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DOSE-RESPONSE RELATIONSHIPS OF INTRAVENOUS HYOSCINE BUTYLBROMIDE AND ATROPINE SULPHATE ON HEART RATE IN HEALTHY VOLUNTEERS

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1 Heart-rate responses to intravenous hyoscine butylbromide, atropine and physiological saline in cumulative dosage regimens have been recorded in six healthy subjects.

2 Atropine sulphate induced bradycardia at low, and tachycardia at higher, dose levels whereas hyoscine butylbromide caused only tachycardia but with a flatter dose-response relationship.

3 Exact potency ratios could not be calculated because of the differing dose-response curves. However, an approximate estimate from a comparison of equiactive doses at the upper part of the curve yielded a value less than one half that obtained from the drugs' affinity constants in guinea-pig ileum.

4 The findings suggest that, in addition to its action as a muscarinic antagonist, hyoscine butylbromide is a ganglion blocker in man as it is in animals.

Keywords hyoscine atropine heart rate dose-response

Introduction

Hyoscine butylbromide is a quaternary derivative of hyoscine which has been widely used for its spasmolytic effect on gastrointestinal, biliary and ureteric muscle. When administered intravenously its action is brief, 20 mg doses producing effects which disappear largely by 20 min.

Quaternary derivatives of atropine and hyoscine are known to have ganglion-blocking actions in animals (Wick, 1951; Lecchini *et al.*, 1969) but it is uncertain whether this contributes to their antispasmodic effects or to their effect on the heart in man. Published formal comparisons between the actions of such compounds and those of atropine in man (Brownlee *et al.*, 1965; Herxheimer & Haefeli, 1966) do not allow evaluation of differences in mode of action and suggest merely that differences in end-organ specificity arise from their disparate extents of distribution.

Information on this point could be deduced from an investigation of the dose-response relationships in the heart because the tachycardia induced by parasympathetic blockade should be partially offset by any sympathetic ganglion block which ocurred. With this objective, a comparison of the heart rate responses to incremental doses of intravenous hyoscine butylbromide and atropine sulphate in healthy volunteers was therefore undertaken and is reported here.

Methods

Six healthy volunteers (3M, 3F) aged 28–40 years took part in the investigation. Each subject was studied on four occasions, separated by at least 4 days. Following a light breakfast, the subject rested supine and an intravenous cannula was placed in an antecubital fossa vein for drug administration. After 15 min incremental doses of either hyoscine butylbromide (A) or atropine sulphate (B) or physiological saline (C) were injected. The treatment order, which was balanced as follows:

Subject	*Treatment order*	*Replicated treatment*
1	ACBC	C
2	BACC	C
3	CBAB	B
4	ABCB	B
5	BCAA	A
6	CABA	A

was designed to make it impossible for the subject to predict the identity of the treatment on any occasion. The following incremental drug doses (or physiological saline):

Treatment	*Drug*	*Dosage protocol*	*Total dosage*
A	hyoscine butylbromide	1, 1, 2, 4, 8, 16 mg	32 mg

B	atropine sulphate	0.075, 0.075, 0.15, 0.3, 0.6, 1.2 mg	2.4 mg

were administered over 5s, each in physiological saline 2 ml, at 2 min intervals. Heart rates and sinus arrhythmia (expressed as the standard deviation of the R-R interval: Smith & Smith, 1981) were measured continuously over 30 s periods before, during and for 40 min after drug administration with a computer-linked ECG monitor.

Reproducibility of the measurements, assessed from the repeated treatment regimens, is given in Table 1.

The volunteers read the experimental protocol and gave written consent to participation. The experiment received ethical approval from the West Lambeth Health District Research Committee.

The log affinity constant of hyoscine butylbromide for muscarinic receptors was measured on guinea pig isolated ileum using carbachol as agonist (Arunlakshana & Schild, 1959). The value for atropine was taken as 9.00.

