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EVALUATION OF THE ANTICHOLINERGIC ACTIONS OF GLYCOPYRRONIUM BROMIDE

R.K. MIRAKHUR, J.W. DUNDEE & C.J. JONES

Department of Anaesthetics, Queen's University of Belfast, Belfast, Northern Ireland and A.H. Robins & Company Ltd, Horsham, Sussex

1 Glycopyrronium was evaluated by intramuscular, intravenous and oral routes in six adult volunteers for its efficacy as an antisialogogue as also for its action on other aspects of cholinergic activity.

2 It was found to be an effective antisialogogue of long duration of action by all three routes. When given orally the effects were delayed in onset and persisted for too long. Intramuscular and intravenous routes were useful. The intramuscular absorption of the drug is rapid and consistent.

3 Sweat gland activity was affected in a similar fashion but less consistently and other parameters were mostly unaffected.

4 Glycopyrronium 0.2 mg intramuscularly was found to be the optimal dose. Larger doses produced subjective discomfort out of proportion to a further reduction in salivary secretion.

5 Intravenous administration causes no changes in cardiovascular stability.

Introduction

Despite their popularity as antisialogogues atropine and hyoscine have certain disadvantages. Both are tertiary compounds and as such cross the blood brain barrier producing some central effects. While the sedative action of hyoscine is beneficial in preoperative medication its use is occasionally associated with restlessness. Hyoscine has a more potent antisialogogue action than atropine (Leigh & Belton, 1946; West & Papper, 1950; Wyant & Dobkin, 1957) but it has a less marked action on the cardiac vagus (Griggs & Adriani, 1954; Orkin, Bergman & Nathanson, 1956). On the other hand Wyant & Dobkin (1957) found atropine to be a less predictable and a less potent antisialogogue. It may cause restlessness, tachycardia and arrhythmias. In addition both drugs have a short duration of action (Wangeman & Hawk, 1942; Eger, 1962).

While investigating a number of pyrrolidinol derivatives Franko & Lunsford (1960) found glycopyrronium bromide (Glycopyrrolate USNF) to be a potent anticholinergic agent. This is a water soluble quaternary ammonium compound (Figure 1) with a molecular weight of 398.34. It is used in the control of gastric hyperacidity (Sun, 1962; Moeller, 1962). Being unable to pass the blood brain barrier, glycopyrrolate is devoid of any central activity. It has been shown to be a long acting effective antisialogogue when used by the intravenous route (Wyant & Kao, 1974), with no serious side effects.

Before evaluating it as an anticholinergic agent in routine preoperative medication it was planned to study it in depth in a limited number of volunteers with emphasis on its efficacy and duration of action as an antisialogogue and to assess its effects on other aspects of cholinergic function. This evaluation also involved a comparison of its efficacy at different dose levels and when given by the intramuscular, intravenous and oral routes. The oral route was included because of the particular interest of this department in oral premedication.

Method

The study was carried out on six adult volunteers to whom its purpose was explained and their consent obtained. Each volunteer had nine doses of the drug by three routes given in a random order. These were 0.1, 0.2 and 0.4 mg intramuscularly, 0.1, 0.14 and 0.2 mg intravenously and 2.0, 4.0 and 8.0 mg orally. These doses were selected after initial pilot studies and from known data about the drug. The study was limited to the first 6 h after the drug administration though any subjective effects were recorded as long as the volunteers would report them. An interval of at least 1 week was allowed between successive tests in any one individual.

