SOME EFFECTS OF INJECTED HYOSCINE BUTYLBROMIDE: A VERSATILE CLASS EXPERIMENT IN HUMAN PHARMACOLOGY

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1 An experiment with hyoscine butylbromide has been used to demonstrate how drug effects differ in intensity and time course after intravenous (20 mg) and subcutaneous (40 mg) injection with and without massage of the injection site. It also demonstrates how objective and subjective observations may be related, and gives students practice in the interpretation of experimental data.

2 The experiment takes about 2 h, and the effects of the drug have worn off completely after about 3 hours.

3 The structure of the discussion of the experiment and its results with the students are described to draw attention to the questions that can be asked of the data. The results obtained with 41 subjects are summarized to illustrate this discussion.

4 Various ways of modifying the experiment to suit other teaching objectives are mentioned. The need to consult the local Ethics Committee before undertaking experiments on students is emphasized.

Introduction

Practical work in human pharmacology for medical students should provide experience illustrating pharmacological principles relevant to the clinical use of drugs without the need to learn complex experimental methods, and without taking up much time. We here describe a half-day class experiment with the following teaching objectives. We want our students (1) to learn how drug effects differ in their intensity and time course when a drug is administered by different routes; (2) to experience or see some of the main effects of an atropine-like drug in man; (3) to learn (a) that drug effects can be simply measured in man and (b) that objective and subjective observations measure different things and the relationship between them needs to be considered; (4) to acquire simple skills needed for the interpretation of data, including the use of control observations, the making of valid comparisons, looking for likely sources of error, and the use of simple statistical tests.

The experiment compares the effects of hyoscine butylbromide administered in three different ways, intravenously, subcutaneously, and subcutaneously with massage of the injection site.

Methods

Timetable and allocation of treatments

The experiment began with a briefing session at 10 h 30 min. By 12 h 30 min all the students had finished their observations. After lunch, at 14.00 h, the results were evaluated and discussed in a session lasting about 1.5 hours. This time was too short to go through all the aspects of the experiment and a longer discussion period would have been advantageous. The 82 students who took part in the experiment were divided into four groups, each of which performed the experiment on a different occasion; thus each time there were 10 or 11 pairs of students under the supervision of two demonstrators. All the students were asked whether they were currently receiving medical treatment or had any other reason for not wishing to be a subject in the experiment. Possible risks or disadvantages were then considered and discussed individually with the student concerned. Reasons for exclusion would have been conjunctivitis, cardiac arrhythmia and other conditions in which an atropine-like drug might cause harm or excessive discomfort. Each pair of students then decided for themselves who was to be the subject.

To reduce distraction between adjacent pairs we spaced them out as far as possible and made use of movable partitions in the laboratory. At the end of the 30 min control observations the observer of each pair asked the supervisor to give the injection. On each occasion the first six to eight subjects to complete their

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Date..... Subject..... Observer..... Treatment & dose.....

Clock time	Time from injection (min)	Pulse (beats/min)	Mouth WD ?*	Saliva	Near point		Clock time	Time from injection (min)	Pulse rate (beats/min)	Mouth WD ?*	Saliva	Near point	
					1	2						1	2
	-30							10					
	-28							12					
	-26				cm	cm		14				cm	cm
	-24				D	D		16				D	D
	-22							18					
	-20							20					
	-18			ml				22					
	-16							24				cm	cm
	-14							26				D	D
	-12				cm	cm		28					
	-10				D	D		30				cm	cm
	-8							32				D	D
	-6			ml				34				cm	cm
	-4							36				D	D
	-2							38					
Injection	0							40				cm	cm
	2							42				D	D
	4				cm	cm		44			ml		
	6				D	D		46					
	8							48					

*D=dry W=wet ?=uncertain

Figure 1 Effects of hyoscine butylbromide: record sheet.

control observations received subcutaneous injections; the toss of a coin determined whether the observer was told to rub the injection site or the corresponding site on the opposite arm. The other subjects received the intravenous doses. All the injections were given by the same member of the staff to reduce variation.

Instructions to students

Before the experiment each student received an instruction sheet explaining the aims and the methods to be used, as follows:

*Observations will be made on (1) pulse rate, (2) near point of accommodation, (3) saliva secretion in response to a standard sweet, (4) subjective dryness or wetness of the mouth.

The subject must remain seated throughout the experiment. Control observations will be made for 30 min before the injection and subsequently the effects will be recorded for 50 minutes. Two-thirds of the subjects will receive a subcutaneous injection of hyoscine butylbromide (40 mg) on the back of the upper arm. In half of these the observer will rub the injection site vigorously for 60 s immediately after the injection. In the others he will rub the corresponding area on the other arm. One-third of the subjects will receive an intravenous injection of hyoscine butylbromide (20 mg).

