

## COMPARISON OF ATROPINE AND GLYCOPYRROLATE IN A MIXTURE WITH PYRIDOSTIGMINE FOR THE ANTAGONISM OF NEUROMUSCULAR BLOCK

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### SUMMARY

Neuromuscular block was antagonized using pyridostigmine  $250 \mu\text{g kg}^{-1}$  in two groups of 50 patients; one group received atropine  $20 \mu\text{g kg}^{-1}$  and the other glycopyrrolate  $10 \mu\text{g kg}^{-1}$  with the anticholinesterase drug. Atropine was associated with a greater initial tachycardia than was glycopyrrolate. The subsequent bradycardia was also greater in this group, although the decreases in heart rate were smaller than those generally observed following mixtures of atropine and neostigmine. Arrhythmias were transient and required no treatment in either group. Better control of secretions was achieved with glycopyrrolate.

Although neostigmine is the drug used most commonly to reverse residual neuromuscular block, pyridostigmine may have certain advantages such as a longer duration of action, a greater therapeutic ratio, and less pronounced muscarinic effects (Katz, 1967; Miller, 1976; Gyermek, 1977).

The advantages of glycopyrrolate over atropine as the antimuscarinic agent (Mirakhur, 1979) include greater stability of heart rate, better protection against secretions and absence of central effects (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977; Baraka et al., 1980; Cozanitis et al., 1980).

In the present study, glycopyrrolate or atropine was administered with pyridostigmine during the reversal of neuromuscular block and their effects compared, emphasis being placed on the effects of the two drugs on heart rate and rhythm, and on oropharyngeal secretions.

### PATIENTS AND METHODS

The study was carried out in 100 adult patients, free from any cardiovascular, respiratory, metabolic or endocrine disorder. All the patients

gave informed consent and the study was approved by the Regional Ethics Committee. The patients were undergoing anaesthesia requiring the use of myoneural blocking drugs. Following premedication with diazepam by mouth, anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and halothane or a combination of fentanyl and droperidol administered i.v. The two techniques of anaesthesia were administered in random fashion. Pancuronium was used to provide neuromuscular blockade. Fluids and blood were administered i.v. as appropriate. The adequacy of ventilation in all the patients was assessed by analyses of arterial blood-gas tensions and adjustments were made, if necessary, to maintain  $P_{a\text{CO}_2}$  between 4.65 and 5.98 kPa. Before the administration of the reversal mixture, the oropharynx was sucked free of secretions. Lead II of the electrocardiogram (e.c.g.) was monitored throughout the operation. Recording was started 1 min before the administration of the antagonist mixture which consisted of pyridostigmine  $250 \mu\text{g kg}^{-1}$  with glycopyrrolate  $10 \mu\text{g kg}^{-1}$  or atropine  $20 \mu\text{g kg}^{-1}$ . The anticholinergic drugs were administered double-blind from specially prepared, coded ampoules. The recording was continued until 10 min following the administration of the antagonizing mixture. Systolic arterial pressure was recorded at 1-min intervals during this time and then heart rate and arterial pressure were recorded at intervals, for a further 110 min, in

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the recovery ward (table II). A further increment of 1 ml of the anticholinergic drug (atropine 0.4 mg or glycopyrrolate 0.2 mg) was administered if the heart rate decreased to 50 beat min<sup>-1</sup> or less in any patient.

As soon as the patient started to reject the endotracheal tube, the oropharynx was suctioned, secretions arbitrarily classified as "minimal", "moderate" or "excessive" and the trachea extubated.

The e.c.g.'s were analysed in detail for changes in rate and rhythm. Student's *t* tests were used for the statistical analyses of the changes in heart rate and a Chi-squared test for non-parametric data.

### RESULTS

The 50 patients in each group were well matched with regard to their physical characteristics (table I).