All studies were carried out in the same air conditioned room with well controlled temperature and relative humidity. The volunteers rested for at least 30 min before the baseline observations were recorded. All tests were carried out from mid morning

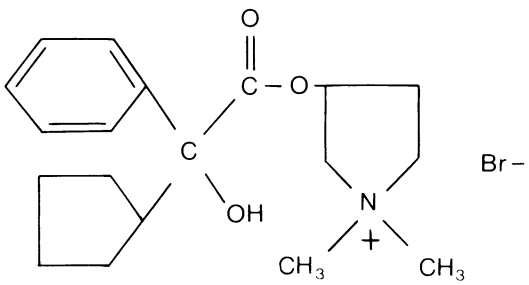

Figure 1 Structural formula of glycopyrronium bromide (glycopyrrolate USNF; 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide).

onwards for 6 h and a standard lunch was taken between the third and fourth hours. Smoking and caffeine-containing drinks were avoided during the period of study but no restriction was placed on fluid intake.

The following parameters were studied at 30 and 60 min and at hourly intervals thereafter for 6 hours:

1. Heart rate measured from the radial pulse for a 1 min period.
2. Blood pressure measured indirectly using the cuff and stethoscope and recorded as mean arterial pressure (diastolic blood pressure plus one-third of the pulse pressure).
3. Oral temperature taken with a standard clinical thermometer.
4. Pupillary measurements made using a transparent pupil gauge (MIE). The size of the pupil is matched against the holes of a gradually increasing diameter when the gauge is placed in front of the eye. These measurements were made under the standard lighting conditions in the room and when a light was shone on the eye.
5. Visual near point measured using an R.A.F. near point scale. A set of letters is brought towards the eye with the instrument kept on the bridge of the nose. The near point is where the absolute clarity of the letters is lost.
6. Sweat gland activity tested according to the method of Wada (1950). A marked area on one of the finger tips is painted with 3% iodine in ethyl alcohol and when dry a paste of starch in castor oil is rubbed in. The excess is then removed leaving a thin covering film. The finger tip is examined under a magnifying glass for small black dots which represent the active sweat glands. The stain is removed with a 15% solution of sodium thiosulphate and the same area is used each time.
7. Salivary secretion measured according to a modification of the method described by Mushin, Galloon & Lewis-Faning (1953). The subject first swallows all the saliva in his mouth. Citric acid 4% (0.2 ml) is placed under the tongue and allowed to remain there for 30 s when 4 ml of water is put into the mouth. After a further 15 s all the contents of the mouth are collected in a measuring jar. The saliva is collected in the same jar over the next 5 min. Any froth at the top is cleared by the addition of one or two drops of capryl alcohol. The net salivary secretion is the total volume in the jar less 4.2 ml.

A Wilcoxon matched-pairs signed-ranks test was applied to determine the statistical significance of the results.

Results

The mean ± s.e. mean ages and weights of the volunteers were 32 ± 1.7 years and 62 ± 6.1 kg respectively.

Effects on salivary secretion

There was great individual variation in the salivary secretion before any drug was given. The effects of the drug varied in a dose-related manner from slight with lower doses to a marked and persistent effect with higher doses (Figure 2). The intramuscular injection of 0.1 mg caused a maximum reduction in salivary secretion to about 38% (7.0 ml to 4.4 ml) at 2 h, this being a significant ($P<0.05$) reduction. Apart from this 0.1 mg intramuscularly produced insignificant reduction in salivation throughout the period of study. Figure 2 shows that the higher doses tended to produce an early and profound effect on salivary secretion. This was reduced to about 35% (6.5 ml to 2.2 ml) and 25% (6.5 ml to 1.6 ml) at 1 or 2 h respectively after 0.2 mg intramuscularly and was significantly depressed up to 4 h after administration. With 0.4 mg intramuscularly the depression in salivation was significant throughout the period of study and secretion was less than 15% of its original volume (6.7 ml to 0.8 ml) between 1 and 3 h.

As expected the effects came on earlier after intravenous administration. The depression in salivary secretion following the smallest dose of the drug did not reach significant levels. Significant ($P<0.025$) depression however did occur from 1 to 3 h with 0.14 mg and throughout the period of study when 0.2 mg was given intravenously, with a maximum depression in the latter case to about 25% of control value (7.0 to 1.7 ml) at 1 h.

