DOSE-RESPONSE STUDIES ON GLYCOPYRROLATE AND ATROPINE IN CONSCIOUS CARDIAC PATIENTS

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- 1 The dose-heart rate response relationship for the two anticholinergics, atropine and glycopyrrolate, were studied in non-anaesthetised patients about to undergo coronary artery surgery.
- 2 Two methods were used, the administration of increasing doses to different groups of patients, and an incremental dose technique in the same patient.
- 3 Both drugs increased heart rate in a dose-related manner with glycopyrrolate being approximately twice as potent as atropine.
- 4 Glycopyrrolate is as effective as atropine in correcting bradycardia prior to open heart surgery.

Keywords atropine glycopyrrolate coronary artery surgery dose-response

Introduction

Glycopyrrolate is a quaternary ammonium anticholinergic compound which has recently been extensively studied in the field of anaesthesia, (for a review see Mirakhur & Dundee (1981)).

Most of the published studies have involved the use of this agent at the time of reversal of residual neuromuscular block and have shown that, because of the synchronous actions of glycopyrrolate and the anticholinesterase neostigmine, changes in heart rate during reversal with glycopyrrolate-neostigmine combinations are much less than those associated with atropine-containing mixtures.

Glycopyrrolate has also been evaluated as a pre-anaesthetic agent; most studies have shown that powerful antisialogogue effects can be produced without undue changes in heart rate (Mirakhur *et al.*, 1978; McCubbin *et al.*, 1979). Many of these data, however, have been produced following intramuscular administration of relatively small (less than 0.4 mg) doses of glycopyrrolate. Little information exists on the cardiovascular effects of glycopyrrolate administered intravenously as pre-anaesthetic medication.

When patients about to undergo coronary artery by-pass surgery present with bradycardia, it is routine practice in this centre to increase heart rate to a satisfactory value in such patients by the use of atropine before induction of anaesthesia. Due to the lack

of information on the effects of intravenously administered glycopyrrolate, particularly in patients with cardiovascular disease, it was decided, therefore, to compare the dose-effect relationship of atropine and glycopyrrolate in such patients.

Two methods of assessing the dose-response relationship of glycopyrrolate and atropine were used, the administration of varying doses to different groups of patients, and an incremental 'step dose' regimen in the same patient.

Methods

Eighty-four patients about to undergo elective aorto-coronary by-pass grafting procedures were studied. Potential patients had been excluded if they had pre-existing dysrhythmias, unstable angina, poor left ventricular function (defined as an ejection fraction of < 0.4 and/or left ventricular end diastolic pressure of > 18 mm Hg) ventricular aneurysms, valvular disease or left main stem stenosis of more than 70%. In addition, patients receiving β -adrenoceptor blocking drugs within the preceding 72 h were excluded from the study.

A preliminary study indicated that glycopyrrolate, in the largest dose used in this study occasionally produced marked and long lasting mydriasis. As there is no scientific data on the effect of intravenous glycopyrrolate on the intraocular pressure in patients,

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as a precautionary measure only, patients about to receive glycopyrrolate were examined preoperatively by an ophthalmologist in order to identify and exclude patients with glaucoma.

All patients received, until the day of surgery, nifedipine (Adalat), chlorazepate potassium (Tranxylum) and isosorbide dinitrate (Isoket). None of the patients was receiving, or had received within 3 days prior to the study, any other drugs. Approximately 1 h before the planned induction of anaesthesia the patients were premedicated with morphine 1 mg/10 kg and droperidol 2.5 mg, given intramuscularly. In the anaesthesia induction room, a 16-G cannula (Abbot) was inserted into a forearm vein and a Teflon microcatheter (Seldicath 3824) was placed percutaneously into a radial artery. Lead II ECG and radial artery pressure were continuously displayed on a 2 channel monitor (Hellige SM 104).

A 'control' period of 5 min was allowed before the administration of the anticholinergics.

In the 'fixed dose' part of the study, atropine sulphate (atropine) or glycopyrrolate was then administered to groups of patients in the following doses:

Atropine: 5, 7.5, 10, 15, 20 and 40 $\mu\text{g/kg}$

Glycopyrrolate: 5, 7.5, 10 and 15 $\mu\text{g/kg}$

In the 'incremental dose' part of the study, doses of atropine or glycopyrrolate were administered at 5 min intervals. The doses of the anticholinergics were as follows:

Atropine: 2.5, 2.5 (5.0), 5.0 (10.0) and 10 (20.0) $\mu\text{g/kg}$

Glycopyrrolate: 1.25, 1.25 (2.5), 2.5 (5.0) and 5.0 (10.0) $\mu\text{g/kg}$

The total cumulative dose administered is shown in parentheses.