Heart rates before the administration of the antagonist mixture were similar in both groups. There was no difference in the pattern of the changes in heart rate between the patients given fentanyl-droperidol or halothane for the maintenance of anaesthesia. Heart rates over the 120 min are shown in table II and the percentage change from values before antagonism in figure 1. The administration of the atropine-containing mixture increased the heart rate from 85 to a maximum of 98 beat min<sup>-1</sup> (16%) at 1 min. The mean heart rate decreased subsequently and was less than control from 4 min, the maximal decrease being about 9% at 10 min. The increases at 1 and 2 min, and the decreases in rate from 4 to 90 min were significant.

The initial increase in heart rate in the group receiving glycopyrrolate was significant over the first 6 min, reaching a maximum of about 9% at 2 min. The rate remained not significantly greater than the control value for up to 20 min. Subsequently, this decreased marginally below the baseline heart rate. This decrease was significant at 50 min, although the heart rate had decreased only 4 beat min<sup>-1</sup> at this time. Figure 1 demonstrates the difference in the pattern of the changes in heart rate between the two anticholinergic drugs. The atropine-containing mixture was associated with a significantly greater increase in heart rate at 1 min in comparison with the glycopyrrolate-containing mixture, but this was followed quickly by a greater decrease which was significant in comparison with the glycopyrrolate group between 4 and 10 min.

TABLE I. Physical characteristics of the patients

Group	Number	Mean age (yr ± SEM)	Mean weight (kg ± SEM)	Sex	
				M	F
Atropine	50	48 ± 1.9	65 ± 1.5	22	28
Glycopyrrolate	50	47 ± 2.2	65 ± 1.8	23	27

TABLE II. Heart rates following the administration of atropine or glycopyrrolate combined with pyridostigmine (mean ± SEM). Significantly different from value before antagonism: \**P* < 0.05; †*P* < 0.005; \*\*\**P* < 0.001

Time (min)	Group	
	Glycopyrrolate	Atropine
Before antagonism	83 ± 1.8	85 ± 2.3
1	85 ± 1.9	98 ± 2.4***
2	90 ± 2.1***	92 ± 2.2***
3	90 ± 2.2***	87 ± 2.4
4	89 ± 2.3†	81 ± 2.5
5	88 ± 2.2*	79 ± 2.4*
6	88 ± 2.2*	79 ± 2.4†
7	86 ± 2.2	79 ± 2.3†
8	86 ± 2.3	77 ± 2.2***
9	87 ± 2.3	77 ± 2.1***
10	86 ± 2.3	76 ± 2.1***
20	81 ± 1.9	78 ± 2.2*
30	81 ± 1.9	79 ± 2.0*
40	80 ± 1.8	80 ± 2.0*
50	79 ± 1.5*	79 ± 1.8*
60	80 ± 1.5	79 ± 2.1*
75	81 ± 1.7	79 ± 1.9*
90	80 ± 1.7	80 ± 2.0*
105	81 ± 1.8	81 ± 1.9
120	81 ± 1.8	81 ± 1.9

The heart rate in three patients in the atropine group decreased to 50 beat min<sup>-1</sup> or less. Two of these received one additional dose of atropine; one required two additional doses. This was not required in any of the patients receiving glycopyrrolate.

The frequency of arrhythmia (table III) was slightly greater in the group receiving atropine. One of the patients in this group showed persistent ventricular ectopic beats in a trigeminal fashion. Overall, the arrhythmias were not serious and did not warrant treatment.

Changes in arterial pressure were clinically insignificant in both groups.

Investigation of the amount of oropharyngeal secretions (table IV) showed that the group receiving glycopyrrolate had a higher proportion of patients with "minimal" secretions (*P* < 0.01).