When given orally 2.0 mg had little effect, 4.0 mg caused significant depression from 4 to 6 h (maximum to 50% of control value at 6 h), while with 8.0 mg, significant reduction occurred after 3 h.

Figure 3 shows the dose response curves for the maximum reduction in salivary secretion irrespective of time at which this occurred. The linearity indicates the predictability of response. Poor absorption after

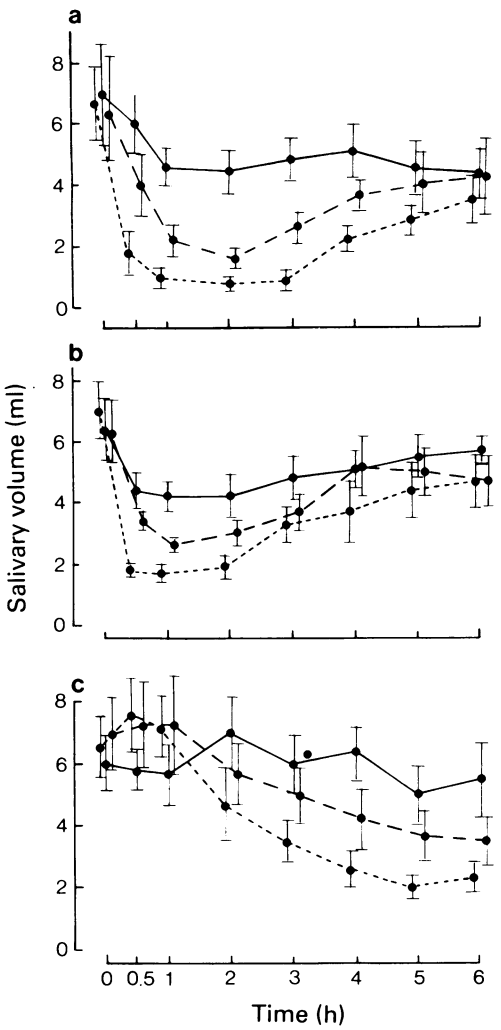

Figure 2 Effects of glycopyrronium administered by (a) intramuscular (— 0.1 mg; — — 0.2 mg; - - - - 0.4 mg), (b) intravenous (— 0.1 mg; — — 0.14 mg; - - - 0.2 mg) and (c) oral (— 2 mg; — — 4 mg; - - - - 8 mg) routes on salivary secretion (mean ± s.e. mean over a period of 6 h).

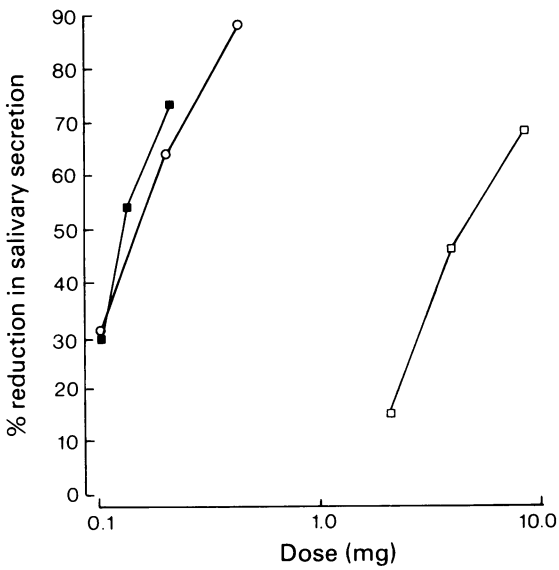

Figure 3 Dose response after glycopyrronium administration (○ intramuscular; ■ intravenous; □ oral) on salivary secretion. The oral dosage to achieve a 50% reduction in salivary secretion was about 35 times the parenteral dose.

