Comparison of the effects of atropine and glycopyrrolate on various end-organs[1]

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Summary: Atropine and glycopyrrolate (glycopyrronium bromide), a quaternary ammonium drug, were evaluated in volunteers following intramuscular administration with respect to effects on various end-organs with cholinergic innervation. Glycopyrrolate appears to be five to six times more potent than atropine in its antisialogogue effect and also exhibits a selective, though prolonged, effect on salivary secretion and sweat gland activity. It has minimal cardiovascular, ocular and central nervous system effects.

Introduction

Atropine has for long been one of the main anticholinergic drugs employed in anaesthetic practice. It has significant actions on most systems which are cholinergically innervated. However, it suffers from some disadvantages. These include a relatively short duration of action (Eger 1962), unreliability as an antisialogogue (Wyant & Dobkin 1957), undesirable central action (Innes & Nickerson 1975) and frequent occurrence of dysrhythmias (Averill & Lamb 1959, Thurlow 1972, Eikard & Andersen 1977).

Glycopyrrolate (glycopyrronium bromide) is a quaternary ammonium anticholinergic compound which, being highly polar, does not cross the blood-brain barrier. Initial studies in volunteers have shown it to be a potent antisialogogue agent (Wyant & Kao 1974, Mirakhur *et al.* 1978). The present paper compares some of the actions of intramuscular atropine and glycopyrrolate in volunteers.

Methods

Six adult volunteer anaesthetists participated in the study, the nature of which had been fully explained to them. Each received three doses of atropine (0.5, 1.0 and 2.0 mg) and three doses of glycopyrrolate (0.1, 0.2 and 0.4 mg) given by deep intramuscular injection. The subjects were each studied for six hours, at intervals of one week. Drugs were given in random order and observations made before and for six hours after administration.

Baseline observations were recorded after resting for 30 minutes. Measurements included heart rate, blood pressure, salivary secretion, sweat gland activity, pupillary size, oral temperature and the near point of vision. The detailed methodology has been described previously (Mirakhur *et al.* 1978).

Due to the skewed distribution of measurements of salivary secretion and sweat gland activity, these data were subjected to a Wilcoxan matched-pairs signed-ranks test for determination of their statistical significance, other results being subjected to a paired *t* test. The dose-response curves were subjected to an analysis of covariance.

Results

The means ages and weights of the volunteers were 32 years and 62 kg respectively.

Salivary secretion: The effects of both drugs were dose-related (Figure 1). The salivary secretion was reduced by 43, 72 and 85% with 0.5, 1.0 and 2.0 mg atropine respectively, the peak effect

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being attained in one hour. The reduction was statistically significant at one and two hours following 0.5 mg, between 0.5 and 4 hours following 1.0 mg and throughout the six hours following 2.0 mg.

The effects of glycopyrrolate were similar to those of atropine, but the depression in salivary secretion was more prolonged. Peak actions with 0.1 and 0.2 mg were attained by two hours, but the effect of 0.4 mg was similar at one and two hours. The reduction was statistically significant at two hours following 0.1 mg, between 0.5 and 4 hours following 0.2 mg and throughout the six hours of observation following 0.4 mg; the average maximal reduction with these three doses was 43, 74 and 94% respectively.

Analysis of the dose-response curves showed that for neither drug did the curve differ from linearity and there was no significant difference between the slopes of the two curves. From the estimate of the common slope, it was found that a reduction in salivation of 23.2% occurred for each doubling of the dose. Using this and an estimate of the intercepts, it was determined that glycopyrrolate had 5.6 times the potency of atropine.

Heart rate: The peak effects of atropine on heart rate were maximal at one hour. The smallest dose (0.5 mg) produced only bradycardia (a fall of 22%); 1.0 mg increased the heart rate by a maximum of 19% following a slight initial bradycardia, the rate returning to near basal values by three hours. Neither the initial bradycardia nor the tachycardia reached statistical significance. Following 2.0 mg the heart rate increased by a maximum of about 47% without any initial bradycardia. This increase was significant ($P<0.05$–$P<0.005$) from 1 to 4 hours.

