INTERACTION BETWEEN DEBRISOQUINE AND PHENYLEPHRINE IN MAN

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- 1 The interaction between phenylephrine and debrisoquine was studied using normal and hypertensive human volunteers, measuring blood pressure, pulse rate and pupil diameter. Single doses of phenylephrine were given before, during and after a short course of debrisoquine treatment.
- 2 The circulatory effects of phenylephrine are potentiated by debrisoquine; in a few subjects this potentiation was marked and a potential hazard.
- 3 Limited deductions could be made about the effects of debrisoquine on baroreceptor responses and adrenergic mechanisms.

Introduction

During attempts to measure baroreflex responses to phenylephrine in man some exaggerated increases in blood pressure were noted in hypertensives taking debrisoquine (3,4-dihydro-2 (1H) isoquinoline carboxamide sulphate) (Aminu, D'Mello & Vere, 1970).

A detailed account of the interaction is presented; this has more than pharmacological interest because phenylephrine is a constituent of some over-the-counter remedies for colds and debrisoquine is commonly prescribed for hypertensives.

Methods

Four healthy subjects took part, two female and two male. They equilibrated, supine, for 20 min before each experiment in similar ambient conditions.

Heart rate was measured from five randomly drawn beats on the electrocardiograph, except when measuring the Valsalva overshoot, when successive beats were taken.

Blood pressure was measured by auscultation, using a zero-muddled sphygmomanometer to avoid digit preference. The machine was fitted with a constant air leak chosen to standardize the rate of mercury fall to 21 s with a variance in the blood pressure estimates of less than 20 mmHg.

Pupil sizes were measured under standard conditions of bright and dim illumination by comparison with a pupil chart (0.5 mm steps). The

palpebral fissure was measured by photography.

Passive tilting was done to a slope of 80° using a motor driven table with a high friction back rest.

The subjects exercised by stepping on and off a platform (25 cm steps 120 times/min for females, 50 cm steps 100 times/min for males).

Valsalva manoeuvres were done by blowing an aneroid gauge to 40 mmHg to the limit of the subject's tolerance. The overshoot tachycardia was measured by ECG for five heart beats immediately after breath-holding had ceased, and compared with heart rate immediately before breath-holding. Baroreceptor sensitivity was estimated by a modification of the method of Bristow, Honour, Pickering, Sleight & Smyth (1969) using oral phenylephrine and auscultated blood pressures. This has been shown to yield satisfactory slopes relating heart rate and blood pressure (Aminu, 1972).

The design of the experiments was as follows. The subjects' response to debrisoquine was calibrated by a double-blind cross-over trial of debrisoquine capsules and matching lactose placebo. The subjects began by taking increasing doses of debrisoquine until they had symptoms of tiredness or postural hypotension. Doses were then selected for each subject just below their symptom threshold. They took 0.5 to 0.75 (mg/kg)/day in capsules as divided doses. A matching lactose placebo was also used. These were then used in the trial, which was planned as four successive four day periods (two drug and two placebo), allocated at random. On each of the last three days of each

period the subjects performed the following routine:

Equilibrate	20 min	} Repeated once
Supine	5 min	
Passive tilt (80°)	5 min	
Active standing	5 min	
Exercise	2 min	
Supine	10 min	
Two Valsalvas later in the same day.		

Drug interaction was studied using the dose of debrisoquine found in the previous trial, and the dose of phenylephrine known from other work to raise the blood pressure by 10 mmHg (0.75 mg/kg). Syrup was used either as a placebo, or to contain single doses of phenylephrine (0.75 mg/kg). Blood pressures and heart rate were measured every 2 min during the routine:

Supine	6 min
Tilt to 80°	6 min
Supine	6 min

The phenylephrine was then taken, and the routine repeated until all measures returned to pre-treatment levels. Each subject then took the debrisoquine for four days. The phenylephrine routine was repeated on the morning and afternoon of the third day, either syrup alone or syrup with phenylephrine being taken according to a random double-blind code. Debrisoquine was then withdrawn, and the same phenylephrine routine repeated three days after withdrawal.

Phenylephrine eyedrops (10%) were also used, and a saline placebo. Measures of pupil size with phenylephrine eyedrops or saline were made two days before debrisoquine, on the four days of debrisoquine treatment, and for several days after it had been withdrawn.

It was agreed that should the blood pressure exceed 180 mm systolic or 120 mm diastolic, phentolamine would be given.

Results

Calibration of subjects with debrisoquine

The results using doses of debrisoquine just below those which evoked symptoms are shown in Table 1. In each case the dose worked out to be in the range 0.5-0.75 mg/kg, i.e. at the lower end of the clinically useful range. The table does not show the direction of change in each measurement, but that of the differences between debrisoquine and placebo results.