The maximum heart rate reached, independent of time, in the first 10 min after drug administration was used to determine the effects of the drug in the single dose study. In the incremental dose study, the mean heart rate in the third, fourth and fifth minute after drug administration was used to determine the effects of the drug.

Patients who, following injection of the anticholinergic, developed ST segment changes or angina were immediately treated with an intravenous infusion of nitroglycerin (Trinitrosan) and/or an intravenous injection of propranolol (Dociton).

The study protocol was approved by the Ethics Committee of the Benedikt Kreutz Rehabilitation Centre and all patients gave their informed consent to participate in the study.

Regression equations were calculated from the linear segment of the appropriate dose-response curve using the MINITAB computer program.

Results

The physical characteristics of the patients studied are shown in Table 1. The patients are reasonably well matched with regard to age and weight. Baseline heart rate and blood pressure data are shown in Table 2. Apart from slightly lower pressures in the patients receiving glycopyrrolate 5 $\mu\text{g/kg}$, the patients were well matched.

Single dose study

Figure 1 shows the maximum increase in heart rate produced by both atropine and glycopyrrolate, together with the calculated regression lines from the linear part of the dose-response relationship. With glycopyrrolate the maximum increase in heart rate, 36 ± 4 (s.e. mean) (range 24–54) beats/min, was achieved with a dose of 10 $\mu\text{g/kg}$; increasing the dose to 15 $\mu\text{g/kg}$ did not result in any further increase in heart rate (mean increase 34 ± 5 , range 27–58 beats/min). The increases in heart rate were statistically significant at most times following all the doses.

Atropine produced a dose-related increase in heart rate. Again, apart from the response to the lowest dose of the drug, the increases in heart rate were statistically significant. Atropine in a dose of 40 $\mu\text{g/kg}$ produced a maximum increase of 38 ± 3.5 (range 22–47) beats/min 2–3 min after its administration. The lower dose of atropine, 20 $\mu\text{g/kg}$, produced a similar increase in heart rate of 32 (range 24–42) beats/min. The maximal increases in heart rate produced by the top two doses of the two anticholinergics are similar; the differences between the two drugs are not statistically significant.

Figure 2 shows the relationship between the dose and the time taken for the maximum increase in heart rate to be achieved. The speed of onset of atropine is greater than that of glycopyrrolate—the peak effect of the former being shown within 2–4 min whereas the peak effect of glycopyrrolate was not observed until 7–9 min after its administration.

Analysis of variance revealed that the accuracy of fit of the computed regression line was less with glycopyrrolate than it was for atropine. Due to the non parallel nature of the regression lines, the potency ratio for glycopyrrolate: atropine ranged from 1.5 to 2.5 on a mg for mg basis.

Incremental dose study

The increase in heart rate produced by cumulative doses of atropine and glycopyrrolate, together with the dose-response regression lines obtained from the linear part of the dose-response relationship, are shown in Figure 3. Again, both atropine and glyco-

Table 1 Physical characteristics of the patients studied. Mean values are followed by their s.e. mean.

<i>Drug</i>	<i>n</i>	<i>Dose</i> ($\mu\text{g/kg}$)	<i>Weight</i> (<i>kg</i>)	<i>Age</i> (<i>years</i>)
<i>Single dose study</i>				
Glycopyrrolate	7	5.0	67 $\pm$ 2.5	53 $\pm$ 2.2
	7	7.5	79 $\pm$ 2.9	48 $\pm$ 2.2
	7	10.0	77 $\pm$ 3.9	47 $\pm$ 1.8
	6	15.0	74 $\pm$ 2.1	54 $\pm$ 2.4
Atropine	7	5.0	73 $\pm$ 2.2	50 $\pm$ 4.6
	7	7.5	71 $\pm$ 2.8	54 $\pm$ 7.0
	7	10.0	72 $\pm$ 3.6	47 $\pm$ 7.2
	6	15.0	81 $\pm$ 4.5	53 $\pm$ 5.0
	6	20.0	72 $\pm$ 2.3	55 $\pm$ 5.0
	7	40.0	75 $\pm$ 2.0	51 $\pm$ 7.2
<i>Incremental dose study</i>				
Glycopyrrolate	9	—	75 $\pm$ 1.5	55 $\pm$ 1.9
Atropine	7	—	79 $\pm$ 3.8	48 $\pm$ 2.4

pyrrolate produced a dose related increase in heart rate.

In this case the regression lines did not differ significantly from parallelism and the potency ratio for glycopyrrolate:atropine was 2.4 on a mg for mg basis.

The detailed effect of the two anticholinergics on haemodynamics will be reported separately. However, clinically significant changes in systemic, arterial, systolic and diastolic blood pressure did not occur.