Table 1 Reproducibility of measurements

	Coefficient of variation (%)	*Intrapair correlation coefficient*
Heart rate	5.4	0.975
Heart rate decline during recovery	23.5	0.910

Results

The mean heart responses to hyoscine butylbromide, atropine sulphate and saline injection are shown in Figure 1. Both drugs produced a tachycardia but at low dosage atropine sulphate alone slowed the heart to a small but significant extent. Log dose-response curves based on cumulative dosage and obtained from the maximum increment in heart rate between drug and saline treatments during the period 1–2 min after each injection are indicated in Figure 2. This shows the biphasic response to atropine sulphate and the monophasic response to hyoscine butylbromide. The maximum slope of the log dose-response curve of atropine sulphate was approximately twice that of hyoscine butylbromide.

Strict comparison between the drugs' potencies could not be made because of the differing dose-response relationships. Calculation by extrapolation of the dose of hyoscine butylbromide needed to in-

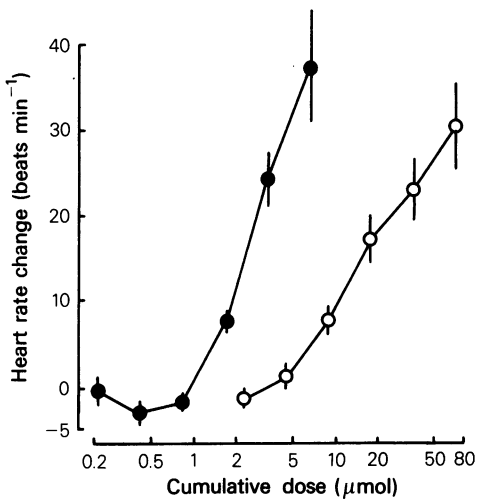

Figure 2 Cumulative dose-heart rate response curves to intravenous atropine sulphate (●) and hyoscine butylbromide (○) in six healthy volunteers (mean ± s.e. mean).

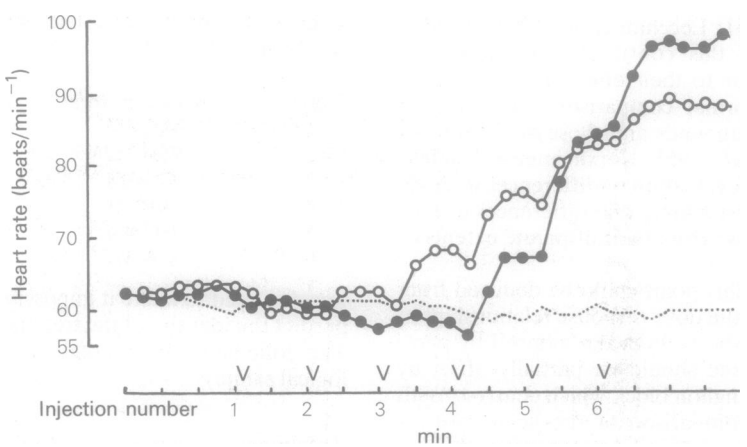

Figure 1 Mean heart rate responses of six healthy volunteers to intravenous saline (....), atropine sulphate (●), and hyoscine butylbromide (○).

Table 2 Calculated dose of hyoscine butylbromide equivalent to atropine sulphate 2.4 mg

Subject	*Maximum atropine response (beats min^{-1})*	*Extrapolated dose hyoscine butylbromide (mg)*	*Potency ratio (weight)*	*Potency ratio (M)*	*Log M potency ratio**
1	14	40.6	16.9	13.3	1.13
2	38.5	44.4	18.5	14.6	1.16
3	36.5	174.0	72.5	57.2	1.76
4	63.5	77.4	32.3	25.4	1.41
5	41	81.2	33.8	26.7	1.43
6	30.5	27.0	11.2	8.9	0.95
Mean	37.3	60.1	25.0	19.8	1.30

* log M potency ratio *in vitro* = 1.72

crease the heart rate to the maximum level achieved after atropine sulphate yielded a mean log molar potency ratio of 1.30 (range 0.95–1.76) (Table 2).