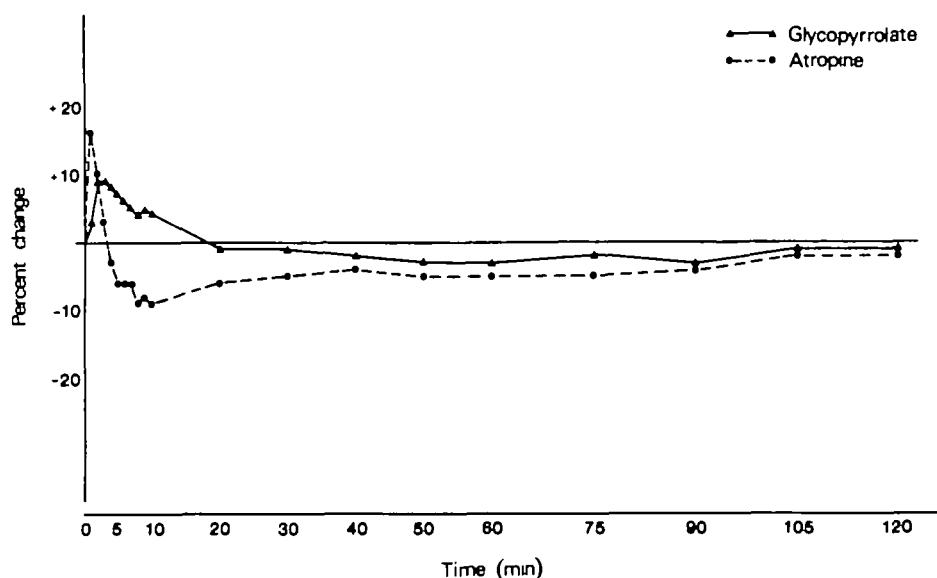


FIG. 1. Percentage changes in heart rate following the administration of reversal mixtures.

TABLE III. Number of patients showing arrhythmia. \*Present before antagonism in one patient; \*\*Present before antagonism in two patients

Group	Total number of patients	Increased PR interval	Nodal/junctional rhythm	Wandering pacemaker	Atrial ectopic beats	Atrial tachycardia + increased QT interval	Ventricular ectopic beats
Atropine-pyridostigmine	13	0	3	2	1	1	6* (one in trigeminal fashion)
Glycopyrrolate-pyridostigmine	9	1	3	1	0	0	4**

TABLE IV. Number of patients with various grades of oropharyngeal secretions. \*Significantly different from atropine group ( $P < 0.01$ )

Group	Grade of secretion		
	Minimal	Moderate	Excessive
Atropine	13	33	4
Glycopyrrolate	28*	20*	2*

## DISCUSSION

The present study demonstrated certain advantages in the use of glycopyrrolate, when compared with atropine, as the anticholinergic component of the antagonist mixture when pyridostigmine was used to antagonize residual

neuromuscular block. There was less tachycardia immediately following administration of the drug and better protection against subsequent bradycardia. In addition, no patient receiving glycopyrrolate had a heart rate of  $50 \text{ beat min}^{-1}$  or less whereas a further administration of atropine was required in three patients in the atropine group. Similar results were reported when glycopyrrolate was used in a mixture with neostigmine (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977; Cozanitis et al., 1980).

The present combination of pyridostigmine and atropine appears to be superior to the combination of neostigmine and atropine studied previously (Mirakhur et al., 1981) because bradycardia was

less pronounced. Similar results were obtained by Eriksen, Hansen and Hasselstrom (1978). Only 6% of those patients in the present study receiving atropine and pyridostigmine required additional doses of atropine in comparison with 30% in our previous study in which atropine in a similar dose was administered with neostigmine (Mirakhur et al., 1981). In the study of Eriksen, Hansen and Hasselstrom (1978) greater initial increases in heart rate were observed with the use of atropine in a pyridostigmine-containing mixture, but the subsequent decreases in heart rate were also greater compared with glycopyrrolate.