In contrast glycopyrrolate did not cause tachycardia but gave rise to various degrees of bradycardia, the effects being statistically significant for 1–6 hours following 0.1 and 0.2 mg and at the 6 hour reading with 0.4 mg. The dose response curves on heart rate with both atropine and glycopyrrolate are shown in Figure 2. Statistical analysis showed that there was a significant difference between the slopes of the two curves. Whereas for atropine the relationship between dose and heart rate was highly significant ($P<0.0002$), the dose-response relationship for glycopyrrolate was not significant. Due to the non-parallel nature of the two dose-response curves, it was not possible to estimate the dose equivalence ratio.

Sweat gland activity: Both drugs caused a reduction in the number of active sweat glands, again in a dose-related manner. The middle and the highest doses of atropine produced a statistically significant reduction in the number of active sweat glands from one to four hours. The effects of glycopyrrolate were more prolonged and significant reductions were found from one to six hours after administration. The maximal reduction was about 90% with both drugs at the highest dose level.

Pupil size: This was affected only by atropine. The changes were however delayed in onset. The two lower doses produced an increase in size from three hours onwards, though it was

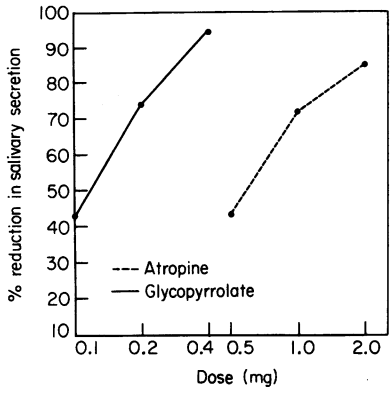

Figure 1. Dose-response of intramuscular atropine and glycopyrrolate on salivary secretion

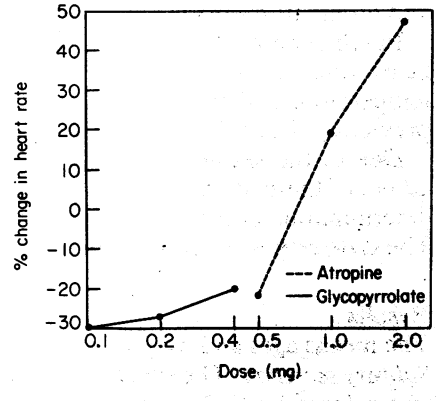

Figure 2. Dose-response of atropine and glycopyrrolate on heart rate

significant at five and six hours only. Administration of 2.0 mg had more pronounced effects, producing a significant increase from two hours onwards. The changes following glycopyrrolate administration were minimal and insignificant.

Visual near point: The effects paralleled those on pupil size, being significant only with 1.0 and 2.0 mg atropine.

Temperature: Both drugs had minimal effects though there was a slight tendency towards a rise, the maximum rise being 0.3°C.

Blood pressure: The changes in mean arterial pressure were inconsistent, minimal and statistically insignificant.

From these results it appears that 1.0 mg atropine and 0.2 mg glycopyrrolate are equipotent regarding effects on salivation and sweat gland activity. The effects of these doses on the most affected parameters are shown in Figure 3.

Subjective impressions: The drying sensation following both drugs was intense especially with higher doses; however, the effect lasted longer with glycopyrrolate. The higher doses of atropine gave rise to sleepiness. One volunteer complained of pain at the site of injection following glycopyrrolate.