(1) *Pulse rate* Count the radial pulse for 30 s every 2 min and record the results as the pulse rate/minute.

(2) *Near point of accommodation* Measure this at the times shown on the record sheet. Cover one eye with the eye shade, hold the near-point rule on the bridge of the nose along the line of forward vision with the nose-piece resting on the zygoma, and move the printed card slowly towards you, focusing on the print, until you find the nearest point

where the print is still clearly in focus. This is the near point of accommodation. Convert the near-point measurement from centimetres into dioptres using the table of reciprocals provided, and record the results both in centimetres and dioptres. At each time of observation make two replicate measurements. If you usually wear glasses make the measurements wearing them.

(3) *Saliva secretion* Measure this at the times shown on the record sheet. For 15 s swallow all the saliva you can collect in your mouth, then put the standard sweet in your mouth and suck it vigorously for 60 s, not swallowing any saliva. Allow the saliva to drool into the funnel and continue spitting for 15 seconds. Allow the graduated tube to stand for 5 min; then read off the volume, disregarding the volume of the froth. Do not tell the subject the result.

(4) *Dryness/wetness of mouth* Record every 2 min whether the mouth feels "dry" (D), "wet" (W), or "uncertain" (?)

(5) *Other effects* Record any other possible effects of the drug noted by subject or observer during the experiment'.

Recording the results

The observations were recorded on a specially designed record sheet (Figure 1). Instructions were as follows:

'Each observer will have three record sheets so that he can make carbon copies of the observations. The top copy will be collected at the end of the experiment and used to work out the results for the whole class. Make the observations in the order in which they appear on the record sheet and record the results in the appropriate spaces, noting also the time at which each observation was made. Make the observations on saliva secretion and near point as close to the times reserved for them as possible.'

Structure of the discussion

To facilitate tabulation and the discussion of the results, the students from each of the three treatment groups (i.e. the 'intravenous group', the 'rub' and the 'non-rub' group) were all seated together. Their task

was (1) to assess differences in effects and in time course between intravenously and subcutaneously administered hyoscine butylbromide and (2) to determine whether rubbing of the subcutaneous injection site influenced intensity and time course of the drug effects.

Results

Assessing the results

First the students were asked to try to predict what differences might be found and to illustrate their predictions by drawing diagrammatic time-action curves on the blackboard. The group then used these curves to decide what specific data were needed for analysis. For each of the effects studied these were (1) the time of onset of the effect, (2) the 'peak time', i.e. interval between the injection and the time at which the effect had reached its maximum, and (3) the time taken for recovery; (4) the maximum (peak) effect, and (5) baseline (control) values. All these measures had to be defined by the group. The control value for the pulse rate was taken to be the mean of the pulse rates at 4, 6, and 8 min before the injection. Controls for measurements of saliva secretion and near point of accommodation were the means of the two pre-injection readings for each. The time of onset of speeding of the pulse was defined as the time at which the pulse rate first exceeded the control level, provided that none of the three subsequent readings returned to this level. For the effects on saliva and near point the time of onset was taken as the time to the first measurement falling below the control level. Peak effects and peak times were obvious, except in some cases where two equal pulse-rate peaks occurred. In these cases the one whose two adjacent values had the

Table 1 Intensity of effects of parenteral hyoscine butylbromide (HBB) (mean $\pm$ s.e. mean)

		HBB 20 mg i.v. (n=13)	HBB 40 mg s.c. + massage (n=14)	HBB 40 mg s.c. no massage (n=14)
Pulse rate (beats/min)	Control	72 $\pm$ 8	70 $\pm$ 7	73 $\pm$ 8
	Peak	114 $\pm$ 15	107 $\pm$ 10	103 $\pm$ 9
	Peak-control	42 $\pm$ 12	37 $\pm$ 8	30 $\pm$ 9
	% increase	59%	53%	42%
Saliva secretion (ml)	Control	7.3 $\pm$ 1.8	6.8 $\pm$ 1.8	8.0 $\pm$ 2.8
	Peak	6.2 $\pm$ 1.7	3.5 $\pm$ 1.2	4.8 $\pm$ 1.9
	Peak-control	-1.1 $\pm$ 0.5	-3.3 $\pm$ 1.0	-3.1 $\pm$ 0.5
	% decrease	16%	49%	38%
Near point (dioptres)	Control	6.4 $\pm$ 2.7	7.1 $\pm$ 2.8	8.0 $\pm$ 2.6
	Peak	3.8 $\pm$ 2.1	3.6 $\pm$ 1.6	3.8 $\pm$ 1.7
	Peak-control	-2.6 $\pm$ 1.7	-3.5 $\pm$ 1.8	-4.2 $\pm$ 2.3
	% decrease	41%	49%	53%

higher mean was taken to be the peak. The recovery time was defined as the time to the first observation after the peak when the measurement had returned to or below the control level. The five measures were easily calculated by each pair of students from their record sheet and were tabulated on the blackboard.

