ml of water were recorded at each level.

The effects of both the injectable and tablet preparations of glycopyrrolate were determined. Two subjects were first tested with the injectable form and the other two with the tablet. In the subjects in whom the injectable form was first tested the normal pressures were first recorded then the tubing assembly was repositioned in the stomach. The recording were repeated half an hour after a subcutaneous injection of 1.5 mg glycopyrrolate, The same subjects were then instructed to take one tablet of glycopyrrolate 30 minutes before each meal and at bedtime for five days after which the intraluminal pressure recordings were repeated. The last tablet was given one hour before the pressure recordings were made. In the two subjects in whom the tablet was first tested the test was repeated with the injectable form at least five days after the last tablet was taken.

The swallowing complex consists of a rise in the average baseline pressure and appears like a plateau and which may be preceded by a brief negative deflection, followed by a positive deflection which represents the peristaltic wave (Fig. 1). The amplitude of the peristaltic wave was determined by measuring the height of the wave from the mean resting pressure to the tip of the wave and expressed in mm Hg pressure.

The velocity of a peristaltic wave was determined by dividing the distance between the two catheter tips (five cm) by the time required for the peristaltic wave to traverse the segment (based on paper speed) as shown in Figure. 1. Only the waves that were clearly progressive were employed in these calculations.

The duration of a swallowing complex was measured from the time of initial deflection to return of the pressure to the baseline (Fig. 1). The duration of the peristaltic wave was calculated from the point of upsweep of the wave to the point where the downsweep reached the baseline. The number and percentage of swallows initiating peristaltic waves and fall in pressure at the lower sphincter were determined for each patient.

Respiratory movements were recorded with a belt pneumograph.

RESULTS

The Normal Pressure Profile of the Esophagus. Sphincter Pressure. In these four normal Pilipinos the lower esophageal sphincter (HPZ) was three to four cm long, the pressure gradually rising from the atmospheric pressure at the fundus of the stomach and abruptly dropping to five mm Hg below the baseline fundal atmospheric pressure as it entered the chest through the hiatus. The mean resting pressure at the peak of the HPZ was seven mm Hg (Fig. 2A). The lower esophageal sphincter responded to 79% of wet swallows with relaxation in the usual manner as indicated by a drop in the resting pressure very shortly after a swallow (Fig. 3).

The upper or pharyngoesophageal sphincter was five to six cm long and the mean resting peak pressure was 15 mm Hg (Fig. 2B). Unlike the lower sphincter the upper sphincter responded everytime to a wet swallow in the usual manner with relaxation indicated by a quick drop in pressure followed just as quickly with a contraction indicated by a

quick rise in pressure.

Peristaltic Waves. The mean amplitude, duration, and velocity of the peristaltic waves are shown in Figure 4. These varied throughout the length of the esophagus originating just below the upper sphincter and dying out before reaching the lower sphincter. The amplitude, duration, and velocity of a peristaltic wave paralleled one another,, i.e. the biggest wave was also the longest and fastest. The biggest waves were about 45 mm Hg with a mean duration of 3.8 seconds and mean velocity of five cm/sec were generated by the middle third of the esophagus. The smallest waves were generated just beyond the distal periphery of the upper sphincter.

Effects of Glycopyrrolate on the Motor Functions of the Esophagus. Sphinc-ter Pressure. The effects of glycopyrrolate on the lower sphincter are shown in Figure 2A and 3. When given by a single subcutaneous injection 1.5 mg of glycopyrrolate reduced the mean resting pressure of the lower sphincter by half. Only 26% of wet swallows initiated relaxation compared to the control of 79% (Figure 3).

When given orally one mg before meals and at bedtime as recommended for five days the last tablet being given an hour before the pressure recordings were made there was no significant effect on the resting pressure. Sixty percent of wet swallows initiated response as compared to the control of 79% (Figure 3).

Whether given by subcutaneous injection or orally as above glycopyrrolate did not have any significant effect on the upper sphincter (Fig. 2B).

Peristaltic Waves. Figure 5 shows the percentage of swallows initiating peristalsis in the four subjects tested. Eighty to 100% of swallows (mean of 94%) initiated peristaltic waves during the control studies. This dropped to 81-95% (mean of 87%) after five days of four tablets a day and 27-60% (mean of 45%) after a subcutaneous injection of 1.5 mg of glycopyrrolate.

The effect of glycopyrrolate on the amplitude of peristaltic waves are shown in Figure 6. Both the tablet and injectable form reduced the amplitude of the peristaltic waves; the effect of the former was less and was confined to the middle third of the esophagus. Following an injection of the drug the waves of the whole esophagus but particularly the distal two-third was affected and the waves that managed to appear were at most half as big as those during the control studies (Fig. 7).

Figure 8 shows the effects of glycopyrrolate on the duration of the peristaltic waves. The duration of peristaltic waves in the distal two-third of the esophagus decreased after both the tablet and injectable glycopyrrolate; the effects of the latter on the peristaltic waves were so profound to allow accurate measurements (Fig. 7).

There was no significant effect of oral glycopyrrolate for five days on the velocities of peristaltic waves as shown in Figure 9.

The velocities could not be determined after the injection because the effects were so great that there were not enough measureable (Fig. 7).

Swallowing Complex. Figure 10 shows the swallowing complexes during control periods and after five days of tablet glycopyrrolate. There was no significant effect although there was a consistent tendency of the swallowing complexes to be longer after oral medication especially on the distal two-third of the eso-

phagus. This was associated with a decrease in the duration of the peristaltic waves.

DISCUSSION

The resting and deglutition esophageal pressures obtained during the control studies in these four subjects are similar to those obtained by others using the same technique.[5,6] The pressures were reproducible in the same subject. Not only the pressures but also the profile are similar to those obtained elsewhere.[3] Locally only one published data using the same technique is available;[4] the present data are similar to these.