During the period 5 to 25 min following the final injection the heart rate declined linearly with time. The rate of offset of action, calculated by the method of least squares, of hyoscine butylbromide was on average 3.4 times that of atropine sulphate ($P < 0.01$) (Table 3). Atropine sulphate alone produced mild dizziness and disorientation for about 1 h after the experiment was completed.

The antimuscarinic log affinity constant of hyoscine butylbromide *in vitro* was 7.28 ± 0.04 (mean ± s.e. mean, $n = 11$). Assuming the value of 9.00 for atropine sulphate, this yields a potency ratio of antilog 1.72 = 52.5.

Table 3 Heart rate decline during recovery (mean ± s.e. mean, beats min^{-1})

Atropine sulphate	0.28 ± 0.05
Hyoscine butylbromide	0.95 ± 0.11
Saline	0.01 ± 0.09

Discussion

The results of this investigation are in accord with previous observations that atropine sulphate slows the heart at low dosage but accelerates it at higher dosage. Hyoscine butylbromide by comparison only accelerates it. The initial effect of atropine is ill-understood but is commonly attributed to a vagotonic influence exerted centrally. Such an influence would not be expected from hyoscine butylbromide because its quaternary structure and ionised state presumably confine it to the extracellular space.

The disparate shapes of the dose-response relationships, in particular their differing slopes at higher dosage, prevent strict comparison between the two drugs' effects on the heart. In an attempt to explain the differing slopes, we considered the possibilities that: firstly, the atropine slope is artificially steepened by a vagotonic influence at low dosage, which is overcome by the peripheral anticholinergic action at higher doses; secondly, the hyoscine butylbromide slope is flattened by its faster offset of action. Attempts to model the dose-response curves on this basis, in a manner similar to that proposed by Szabadi (1977), fail. The slope for the anticholinergic action is flattened slightly but insufficiently to parallel that of the adjusted hyoscine butylbromide slope, the combined adjustments accounting for less than half the slope difference. The alternative possible mechanism that atropine slows the heart by reducing sympathetic outflow can be discounted because of the observation that the slowing occurs even in the presence of propranolol (Chamberlain *et al.*, 1967).

It is therefore apparent that the dose-response curve to hyoscine butylbromide is influenced by an additional factor. One possible explanation is that the quaternary compound produces ganglion blockade in man as it does in animal experiments. This hypothesis is feasible because increasing blockade would progressively remove sympathetic tone from the heart thus flattening the curve in the manner observed. Furthermore, if the drug is distributed within the extracellular space the resultant concentrations from this dose regimen are many times higher than those found by Lecchini *et al.* (1969) to be ganglion blocking *in vitro* (6.0 *vs* 0.23 μmol/l).

The heart rates during the recovery period after both drugs were similar in three subjects, allowing comparisons of sinus arrhythmia. In each of these subjects, sinus arrhythmia, which is vagally mediated, was slightly greater in the presence of hyoscine butylbromide than atropine, indicating that heart rate was modified by a non-vagal influence.

An attempt has been made here to compare the potencies of the two drugs *in vivo* by calculating by extrapolation the dose of hyoscine butylbromide needed to produce the same effect as the largest dose

of atropine (at which point the vagotonic influence of this drug is minimised). Though untenable as a means of obtaining a true estimate of the atropine/hyoscine butylbromide potency ratio, nevertheless the ratio found is of interest because it underestimates by more than two-fold the ratio found *in vitro* despite the interfering influence of what we believe to be the ganglion-blocking action of the hyoscine derivative. This finding possibly indicates differences in the drugs' distribution volumes and perhaps protein binding characteristics. In support of this, at the doses used, atropine induced side-effects indicative of a central action whilst hyoscine butylbromide did not do so.

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