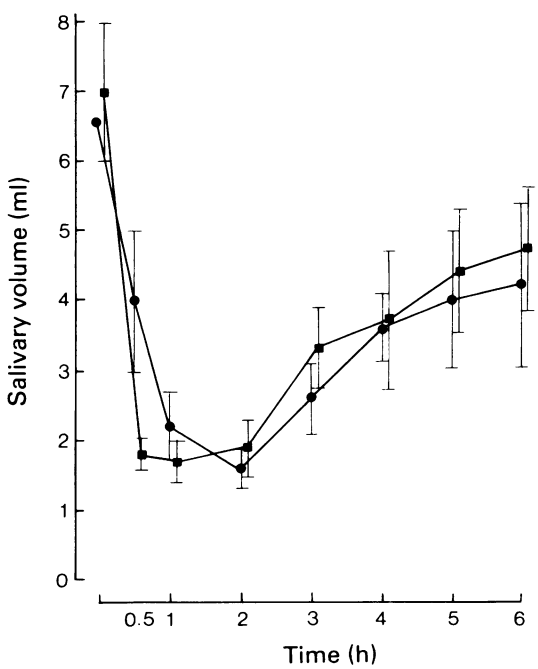

Figure 4 Comparison of the mean ± s.e. mean effects of 0.2 mg glycopyrronium given by intramuscular (●) and intravenous (■) routes on salivary secretion. The effects are indistinguishable except at 0.5 h.

oral administration is demonstrated by the fact that for a 50% reduction in salivary secretion, the oral dose needs to be about 35 times the parenteral dose.

A comparison of the effects of 0.2 mg of glycopyrronium intramuscularly and intravenously on salivary secretion (Figure 4) showed a remarkable similarity except for the 30 min observation when the intramuscularly administered drug exerted about half the effect of the same dose given intravenously.

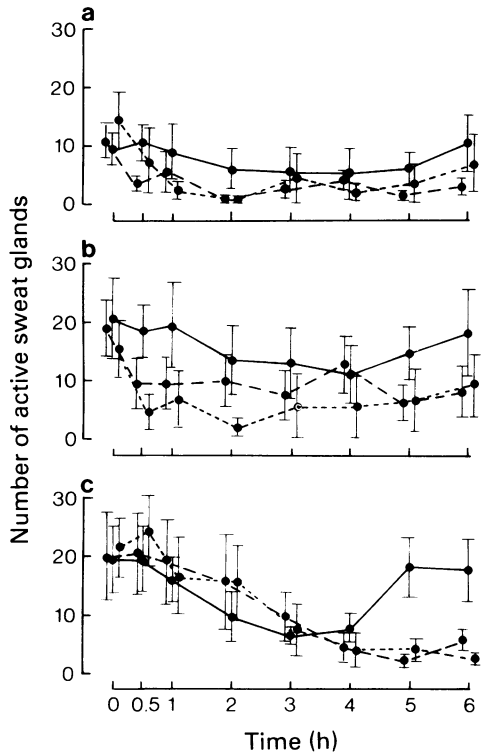

Figure 5 Effects of glycopyrronium administered by (a) intramuscular (— 0.1 mg; – – 0.2 mg; - - - - 0.4 mg), (b) intravenous (— 0.1 mg; – – 0.14 mg; - - - - 0.2 mg) and (c) oral routes (—— 2 mg; – – 4 mg; - - - - 8 mg) on active sweat glands (mean ± s.e. mean over a period of 6 h).

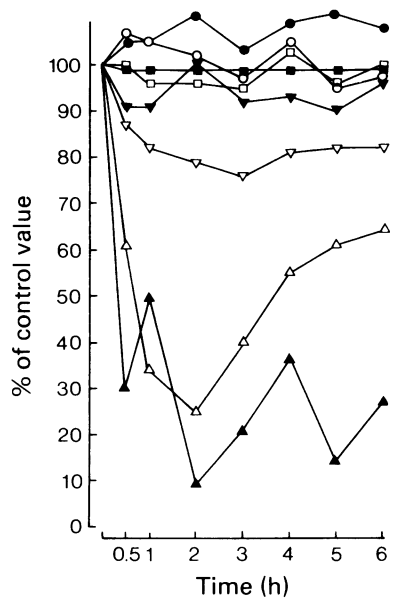

Figure 6 Effects of glycopyrronium 0.2 mg intravenously on various parameters (○ pupil (bright light); □ pupil (dim light); ● near point; ■ temperature; △ salivary secretion; ▲ sweat glands; △ heart rate; ▲ blood pressure). It demonstrates clearly that only sweat gland activity and salivary secretion are affected.