It has been shown that the motor functions of the espohagus are profoundly affected by atropine.[1-3] The resting pressure at the lower sphincter was reduced and this was accompanied by acid reflux into the esophagus. The amplitude of the peristaltic waves in the distal two-third of the esophagus were reduced and the percentage of response in terms of initiation of waves to swallows was markedly reduced. These effects are to be expected because the motor nerves of the esophagus, the vagi, are cholinergic.

Because of the foregoing any potent anticholinergic agent would potentially have the same effects. If these effects are produced two things can be expected to follow, namely, varying degrees of dysphagia and esophageal reflux. The dysphagia may not be troublesome but the reduction of pressure at the high pressure zone would incapacitate its physiologic sphincter function and promote esophageal reflux and subsequently a troublesome esophagitis. This effect is very undesirable in a patient who, to begin with, has esophageal reflux for one reason or another.

A number of potent anticholinergic agents are commonly used in the treatment of peptic ulcer. One of these is glycopyrrolate. The intramuscular injection of 1.5 mg of glycopyrrolate reduced the volume of acid and pepsin output by about 90% in patients with peptic ulcer.[7] It has also been shown capable of suppressing the antral, small intestinal, and colonic motor activities.[8-10] The present study showed that glycopyrrolate, like atropine, can markedly depress the motor functions of the esophagus particularly when given in sufficient dose and parenterally; the high pressure at the physiologic sphincter was reduced by 50% and the number of peristaltic waves initiated by swallows by as much as 57%. Moreover, the waves that were initiated were likewise markedly reduced in amplitude. The subjects had to wait for six to eight hours before attempting to eat because the food would not go down. However, when given by mouth in the recommended dose for five days the effects were significantly less; the high pressure at the physiologic sphincter was not affected and the reduction in the number of waves initiated was not significant and did not produce dysphagia in the subjects. Nonetheless, they complained of dryness of the throat and slight blurring of vision.

The subjects tested in this study were healthy and young. Whether the same effects could be produced in older or, more importantly, those with esophageal disease like hiatal hernia or esophagitis due to esophageal reflux was not determined. Glycopyrrolate or any anticholinergic agent should therefore be used cautiously in these patients.

SUMMARY

The resting and deglutition intraluminal pressures in the lower and upper

sphincters and body of the esophagus were recorded in four healthy young Pilipino volunteers, two men and two women. The amplitude, duration, and velocity of the peristaltic waves and the duration of the swallowing complex throughout the body of the esophagus were determined. The average resting peak pressure was 7 mm Hg at the lower and 15 mm Hg at the upper esophageal sphincter. In these four subjects 79% of wet swallows initiated a relaxation of the lower sphincter; the upper sphincter responded to every swallow. The swallowing complex increased more or less linearly from 4 seconds just below the upper sphincter to 12 seconds just above the lower sphincter. Ninety four percent of wet swallows initiated peristaltic waves. The amplitude, duration, and velocity of a peristaltic wave more or less paralleled one another, i.e. the biggest wave was also the longest and fastest. The peristaltic waves decreased toward the distal portion of the proximal 3rd then increased to its peak at the distal portion of the middle and the proximal portion of the distal third of the esophagus and decreased again and dying out before reaching the lower sphincter. The biggest waves were about 45 mm Hg, mean duration of 3.8 seconds, and mean velocity of 5 cm/sec.

The same subjects were studied an hour after an injection of 1.5 mg and again after taking one 1 mg tablet four times a day of glycopyrrolate for five days. The injection of 1.5 mg of glycopyrrolate had the following effects:

1. The resting pressure at the lower esophageal sphincter decreased 50% and only 26% of wet swallows initiated a relaxation. The upper esophageal sphincter was not effected.

2. Twenty seven to 60% of wet swallows initiated peristaltic waves. Of the peristaltic waves that managed to appear the amplitude were profoundly reduced especially in the distal two-third of the esophagus. The effects on the duration and velocity of the waves could not be determined.

3. The effect on the swallowing complex could not be determined because the peristaltic waves that were initiated could not be measured accurately.

With four mg of glycopyrrolate by mouth per day for five days the following results were obtained in the same subjects:

1. The resting pressures of both the lower and upper sphincters were not affected. However, only 60% of the wet swallows produced a relaxation of the lower sphincter compared to 79% during the control test; the upper sphincter responded to all the swallows.

2. Eighty seven percent of the wet swallows initiated peristaltic waves (compared to 94% during control tests). The amplitude of the peristaltic waves particularly in the middle third of the esophagus were reduced but the reduction was not as profound as those produced by the injection of 1.5 mg. The duration of the waves particularly the proximal portion of the distal third and the distal portion of the middle third of the esophagus was likewise reduced. There was no effect on the velocity of the waves.

3. The swallowing complex increased slightly particularly in the distal two-third of the esophagus.

Potent anticholinergic drugs like glycopyrrolate can potentially compromise the sphincter function of the lower esophageal sphincter by decreasing the