Discussion

The present study has shown that the intravenous administration of glycopyrrolate in doses of 5–15 $\mu\text{g/kg}$ does significantly increase heart rate in conscious cardiac surgical patients. Furthermore, glycopyrrolate is approximately twice as potent as atropine on a mg for mg basis in this respect; the maximum effect of glycopyrrolate on heart rate is obtained

Table 2 Cardiovascular parameters before the administration of anticholinergic. Mean values are followed by their s.e. mean.

<i>Drug</i>	<i>Dose</i> ($\mu\text{g/kg}$)	<i>Heart rate</i> (<i>beats/min</i>)	<i>Systolic BP</i> (<i>mm Hg</i>)	<i>Diastolic BP</i> (<i>mm Hg</i>)
<i>Single dose study</i>				
Glycopyrrolate	5.0	59 $\pm$ 14	109 $\pm$ 6	61 $\pm$ 4
	7.5	62 $\pm$ 5	126 $\pm$ 7	69 $\pm$ 6
	10.0	63 $\pm$ 8	122 $\pm$ 7	71 $\pm$ 10
	15.0	60 $\pm$ 6	129 $\pm$ 5	72 $\pm$ 3
Atropine	5.0	66 $\pm$ 4	123 $\pm$ 9	71 $\pm$ 4
	7.5	60 $\pm$ 7	127 $\pm$ 6	60 $\pm$ 3
	10.0	69 $\pm$ 13	119 $\pm$ 6	68 $\pm$ 2
	15.0	67 $\pm$ 6	123 $\pm$ 3	68 $\pm$ 3
	20.0	61 $\pm$ 6	128 $\pm$ 7	70 $\pm$ 4
	40.0	62 $\pm$ 7	117 $\pm$ 7	67 $\pm$ 6
<i>Incremental dose study</i>				
Glycopyrrolate		58 $\pm$ 4	123 $\pm$ 7	66 $\pm$ 3
Atropine		58 $\pm$ 3	124 $\pm$ 6	70 $\pm$ 3

Figure 1 Increase in heart rate following intravenous administration of glycopyrrolate and atropine. The lines are the calculated regression lines. (○ glycopyrrolate, ● atropine).

Figure 3 Increase in heart rate following incremental doses of glycopyrrolate and atropine. Doses refer to the total cumulative dose. The lines are the calculated regression lines. (○ glycopyrrolate, ● atropine)

following administration of 10 or 15 $\mu\text{g/kg}$ whereas the maximum effect of atropine is observed after 20 or 40 $\mu\text{g/kg}$.

The incremental dose design provided a better fit of the computed regression lines, due, presumably, to a smaller source of variance and such data can be produced using a relatively small number of patients. Reasonable correlation existed between the response of the patients receiving single doses of both anticholinergics and the response of the patients receiving cumulative doses every 5 min. This method of producing dose-response curves is thus quite applicable to atropine and glycopyrrolate and is, indeed, preferable.

Glycopyrrolate offers some advantages over atropine as a premedicant. For example, the antisialogogue effects of glycopyrrolate are more prolonged than those of atropine (Mirakhor *et al.*, 1978), and the drug is devoid of any central actions (Proakis & Harris, 1978). In the present study the duration of

Figure 2 The relationship between dose and time taken to achieve peak increase in heart rate. The more rapid onset of atropine is apparent. (○ glycopyrrolate, ● atropine).

action of glycopyrrolate on the cardiovascular system was not measured. Clinical observations suggest that it is more persistent than atropine. Further work is necessary to measure the duration of action of the two anticholinergics.

This new anticholinergic has also been studied as an adjunct to reversal by neostigmine of residual neuromuscular block. One such study (Cozanitis *et al.*, 1980) examined a group of patients with pre-existing cardiovascular dysfunction and found that the use of glycopyrrolate with neostigmine was associated with more stable heart rates than was an atropine containing mixture. A further study (Bali & Mirakhor, 1980) showed that when residual neuromuscular block was reversed in patients who had undergone closed mitral valvotomy, glycopyrrolate-neostigmine 'reversal mixture' produced a significantly smaller increase in heart rate than an atropine-neostigmine mixture.

After this study had been completed, Mirakhor *et al.* (1981) reported their results from a study in which both glycopyrrolate and atropine were administered in similar dose to the doses used in the present study to anaesthetised patients. These authors showed that glycopyrrolate was twice as potent as atropine in increasing the heart rate in such patients. Furthermore, the onset of action of glycopyrrolate was significantly slower than that of atropine. The present findings obtained in non-anaesthetised patients are thus in agreement with those of Mirakhor *et al.* (1981).

Glycopyrrolate is thus as effective as atropine at correcting preoperative bradycardia prior to coronary artery surgery.

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