Effects on sweat gland activity

The control values for the count of active sweat glands showed even larger individual variations than those for salivary secretion. In general, a significant diminution in the number of active sweat glands, while occurring less often and with less consistency, paralleled the depression in salivary secretion. The effects were less obvious with the lower dose of the drug (Figure 5) and again came on late when the oral route was employed.

Effects on other parameters

The effects on pupillary size (in room light and with bright light on the eye), near point of vision and heart rate are given in Tables 1, 2 and 3. The changes were minimal, inconsistent and statistically not significant. There was however some slowing in heart rate. Blood pressure and temperature showed only minimal variations over the 6 h period of study.

Figure 6 shows the effects of a representative dose (0.2 mg glycopyrronium intramuscularly) on all the parameters. It clearly demonstrates that those affected by the drug are only sweat gland activity and salivary secretion apart from slight lowering of the heart rate; other parameters remaining largely unaffected.

Subjective impressions

Three out of six volunteers felt drowsy at different times after drug administration. This did not appear to be a dose related effect and no detailed evaluation of this aspect was attempted. Headache was occasionally reported. There was some pain on injection when the largest dose of the drug was administered intramuscularly.

The most consistent and common feeling was a dryness of the mouth for prolonged periods, persisting for nearly 24 h after oral intake. Even after intramuscular and intravenous administration subjective dryness persisted for about 8 h.

Discussion

This study was designed to evaluate the efficacy of glycopyrronium bromide as an antisialogogue and to

Table 1 Effect of glycopyrrolate on pupil size (mean ± s.e. mean). The values in brackets are when the pupils are under bright light.