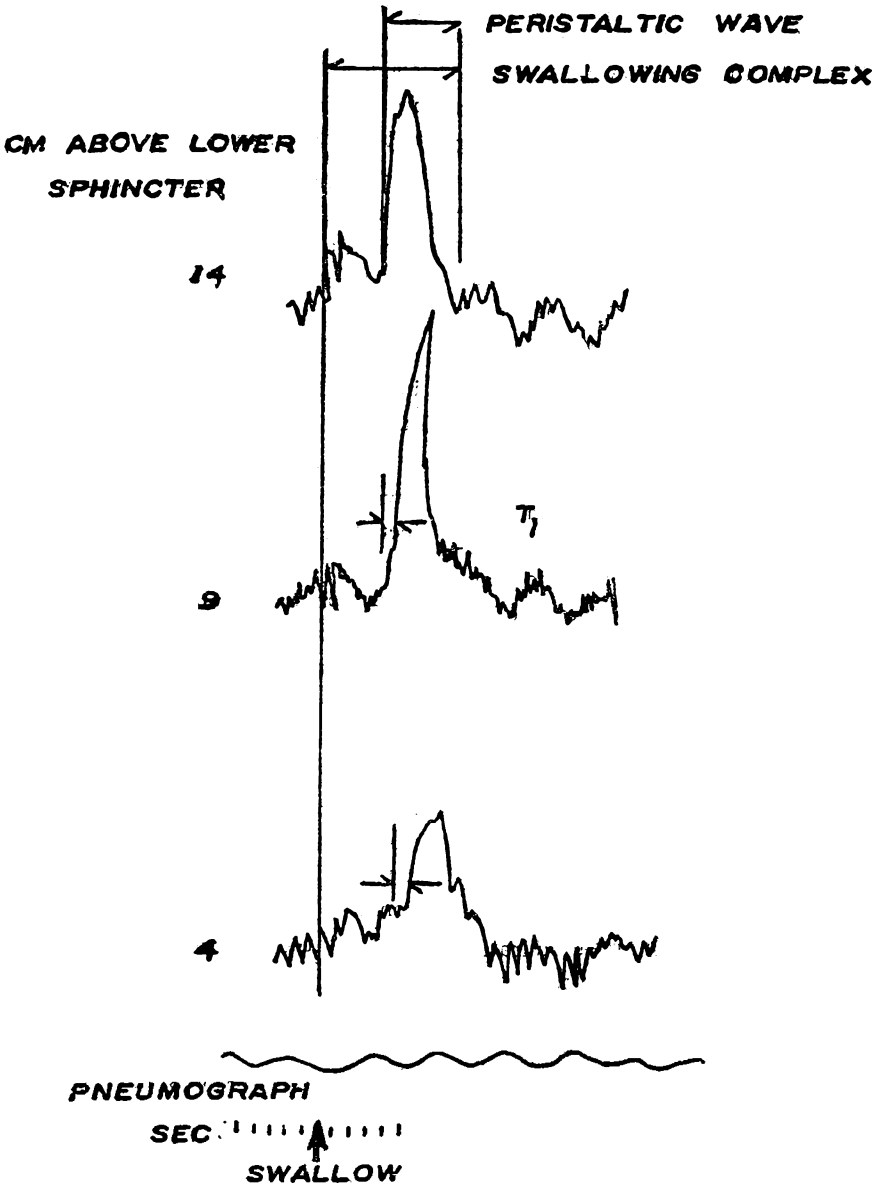

Figure 1. This strip of tracing shows the normal response of the esophagus four to 14 cm above the lower sphincter to a swallow. The method in determining the amplitude, duration, and velocity of peristaltic waves and the swallowing complex is indicated.

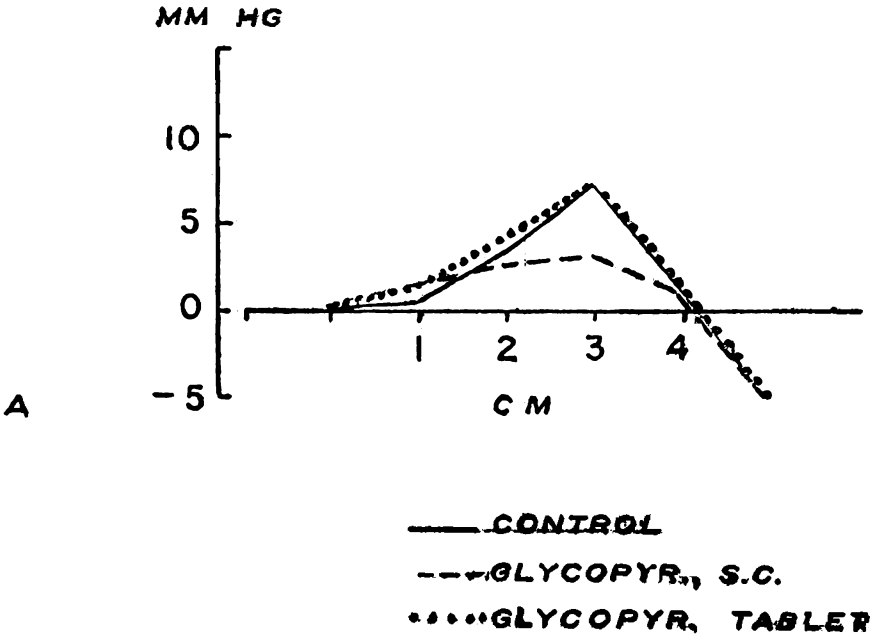

Figure 2A. Mean pressures at the lower esophageal sphincter of four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

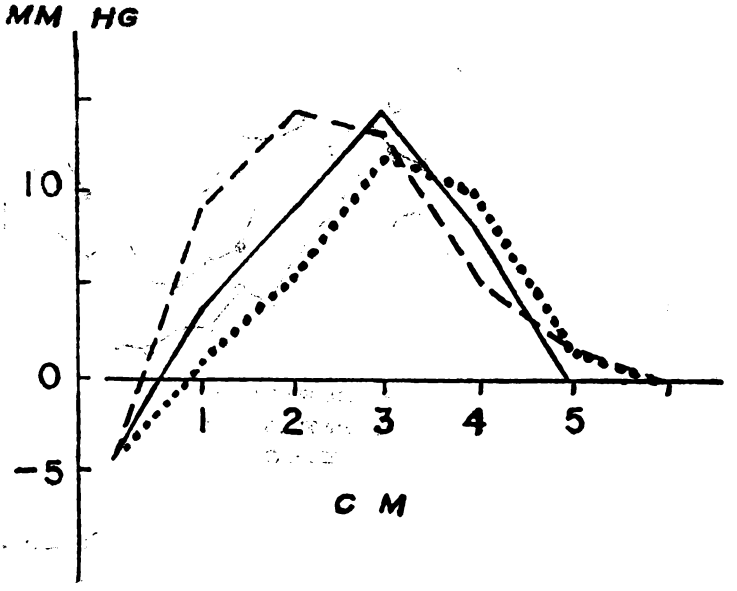

Figure 2B. Mean pressures at the upper esophageal sphincter of four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