The use of a combination of pyridostigmine and glycopyrrolate does not appear to have any advantages over a combination of glycopyrrolate with neostigmine when the data from the present study are compared with previous reports (Mirakhur, Dundee and Clarke, 1977; Cozanitis et al., 1980; Mirakhur et al., 1981). Muravchick, Owens and Felts (1979) found a mixture of glycopyrrolate and neostigmine to be superior to a mixture of glycopyrrolate and pyridostigmine in elderly patients. In contrast to our previous studies involving glycopyrrolate and neostigmine (Mirakhur, Dundee and Clarke, 1977; Mirakhur et al., 1981), a significant initial tachycardia was observed with the glycopyrrolate-pyridostigmine mixture, but this was significantly less than that produced by the atropine-containing mixture. This could be expected for two reasons. First, since pyridostigmine is known to possess less marked muscarinic effects than neostigmine (Katz, 1967; Miller, 1979), the effects of concomitantly administered anticholinergic drugs are consequently more pronounced. Second, the initial increase in heart rate induced by glycopyrrolate may be more apparent since the effects of this drug become evident before those of pyridostigmine. Mirakhur, Jones and Dundee (1981), have shown that glycopyrrolate exerts its peak effect at around 3–4 min, whereas Miller and colleagues (1974) noted that pyridostigmine acted in 5–6 min. Although the times to the peak action of glycopyrrolate and neostigmine may be alike (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Mirakhur et al., 1981), glycopyrrolate can be used safely with pyridostigmine. However, a combination of glycopyrrolate and pyridostigmine would be more appropriate on account of the long duration of action of both drugs.

A smaller number of patients in the glycopyrrolate group showed cardiac arrhythmias, although the differences were not significant. The use of glycopyrrolate has been associated with a lower frequency of arrhythmias when used with neostigmine (Klingenmaier et al., 1972; Ostheimer, 1977). However, experience with glycopyrrolate-neostigmine mixtures has shown the frequency to be similar to that of an atropine-neostigmine mixture, serious arrhythmias being absent (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Eriksen, Hansen and Hasselstrom, 1978; Mirakhur et al., 1981). However, when the frequency of arrhythmia in the present series is compared with data on neostigmine (Mirakhur et al., 1981) the frequency is less with pyridostigmine, irrespective of whether the anticholinergic is atropine or glycopyrrolate. A similar observation was made by Eriksen, Hansen and Hasselstrom (1978). Owens, Waldbaum and Stephen (1978) confirmed these results in elderly patients, although the latter group (Muravchick, Owens and Felts, 1979) subsequently found no differences when the drugs were administered on a weight-related basis.

Oropharyngeal secretions were controlled better, both qualitatively and quantitatively, with glycopyrrolate. This is a recognized feature of the drug and has been demonstrated consistently in combination with neostigmine (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977) and pyridostigmine (Gyermeik, 1977; Eriksen, Hansen and Hasselstrom, 1978). Glycopyrrolate has been reported to have a more selective antisialagogue effect (Mirakhur, Dundee and Jones, 1978; Mirakhur, 1979; Mirakhur and Dundee, 1980).

Although the potency ratio of pyridostigmine has been variously reported to be one-half (Gotta and Sullivan, 1970), one-eighth (Randall et al., 1955) or one-twentieth (Smith, Mead and Unna, 1957) that of neostigmine, more recent and accurate assessments have shown it to be around one-fourth to one-fifth (Fogdall and Miller, 1973; Miller et al., 1974; Miller, 1979). Our dosage of pyridostigmine  $250 \mu\text{g kg}^{-1}$ , which is five times the usual dose of neostigmine  $50 \mu\text{g kg}^{-1}$ , was appropriate clinically. All the patients could lift the head against gravity before leaving the operating room. Although at this time all the receptors may not be completely free of neuromuscular blocking agents, this test is nonetheless considered

to be a sensitive index of recovery from neuromuscular block (Miller, 1976).