	Glycopyrronium bromide								
	Intramuscular (mg)			*Intravenous (mg)*			*Oral (mg)*		
Time (h)	0.10	0.20	0.40	0.10	0.14	0.20	2.0	4.0	8.0
	Pupil size (mm)								
Control	4.83 ± 0.30 (3.50 ± 0.22)	5.83 ± 0.40 (4.00 ± 0.25)	4.75 ± 0.30 (3.41 ± 0.20)	4.66 ± 0.21 (3.33 ± †.21)	4.66 ± 0.42 (3.16 ± 0.30)	5.33 ± 0.42 (3.50 ± 0.22)	5.33 ± 0.21 (3.83 ± 0.16)	5.66 ± 0.42 (3.66 ± 0.21)	4.83 ± 0.30 (3.16 ± 0.40)
0.5	5.00 ± 0.36 (3.33 ± 0.21)	5.83 ± 0.40 (4.33 ± 0.21)	5.00 ± 0.25 (3.50 ± 0.22)	4.33 ± 0.21 (3.00 ± 0.00)	4.16 ± 0.16 (3.00 ± 0.00)	4.75 ± 0.30 (3.16 ± 0.16)	5.16 ± 0.30 (3.50 ± 0.22)	5.83 ± 0.40 (3.66 ± 0.21)	4.83 ± 0.30 (3.16 ± 0.30)
1	5.16 ± 0.30 (3.33 ± 0.21)	5.66 ± 0.49 (4.25 ± 0.24)	5.16g80.40 (3.16 ± 0.16)	4.66 ± 0.21 (3.33 ± 0.21)	4.33 ± 0.21 (3.00 ± 0.00)	5.16 ± 0.16 (3.33 ± 0.21)	5.50 ± 0.42 (3.33 ± 0.21)	5.66 ± 0.33 (3.66 ± 0.21)	4.83 ± 0.40 (3.66 ± 0.21)
2	4.66 ± 0.33 (3.16 ± 0.16)	5.66 ± 0.37 (4.16 ± 0.33)	5.16 ± 0.30 (3.33 ± 0.21)	4.66 ± 0.21 (3.33 ± 0.21)	4.33 ± 0.21 (3.16 ± 0.16)	4.66 ± 0.33 (3.33 ± 0.21)	5.50 ± 0.22 (3.66 ± 0.21)	5.50 ± 0.42 (3.66 ± 0.33)	4.58 ± 0.61 (3.33 ± 0.33)
3	5.00 ± 0.36 (3.16 ± 0.30)	5.50 ± 0.22 (3.91 ± 0.32)	5.16 ± 0.40 (3.50 ± 0.34)	4.66 ± 0.21 (3.16 ± 0.16)	4.66 ± 0.33 (3.16 ± 0.16)	4.83 ± 0.30 (3.00 ± 0.25)	5.33 ± 0.33 (3.66 ± 0.33)	5.33 ± 0.33 (3.66 ± 0.21)	5.00 ± 0.36 (3.16 ± 0.16)
4	5.00 ± 0.25 (3.33 ± 0.21)	6.00 ± 0.34 (4.25 ± 0.30)	5.33 ± 0.42 (3.33 ± 0.21)	5.00 ± 0.36 (3.50 ± 0.22)	4.50 ± 0.34 (3.00 ± 0.00)	4.16 ± 0.16 (3.00 ± 0.25)	5.16 ± 0.30 (3.33 ± 0.21)	5.16 ± 0.30 (3.16 ± 0.16)	5.00 ± 0.36 (3.50 ± 0.22)
5	4.83 ± 0.40 (3.50 ± 0.22)	5.66 ± 0.42 (3.83 ± 0.38)	5.00 ± 0.25 (3.16 ± 0.16)	4.83 ± 0.16 (3.50 ± 0.22)	4.41 ± 0.27 (3.03 ± 0.20)	4.83 ± 0.30 (3.16 ± 0.30)	5.66 ± 0.33 (3.66 ± 0.21)	5.33 ± 0.33 (3.66 ± 0.33)	5.00 ± 0.36 (3.33 ± 0.21)
6	4.66 ± 0.33 (3.16 ± 0.16)	5.83 ± 0.38 (3.91 ± 0.32)	5.16 ± 0.40 (3.66 ± 0.33)	5.16 ± 0.47 (3.66 ± 0.49)	4.33 ± 0.33 (2.66 ± 0.21)	5.00 ± 0.25 (3.33 ± 0.21)	5.16 ± 0.30 (3.50 ± 0.22)	5.33 ± 0.42 (3.66 ± 0.21)	5.00 ± 0.25 (3.50 ± 0.22)

Table 2 Effect of glycopyrrolate on visual near point (mean ± s.e. mean)