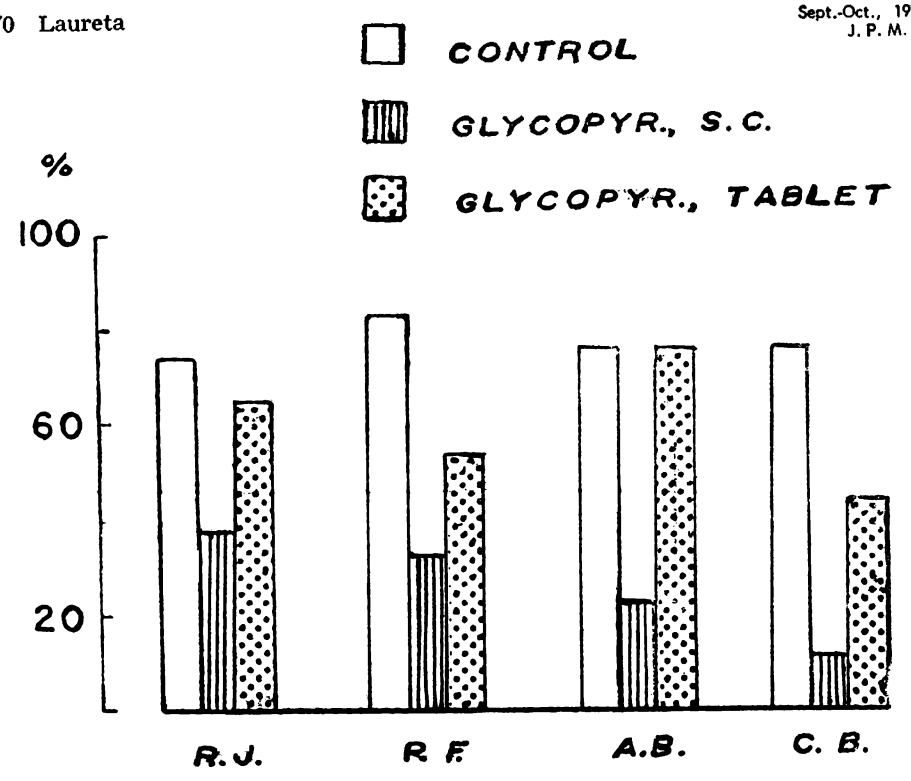

Figure 3. Percentage of swallows initiating fall in pressure at the lower esophageal sphincter in four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

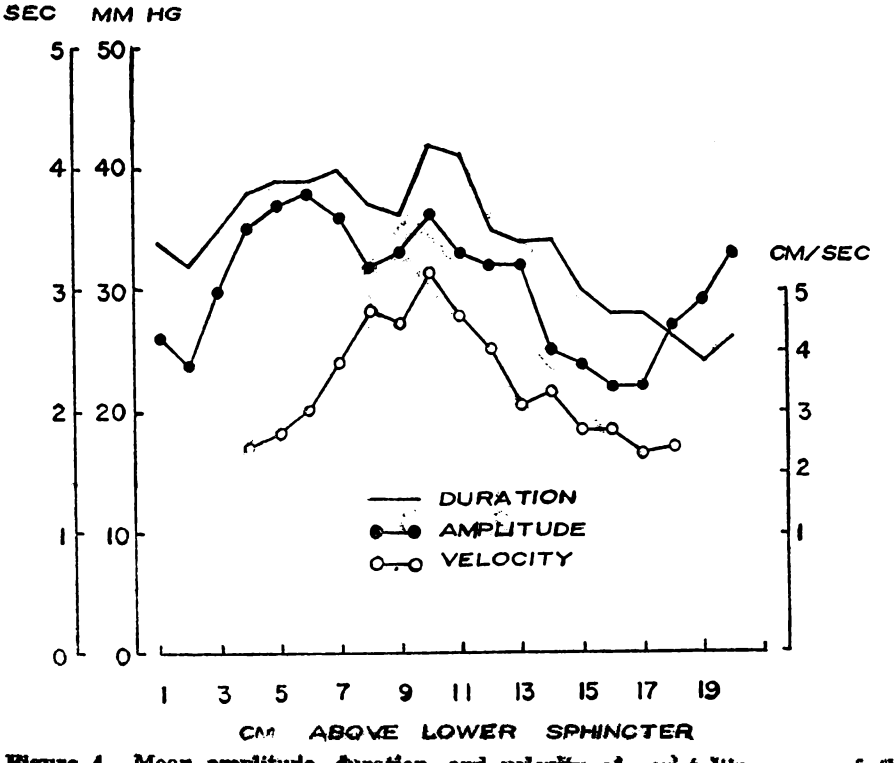

Figure 4. Mean amplitude, duration, and velocity of peristaltic waves of the esophagus of four normal subjects.

Table 1. LOWER ESOPHAGEAL SPHINCTERIC PRESSURES IN NORMAL SUBJECTS BEFORE AND AFTER AN INJECTION OF ONE MG OF ATROPINE.

Esophagel Sphincteric Pressures and Pulse Rates

	Before Atropine		After Atropine	
Subject	Pressure* mm H	Pulse Rate per min	Pressure* mm Hg	Pulse Rate pre min
A	14.0	77	1.5	101
B	8.0	62	1 5	118
C	11.0	68	3.0	102
D	4.0	63	1.0	109
E	9.5	68	2.0	111

*Mean of three pressure recordings.