Comparison of intravenous and subcutaneous administration

The intravenous injection produced a greater increase in pulse rate than the subcutaneous injection, but smaller effects on saliva secretion and near point (Table 1). Possible explanations for these differences were discussed, bearing in mind that the intravenous dose was half the subcutaneous dose. The differences in time course of the effects of intravenous and subcutaneous injection were clear except that no difference was found in the time of onset of the effect on saliva secretion. This was attributed to the 10 min interval between the injection and the first saliva measurement, which made it likely that the time of onset was missed in the intravenous group. To test this explanation the students examined the subjective data on dryness of the mouth and indeed found that in the intravenous group dryness usually began well before the first observation on saliva secretion was made.

The students were also asked to compare the time courses of the three effects studied and to comment on any differences they found. Both after intravenous and subcutaneous injection of hyoscine butylbromide the effect on the eye began later, reached its peak later, and took longer to wear off than the effects on pulse rate and saliva secretion. Possible explanations discussed included the suggestion that the aqueous humour might be acting as a reservoir for the drug (Herxheimer & Haefeli, 1966).

Lastly the implications of the results for clinical use of parenteral hyoscine butylbromide were briefly considered, contrasting the quick and transient relaxation of smooth muscle required in radiology of the alimentary tract with the more sustained effect desirable in the treatment of colic.

Effects of rubbing the injection site

Comparisons were next made of the time course and the intensity of the drug effects in the 'rub' and 'non-rub' groups. Rubbing the injection site appeared to accelerate the action of the drug slightly, but the experiment was too short to allow comparison of the recovery time. The peak effects on pulse rate and saliva secretion also appeared to be greater in the 'rub' group, and the students discussed whether these differences were likely to have occurred by chance and what would be appropriate statistical tests. They were asked how they might explain the differences if these turned out to be significant, for example 'rubbing' could spread the injected fluid or increase blood flow at the injection site. The group then considered how these possibilities might be investigated further.

Other aspects

The relationship between objective and subjective measures was discussed with reference to saliva secretion and the feeling of dryness of the mouth. The results were examined to see whether the time courses of the subjective and objective effects were compatible and to compare their apparent sensitivity to the drug. There was no time to discuss these data on the day of the experiment, and they were analysed later for the whole class.

Table 2 Time course of four different effects after hyoscine butylbromide (HBB): Median times of onset, of peak intensity, and of recovery

		HBB 20 mg i.v. (n=13)	HBB 40 mg s.c. + massage (n=14)	HBB 40 mg s.c. no massage (n=14)
Time of onset (min)	Pulse rate	1	6	8
	Dryness of mouth	2	4	8
	Saliva secretion	10	10	10
	Near point	5	10	15
Time of peak (min)	Pulse rate	2	16	21
	Dryness of mouth	4	8	8
	Saliva secretion	10	17	25
	Near point	15	30	35
Recovery time (min)	Pulse rate	26	>48	>48
	Dryness of mouth	14	38	46
	Saliva secretion	25	>48	>48
	Near point	40	>40	>40

Transient initial slowing of the pulse occurred in 8 of the 28 subjects given subcutaneous hyoscine butylbromide and lasted up to 4 min after injection before acceleration began. Possible explanations were discussed, including (1) relief from anxiety about the injection (2) a central vagal stimulant effect of the drug (the often alleged explanation of the slowing seen with atropine) (3) a direct stimulant effect of hyoscine butylbromide at the vagal receptor site such as might be expected from a partial agonist.

The need for further controls Questions discussed were: the advantages and disadvantages of including one or more groups given placebo injections; in what ways a comparison between i.v. and s.c. injection of a drug might be misleading; the validity of such a comparison if the dose given differs for the two routes; whether the dose an individual receives should depend on his weight.

Analysis of results for the whole class

The results were analysed after all four groups of students had performed the experiment. They were then discussed with the whole class. Tables 1 and 2 summarize the results. The differences between 'rub' and 'non-rub' groups in the intensity of the effects on pulse rate and saliva secretion were tested after subtracting the control value for each subject from the corresponding peak value. *t*-Tests were performed both on these differences and on the same differences expressed as a percentage of the control value. The difference in the effect on the pulse rate was significant ($P < 0.05$). The difference in reduction of saliva secretion reached the 0.05 level on the percentage figures but not on the untransformed ones.