Although it is thought that pyridostigmine takes longer to exert its effect compared with neostigmine (Miller, 1976), care in the administration of the neuromuscular blocking drug with respect to dosage and time of administration helped us to achieve antagonism in a reasonable time. Extubation of the trachea was carried out at an average of 7 min following administration of the mixture and the ability to raise the head was attained within 10 min. This is similar to our experience with neostigmine.

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#### COMPARAISON DE L'ATROPINE ET DU GLYCOPYRROLATE PREPARES EN SOLUTION AVEC DE LA PYRIDOSTIGMINE COMME ANTAGONISTE DU BLOCAGE NEUROMUSCULAIRE

#### RESUME

On a provoqué l'antagonisme du blocage neuromusculaire en utilisant  $250 \mu\text{g kg}^{-1}$  de pyridostigmine sur deux groupes de 50 patients; un groupe a reçu  $20 \mu\text{g kg}^{-1}$  d'atropine et l'autre groupe a reçu  $10 \mu\text{g kg}^{-1}$  de glycopyrrolate associé au médicament anticholinestérase. L'atropine a été associée à une tachycardie initiale plus prononcée que ne l'a été le glycopyrrolate. La bradycardie qui a suivi a aussi été plus prononcée dans ce groupe, bien que les diminutions de la fréquence cardiaque aient été plus faibles que celles que l'on constate normalement après l'administration de mélanges d'atropine et de néostigmine. Les arythmies ont été transitoires et n'ont exigé aucun traitement dans aucun des deux groupes. On a obtenu une meilleure régulation des sécrétions avec le glycopyrrolate.

VERGLEICH VON ATROPIN UND  
GLYCOPYRROLAT IN EINER MISCHUNG MIT  
PYRIDOSTIGMIN BEI DER BEKÄMPFUNG VON  
NEUROMUSKULÄRER BLOCKADE

ZUSAMMENFASSUNG

Die neuromuskuläre Blockade wurde bei zwei Gruppen von 50 Patienten mittels Pyridostigmin  $250 \mu\text{g kg}^{-1}$  bekämpft; die eine Gruppe bekam Atropin  $20 \mu\text{g kg}^{-1}$  und die andere bekam Glycopyrrolat  $10 \mu\text{g kg}^{-1}$  zusammen mit der Anticholinesterasedroge. Atropin zeichnete sich durch eine stärkere anfängliche Tachykardie als Glycopyrrolat aus. Die anschließende Bradykardie war ebenfalls grösser als bei der ersten Gruppe, obwohl die Verringerungen des Herzschlags geringer waren als die, die im allgemeinen bei Mischungen von Atropin und Neostigmin beobachtet werden. Arrhythmien waren von kurzer Dauer und erforderte bei keiner der beiden Gruppen eine Behandlung. Eine bessere Kontrolle der Sekretionen wurde mit Glycopyrrolat erreicht.

COMPARACION DE LA ATROPINA Y DEL  
GLICOPIRROLATO CON LA PIRIDOSTIGMINA EN  
UNA MEZCLA EN LO TOCANTE A LA ANTERGIA  
DEL BLOQUEO NEUROMUSCULAR

SUMARIO

Se contrarrestó el bloqueo neuromuscular en dos grupos de 50 pacientes, usando  $250 \mu\text{g kg}^{-1}$  de piridostigmina; un grupo recibió  $20 \mu\text{g kg}^{-1}$  de atropina y el otro grupo recibió  $10 \mu\text{g kg}^{-1}$  de glicopirrolato, junto con la droga anticolinesterasa. La atropina vino asociada con una mayor taquicardia inicial de lo que lo fue el glicopirrolato. La bradicardia subsiguiente fue también superior en este grupo, aunque las disminuciones del ritmo cardíaco fueron menores que las que se observaron, por lo general, a raíz de las mezclas de atropina y de neostigmina. Las arritmias fueron momentáneas y no necesitaron tratamiento alguno en ninguno de los grupos. Usando el glicopirrolato se obtuvo un mejor control de las secreciones.