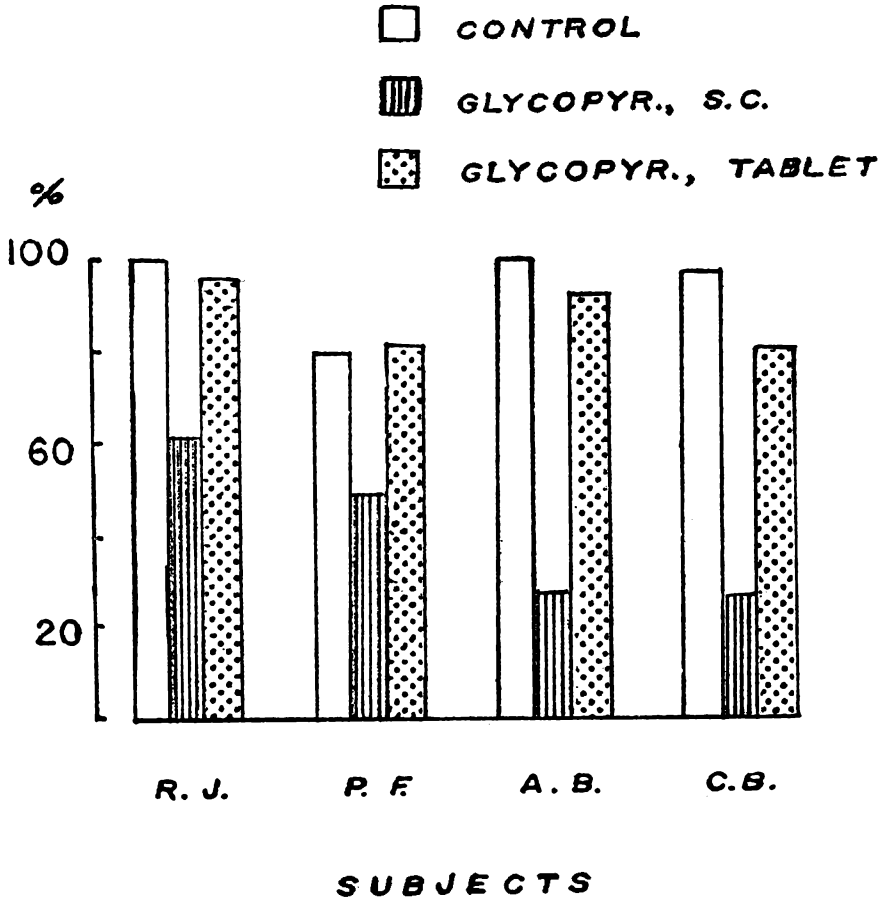

Figure 5. Percentage of swallows initiating esophageal peristaltic waves in four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

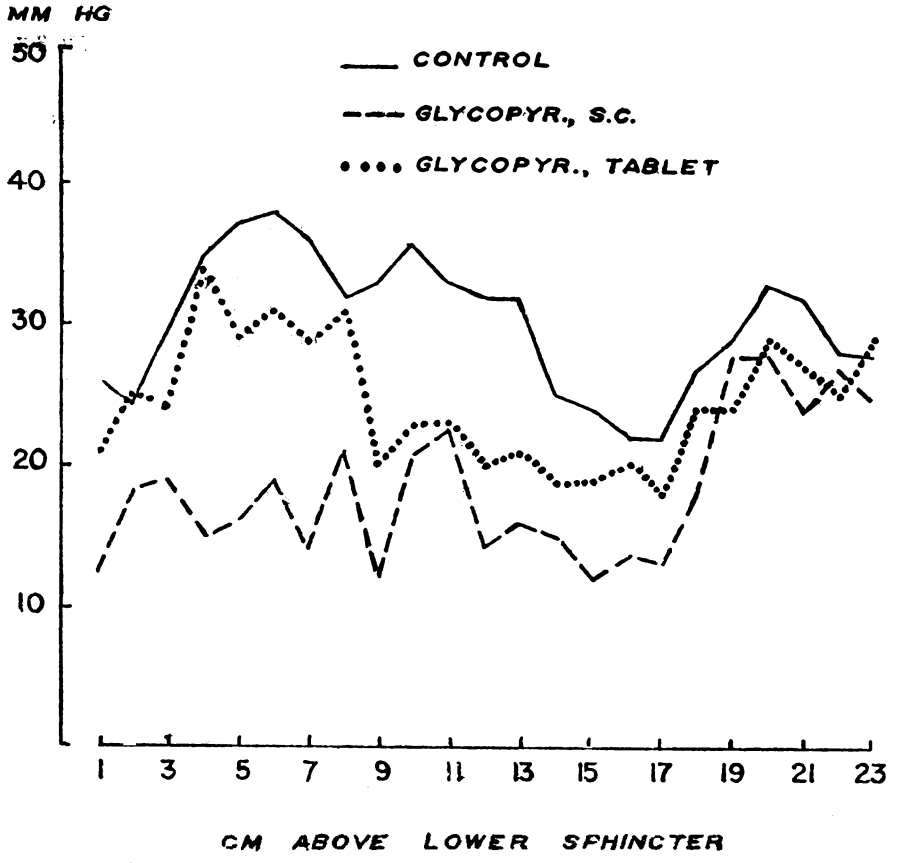

Figure 6. Mean amplitude of esophageal peristaltic waves of four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