	Glycopyrronium bromide								
	Intramuscular (mg)			*Intravenous (mg)*			*Oral (mg)*		
Time (h)	0.1	0.2	0.4	0.1	0.14	0.20	2.0	4.0	8.0
	Visusal near point (dioptres)								
Control	8.21 ± 0.40	9.50 ± 0.34	8.36 ± 0.34	8.28 ± 0.63	8.48 ± 0.37	8.30 ± 0.45	9.06 ± 0.75	9.50 ± 0.65	9.58 ± 0.89
0.5	8.30 ± 0.38	9.15 ± 0.28	8.66 ± 0.33	7.98 ± 0.56	8.00 ± 0.68	8.03 ± 0.50	9.40 ± 0.74	9.63 ± 0.44	9.56 ± 0.66
1	8.20 ± 0.58	9.00 ± 0.48	7.95 ± 0.46	7.78 ± 0.68	7.65 ± 0.69	8.11 ± 0.59	9.36 ± 0.73	9.06 ± 0.66	9.41 ± 0.76
2	8.08 ± 0.3p	8.73 ± 0.53	8.06 ± 0.52	7.50 ± 0.59	8.21 ± 0.34	7.81 ± 0.46	9.03 ± 0.94	9.20 ± 0.58	9.41 ± 0.93
3	8.00 ± 0.31	8.91 ± 0.38	7.78 ± 0.50	7.53 ± 0.65	8.65 ± 0.45	7.73 ± 0.63	9.16 ± 0.70	9.18 ± 0.75	9.55 ± 0.89
4	7.80 ± 0.34	8.78 ± 0.49	7.78 ± 0.46	7.51 ± 0.69	8.35 ± 0.36	7.76 ± 0.42	9.11 ± 0.86	8.90 ± 0.70	9.40 ± 0.78
5	8.05 ± 0.36	8.61 ± 0.53	7.98 ± 0.40	7.65 ± 0.56	8.38 ± 0.44	7.80 ± 0.62	8.88 ± 1.00	8.53 ± 0.87	9.20 ± 0.79
6	7.91 ± 0.31	9.26 ± 0.43	7.81 ± 0.59	8.13 ± 0.65	8.38 ± 0.44	8.06 ± 0.68	9.45 ± 0.70	8.08 ± 0.91	8.73 ± 0.78

Table 3 Effects of glycopyrrolate on heart rate (mean ± s.e. mean)

	Glycopyrronium bromide								
	Intramuscular (mg)			*Intravenous (mg)*			*Oral (mg)*		
Time (h)	0.10	0.20	0.40	0.10	0.14	0.20	2.0	4.0	8.0
	Heart rate (beats/min)								
Control	82.8 ± 1.72	90.0 ± 4.47	82.1 ± 3.70	75.8 ± 4.21	80.3 ± 3.59	81.3 ± 3.92	82.1 ± 4.10	87.3 ± 3.78	74.0 ± 4.00
0.5	75.6 ± 2.84	78.3 ± 4.27	78.3 ± 3.94	77.5 ± 4.70	68.6 ± 3.74	72.1 ± 4.73	77.5 ± 2.09	79.3 ± 3.16	71.0 ± 3.99
1	71.0 ± 2.17	74.0 ± 3.50	81.3 ± 3.67	65.3 ± 3.67	64.0 ± 4.97	68.3 ± 4.27	74.6 ± 3.37	75.0 ± 2.51	68.6 ± 4.99
2	67.6 ± 4.27	71.6 ± 2.25	78.5 ± 4.31	65.5 ± 5.00	66.0 ± 4.56	71.3 ± 4.63	68.0 ± 4.13	72.6 ± 4.46	61.6 ± 3.51
3	63.6 ± 4.27	68.6 ± 3.78	71.3 ± 6.05	68.5 ± 2.91	64.6 ± 4.05	67.3 ± 4.86	65.3 ± 5.23	69.0 ± 3.71	62.3 ± 6.58
4	64.0 ± 4.61	73.0 ± 3.33	72.3 ± 5.07	68.6 ± 4.75	66.3 ± 2.84	71.6 ± 3.51	69.3 ± 3.95	69.6 ± 3.94	66.3 ± 5.27
5	71.0 ± 3.71	73.6 ± 4.36	75.8 ± 5.64	67.6 ± 4.80	68.6 ± 2.85	72.3 ± 4.14	69.3 ± 3.67	74.6 ± 4.34	69.3 ± 2.85
6	68.6 ± 3.04	73.6 ± 5.61	66.6 ± 5.52	70.5 ± 4.37	70.0 ± 3.93	70.3 ± 4.68	70.6 ± 3.95	75.3 ± 5.20	72.3 ± 6.54

assess its effects on other parameters of cholinergic function. The method of Mushin *et al.* (1953) was preferred for study of the antisialogogue action to that used by Wyant & Dobkin (1957) in which the secretion from one gland only is considered. There are great variations in the secretion of salivary glands even in the same person and the method of Mushin *et al.* (1953) which takes account of the total secretions present is of more clinical interest. The drug was found to be an effective antisialogogue especially when administered by the intramuscular and intravenous routes. The effects were however minimal with the smallest doses given by each route.