The differences between the 'rub' and 'non-rub' group in the times of onset and of peak for pulse rate and near point, the times of onset of subjective dryness, and the times of peak effect on saliva secretion were tested using the Mann-Whitney U test; they were not significant at the 5% level. However, all six differences were in the predicted direction. The time of onset of the effect on saliva secretion did not differ between the groups, but saliva secretion was first tested only 10 min after the injection, which was probably too late to detect a difference. Subjective dryness of the mouth, however, began slightly earlier in subjects whose injection site had been rubbed. By chance all six differences would turn out to be in the predicted direction only once in 64 trials and the finding is therefore significant ($P = 0.016$). As Aladdin might have concluded, taking all the differences together it seems reasonable to attribute them to rubbing rather than to chance.

The time courses of the subjective and objective effects on saliva secretion were compatible in all but three of the forty subjects for whom they were validly recorded. Two of these three felt no dryness at all though saliva secretion decreased by 28% and 38%; the third noted dryness only some time after saliva secretion had begun to fall. The subjective and objective measures appeared to be similarly sensitive in 22 subjects; saliva secretion was more sensitive to the drug (i.e. was impaired longer) than the subjective report in 16 subjects, and the subjective report more sensitive than the measurement of secretion in two subjects. The relative insensitivity of 16 individuals to subjective dryness might mean that saliva production, though still impaired, had recovered sufficiently to make the mouth feel normal, or that sensory

Table 3 Points dealt with in eighteen students' written accounts of the experiment

	<i>Number of students mentioning the point</i>	
	<i>adequately</i>	<i>inadequately or not at all</i>
Data needed for comparisons	13	5
The controls used	8	10
Tabulation of data for whole group	18	0
Comparison: i.v. v. s.c.: intensity of effects	16	2
time course	18	0
Comparison: rubbing v. not rubbing		
intensity of effects	15	3
time course	18	0
Later occurrence of near-point changes	17	1
Initial slowing of pulse	10	8
Subjective dryness of mouth	16	2
Relation of subjective and objective effects	5	13
Pharmacology of atropine-like drugs	14	4
Statistics	2	16

adaptation to the sensation of dryness occurred more rapidly than the recovery of saliva production.

What the students wrote

As part of the pharmacology course our students are required to write up experiments and demonstrations. To check how far the aims of the experiment had been achieved, the practical notebooks of 18 of one group of 20 students were examined; the other two did not hand in their books. All had done the experiment on the same day. Table 3 shows that most students dealt with the major points. The main shortcomings were in the use of statistics and in discussion of the controls used. Most students also failed to discuss the relationship between subjective and objective measures. Better results might be achieved if students were given specific questions to discuss in their accounts of the experiment.

Discussion

Experiments in man with atropine or related drugs have long been a part of many pharmacology courses because they help students to understand some of the functions of the parasympathetic nervous system. However, atropine itself has an inconveniently long duration of action, especially on the eye, and after a dose that is big enough to produce convincing effects it may be difficult for the subject to find his way home or to do anything useful when he gets there. As far as we know hyoscine butylbromide given by injection has a shorter action than any other atropine-like drug. The subject has recovered fully from a subcutaneous dose

of 40 mg within 2.5–3 h of the injection, and after smaller doses or intravenous ones recovery is often quicker. The drug can also be given intramuscularly and is then absorbed more slowly than after subcutaneous injection (Herxheimer, 1967). Its main disadvantage is that it is very poorly absorbed by mouth (Herxheimer & Haefeli, 1966; Beermann, Hellström & Rosén, 1972). Inclusion of a group of subjects given an oral dose (say 100 mg) in a class experiment would demonstrate this, and could at the same time be used as a control. Many other experimental designs apart from the one described here are thus possible. Different groups can be given different doses so that dose/response curves can be constructed (Herxheimer & Haefeli, 1966). Comparisons can be made with atropine and with placebo (Brownlee, Wilson & Birmingham, 1965), though if atropine or other atropine-like drugs are used (Herxheimer, 1963; Kingsley & Turner, 1974) the experiment takes much longer than the one described here.

Whatever experiment is planned, it is important to consult the local Ethics Committee. This is the best way of ensuring that the interests of students, staff and institution are properly considered from all relevant aspects.

Our experience during this experiment, the subsequent discussions with students, and their written accounts indicate that it can achieve much of what we intended it to do, and while one experiment is not enough to teach simple skills needed for the interpretation of data, it can make a useful contribution in this direction.

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