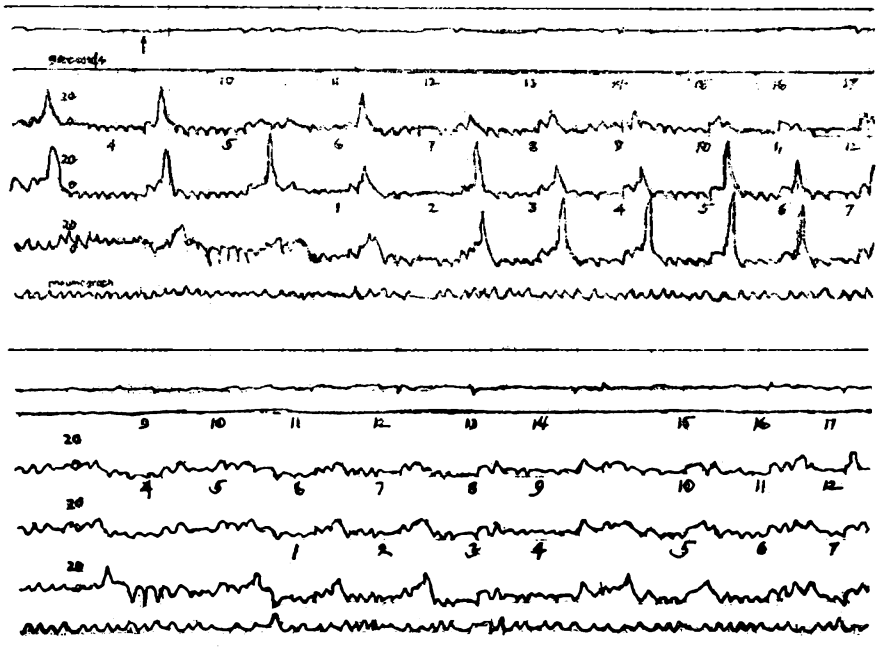

Figure 7. These tracings of one of the subjects show the normal responses of the distal esophagus to wet swallows (upper tracing) and one hour after a subcutaneous injection of 1.5 mg of glycopyrrolate (lower tracing).

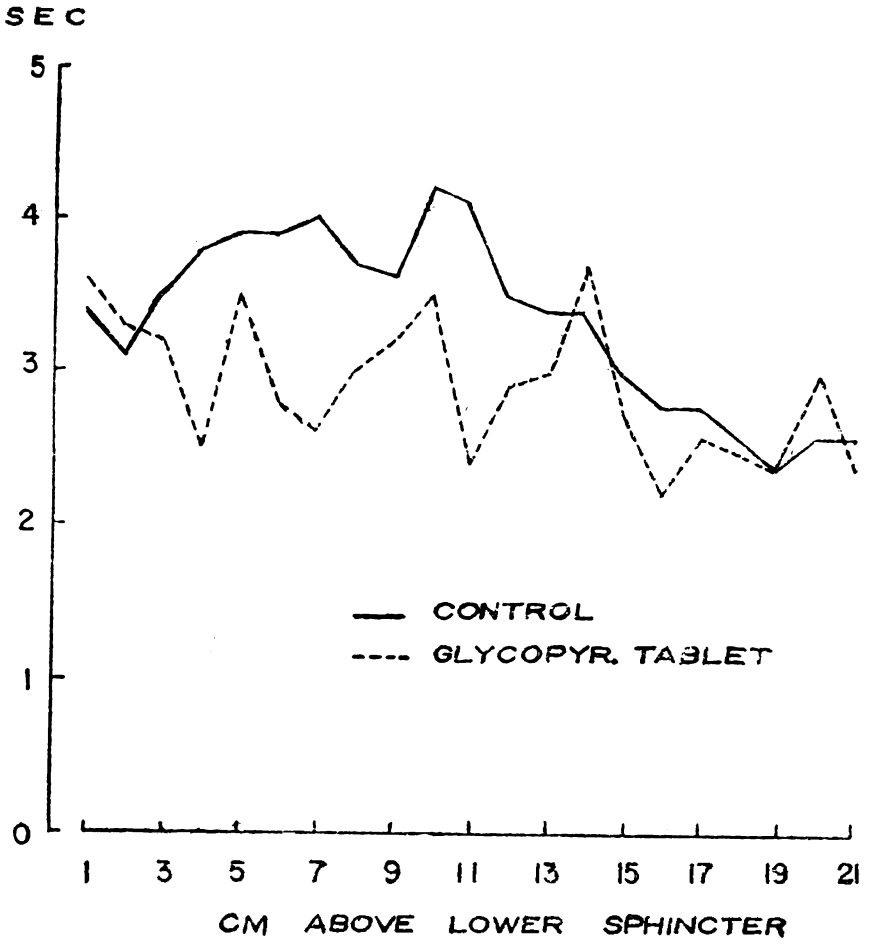

Figure 8. Mean duration of peristaltic waves of four normal subjects before and after glycopyrrolate one mg tablet q.i.d. for five days.

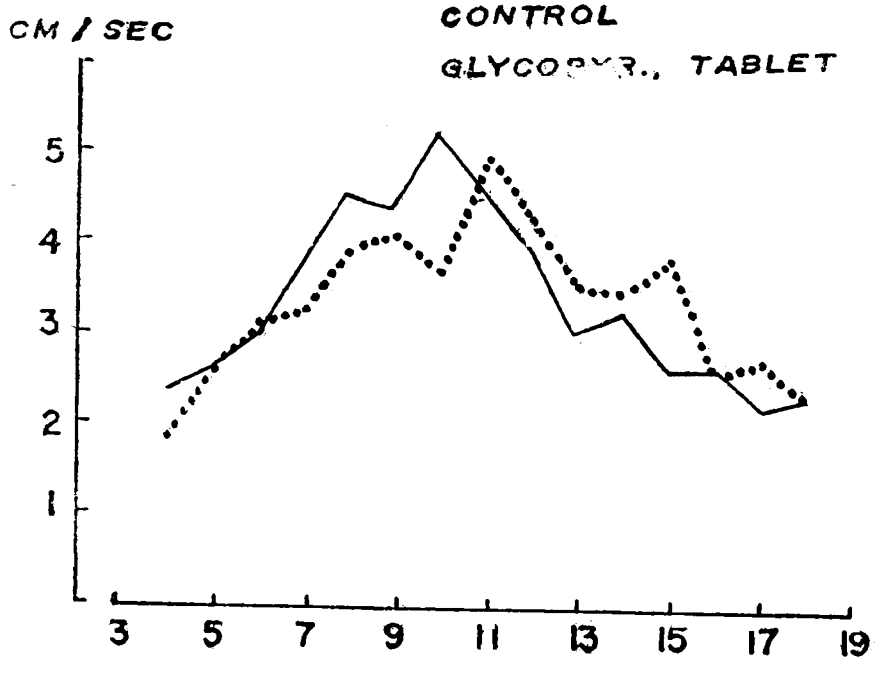

Figure 9. Mean velocity of esophageal peristaltic waves of four normal subjects before and after glycopyrrolate one mg tablet q.i.d. for five days.