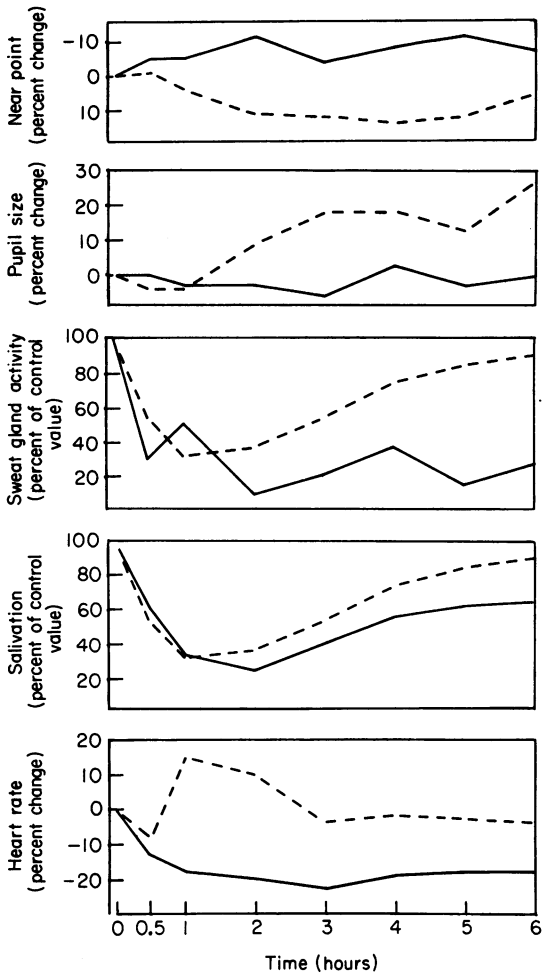

Figure 3. Effects of atropine (-----) and glycopyrrolate (———) on some aspects of cholinergic function

Discussion

While more detailed observations on some aspects of the action of the individual drugs have been described elsewhere (Mirakhur 1978, Mirakhur *et al.* 1978) the present paper

demonstrates the similarities and the differences between the two anticholinergic drugs. Such comparisons have not been reported previously at these dose levels in the same subjects. Both drugs produce marked depression of salivary secretion though the effects of glycopyrrolate are clearly more intense and prolonged. This was also demonstrated in the study of Wyant & Kao (1974). On the basis of antisialogogue activity, Wyant & Kao suggested that 0.2 mg glycopyrrolate and 0.4 atropine (ratio of 1:2) were equipotent. From the present study, however, 0.2 mg glycopyrrolate and 1.0 mg atropine (ratio of 1:5) appear to be equipotent. The difference could perhaps be due to the different methods of measuring the salivary secretion. We believe that the method of Mushin *et al.* (1953) adopted in this study takes into account the total secretion from all the salivary glands, whereas Wyant & Kao's study depended upon the secretions from one gland. Individual variations in the secretion of different salivary glands are well known. The ratio of potency in our study was obtained from the dose-response curves (Figure 1) and holds true at any point on these curves. On the other hand, Wyant & Kao (1974) concluded that glycopyrrolate was twice as potent as atropine. However, they compared only one dose of atropine to two doses of glycopyrrolate, the higher dose having a virtually 100% effect. It is possible that the results would differ if varied doses of the two drugs were employed and the comparative doses obtained from dose-reponse curves.

Whereas atropine in higher doses affects salivary secretion, sweat gland activity, heart rate and eyes, glycopyrrolate seems to affect only the first two. This reflects some selectivity of action of the latter drug. Doses of glycopyrrolate as high as 0.4 mg did not give rise to any tachycardia whereas an equipotent antisialogogue dose of atropine (approximately 2.0 mg) increased the heart rate by 45%. However, it is possible that doses in excess of those used here may produce tachycardia, but then the dryness would be very intense and extremely unpleasant. Though studies of the heart rate with doses of glycopyrrolate up to 0.2 mg intravenously showed no significant rise in heart rate (Wyant & Kao 1974, Mirakhur 1979), doses of 0.5 mg administered in a mixture with 2.5 mg neostigmine have effectively prevented bradycardia induced by neostigmine (Ramamurthy *et al.* 1972, Ostheimer 1977, Mirakhur *et al.* 1977). However, we do not recommend the routine use of glycopyrrolate as a premedicant, because of its prolonged action. Further studies of mixtures of neostigmine and anticholinergics are still in progress.

The lack of action on the eye and indeed the absence of other central effects in the case of glycopyrrolate is a great advantage. This is a reflection of poor penetration of this drug across the blood-aqueous and blood-brain barriers. The poor passage across the blood-brain barrier is a property of quaternary ammonium compounds (Paton & Zaimis 1952).

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