Wyant & Kao (1974) using the intravenous route also found intense and prolonged reduction in salivary secretions with this drug in comparison to atropine. There was a considerable delay in attaining a significant reduction when the drug was taken by mouth though some reduction was obtained from about 2 h onwards. This was not unexpected since quaternary ammonium compounds are known to be poorly absorbed from the gastro-intestinal tract (Innes & Nickerson, 1975) as are water soluble substances (Lancet, 1975) of which this is one. The delayed onset of action when administered orally may be clinically acceptable if the drug is being taken on a regular basis for a medical condition, but would be unlikely to be acceptable in a premedicant.

Water solubility is considered to be a factor which delays absorption after both intramuscular injection and oral administration (Lancet, 1975). However Jonkman, Wijsbeek, Boer, de Zeeuw, van Bork & Orie (1975) showed good intramuscular absorption of thiazinamium, a quaternary water soluble anticholinergic compound. We also observed a remarkable similarity in the effects of equivalent doses of glycopyrronium administered intramuscularly and intravenously. We would hence consider water solubility to be a favourable factor for absorption after intramuscular injection and this property makes glycopyrronium a useful and reliable drug for intramuscular administration. Poor absorption after oral administration has already been mentioned (see results).

The effects of glycopyrronium were most profound on salivary secretion and sweat gland activity while other parameters remained largely unaffected (Figure 4). This may in part be a reflection of poor penetration of a quaternary compound, but although this may be true for the blood-aqueous humour barrier, it is unlikely to explain its lack of action on the heart. In comparing the anticholinergic activity of certain atropine-like drugs, Herxheimer (1958) found that the quaternary drugs methanthelinium, propantheline and oxyphenonium had a greater action on heart rate than atropine itself. He also found that changes in salivation, sweating and heart rate appeared sooner than changes in the pupillary size and the visual near point. The changes in heart rate were minimal with glycopyrronium. There was an insignificant slowing in heart rate but there was no tachycardia throughout the 6 h period of observation even with the highest doses employed in this investigation. The initial slowing of heart rate with small doses of atropine and similar drugs is considered to be a stimulant effect on medullary vagal nuclei and is not usually seen after large doses given intravenously (Morton & Thomas, 1958; Innes & Nickerson, 1975). It seems therefore that glycopyrronium *per se* does not have much effect on heart rate.

Another possible explanation could be the 'rigid ring' structure of glycopyrronium which endows it with the property of specificity of action. It is however not clear which of the end organs are specifically affected by such a structure.

Changes in salivary secretion appeared to be a more reliable index of anticholinergic activity than the activity of sweat glands although there was a fairly good correlation between the two parameters. In contrast, Juniper (1967) while evaluating the use of glycopyrronium for peptic ulcer disease, found that the sweat gland activity was a better index than salivary secretion in the assessment of anticholinergic activity. We found that minute to minute variations were greater in the sweat gland activity.

The occasional occurrence of drowsiness unrelated to dosage and route is difficult to explain in view of the poor passage of quaternary ammonium compounds across the blood-brain barrier (Paton & Zaimis, 1952). Prolonged observations over a 6 h period in one place may have induced sleepiness. No explanation can be offered for the occasional occurrence of headache which has not been reported by others.

This study suggests that glycopyrronium is a potent antisialogogue, and that its actions on heart and eye are minimal. However, in view of the long duration of action its usefulness would be greatest in cases of moderate to long duration. While the delayed onset of action of the drug which given orally would make it unsuitable for routine premedication given 60 to 90 min preoperatively, it could be used for long operating lists with cases of uncertain duration. The drug has only minimal central effects which is an advantage. Its advantageous use with neostigmine at the time of reversal of neuromuscular block has already been established and it would seem worthy of a trial for routine preoperative medication.

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