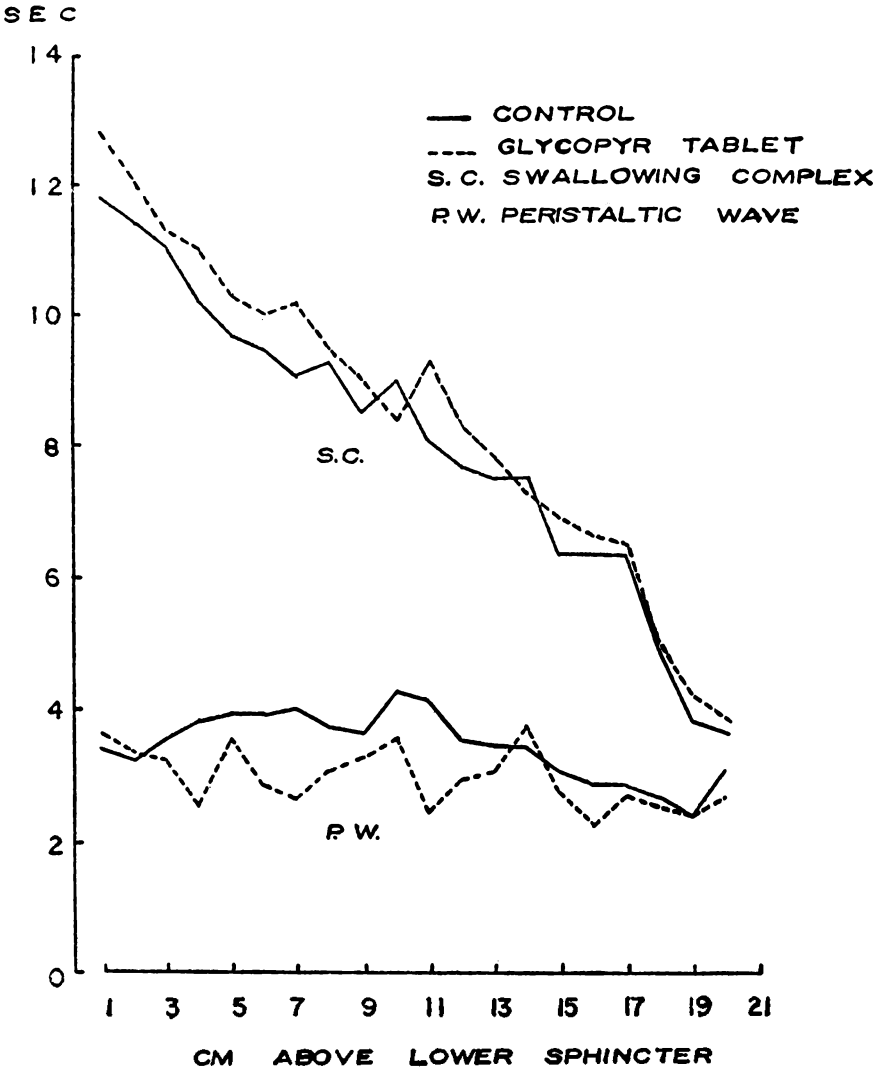

Figure 10. Mean duration of swallowing complexes (S.C.) and esophageal peristaltic waves (P.W.) of four normal subjects before and after glycopyrrolate one mg tablet q.i.d. for five days.

pressure at the HPZ. Potent anticholinergic drugs should be used with particular caution in patients with esophageal reflux or any problem affecting the distal esophagus.

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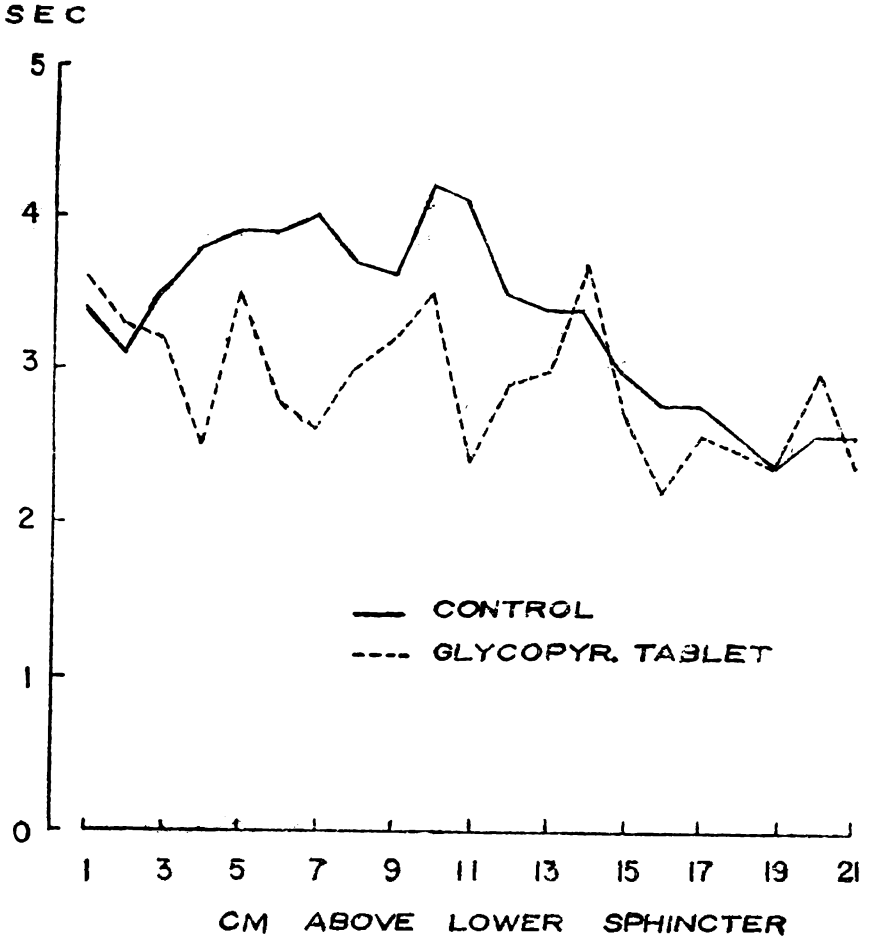

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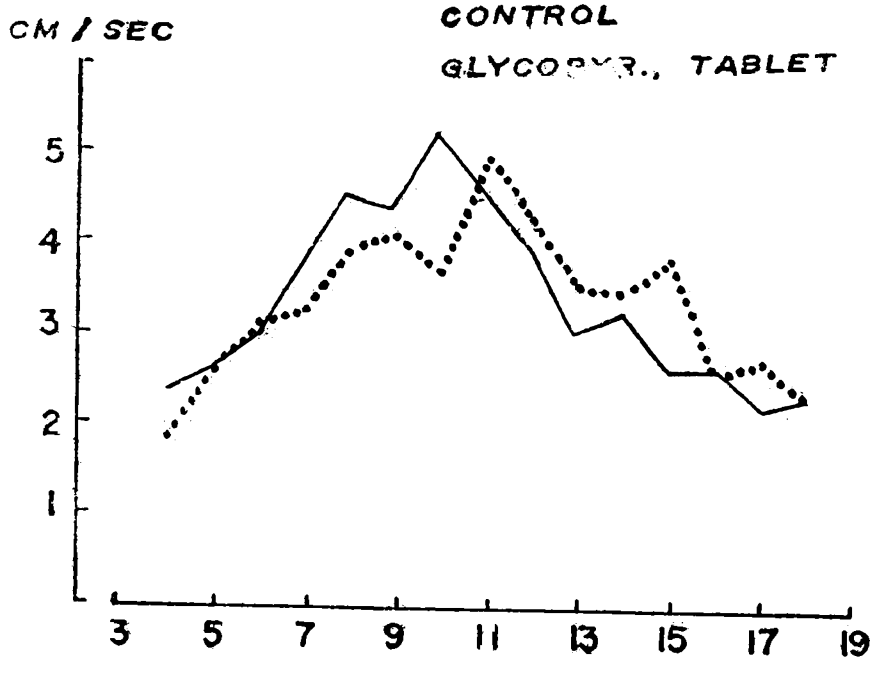

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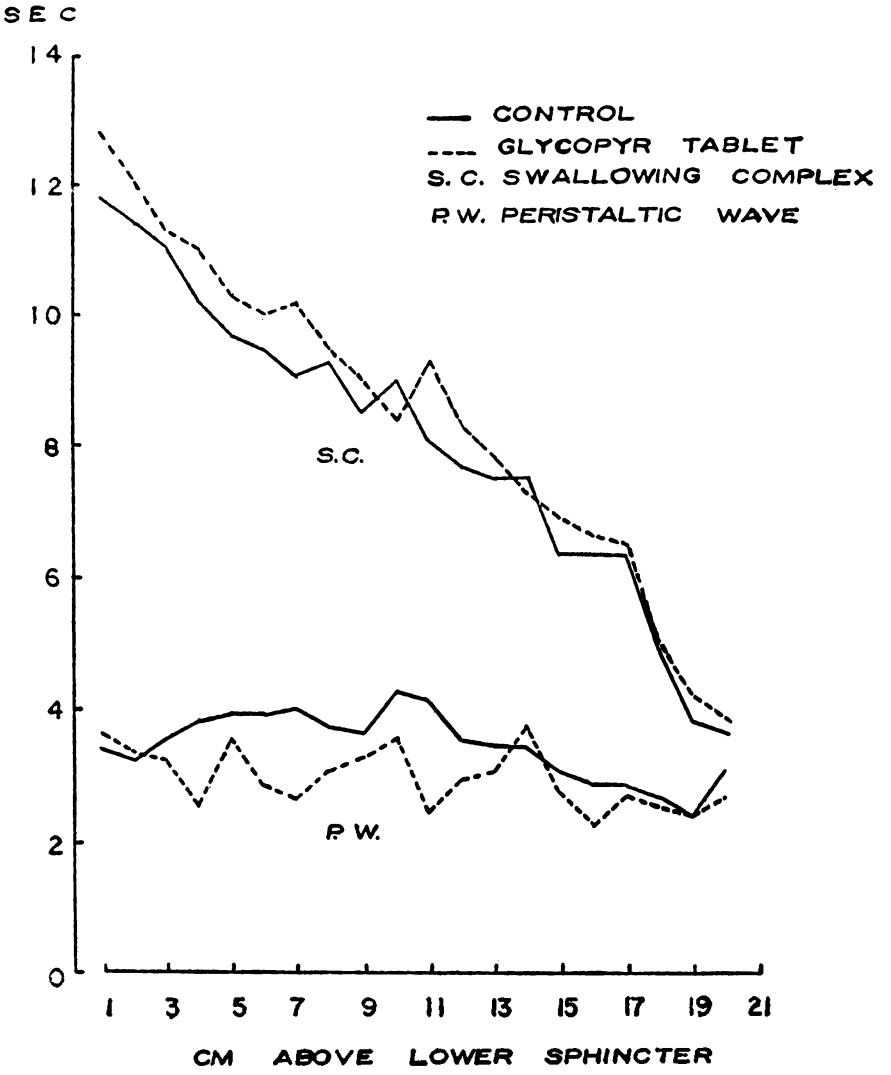

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