The features of greatest interest were the variability of the responses between subjects, the initial rise in blood pressure with debrisoquine

Table 1 Differences between measurements made during debrisoquine and placebo treatments. +, measures where the drug gave greater values than the placebo; — measures where the drug gave lesser values than the placebo. NS not significant; * significant at 0.1% level. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Subject	Daily dose (mg)	Day	Supine			Tilt			Standing			Exercise			Valsalva overshoot
			HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	
AHS ♂	60	2	+	+	+	NS	NS	—	—	—	—	NS	NS	NS	NS
		3	—	—	—	NS	NS	—	—	—	—	NS	NS	NS	—
		4	—	NS	NS	+	+	+	+	+	+	—	—	+	NS
		4	—	NS	NS	+	+	+	+	+	+	—	—	+	NS
WA ♀	30	3	NS	NS	NS	—	—	—	0	+	+	NS	NS	NS	—
		3	—	—	—	NS	NS	—	—	—	—	NS	NS	NS	—
CD ♀	30	2	—	+	+	—	—	—	—	—	—	—	—	—	NS
		3	—	+	+	—	—	—	—	—	—	—	—	—	—
THB ♂	40	3	—	+	+	—	—	—	—	—	—	—	—	—	—
		4	—	+	+	—	—	—	NS	NS	NS	—	—	—	—

Fig. 1 The course of an interaction experiment. Vertical solid lines are supine blood pressures, broken lines are results from the tilted position. Parallel horizontal lines are the highest systolic and diastolic readings in an identical experiment without debrisoquine. Phenylephrine (PE) was given at the vertical arrow (0.75 mg/kg body weight).

shown by both men, and the fact that only tilted and standing diastolic blood pressures, and standing systolic pressure, approached reliability as signs of the early action of debrisoquine. The stronger sympathetic stimuli (exercise, Valsalva overshoot) seemed able to override any neuronal blockade at this stage of the treatment; they were not used in succeeding experiments for this reason.

Debrisoquine-phenylephrine interaction

The results are shown in Table 2. The effects of phenylephrine were markedly augmented by debrisoquine in three subjects, and the effect was strikingly prolonged in two (Fig. 1), being evidenced at 90 min in subject CD even after phentolamine had been given. After debrisoquine had been withdrawn no result differed significantly from controls except for the supine blood pressures in subject CD. It was more interesting to note, however, that only one of the peak blood pressures recorded exceeded its corresponding value with phenylephrine alone; 11 of the 12 results were lower than these corresponding readings. There was therefore no evidence that the observed interaction carried over to the third day after debrisoquine withdrawal, indeed the effect was if anything reversed.

Baroreceptor sensitivity

During the pressor response to phenylephrine, synchronized measurements of systolic blood pres-

sure and pulse interval are collected. These paired observations are expressed as small changes from their starting values and plotted as ordinates and abscissae of a graph. A line of best fit to the points is estimated by regression. The slope of the line is a measure of baroreceptor sensitivity and its intercepts reflect baroreceptor setting.

Aminu (1972) investigated baroreceptor sensitivity in recumbent subjects, hypertensive and normotensive, by a modification of the method of Smyth, Sleight & Pickering (1969) and Bristow *et al.* (1969) and confirmed their findings, showing that oral phenylephrine provides satisfactory slopes relating electrocardiographic R-R interval and systolic blood pressure. In 14 tests in 8 normotensive subjects the slope ranged between 16 and 3.7 ms/mmHg systolic pressure. In 13 tests in 8 matched hypertensive subjects he found the slope to vary between 13 and 0.68 ms/mmHg systolic pressure. The difference between the two sets of slopes was significant. Aminu (1972) also investigated this slope in subjects taking debrisoquine on six occasions; it was in two of these subjects that the interaction between the drugs was first noticed though the remaining four showed no sign of it. The slope constants in this group varied from 1.3-2.7. Though all lay within the range of hypertensive subjects, none was within the normal range, and the difference between the groups was significant. The slopes of those taking debrisoquine were flatter. After the drug had been discontinued for at least a week these subjects showed steeper slopes, with con-

Table 2 Changes from control values of heart rate (Δ HR), systolic blood pressure (Δ SBP) and diastolic blood pressure (Δ DBP) in four subjects. Units are in mmHg for blood pressure, and values are given with ± 1 S.E.M. except where only single readings were obtained. The times of peak values (min) are given beneath them in brackets, C indicates that the results were within 2 S.E.M. of the controls.

Subject	Debrisoquine/Phenylephrine placebo						Phenylephrine alone					
	Supine			Tilted			Supine			Tilted		
	Δ HR	Δ SBP	Δ DBP	Δ HR	Δ SBP	Δ DBP	Δ HR	Δ SBP	Δ DBP	Δ HR	Δ SBP	Δ DBP
AHS δ												
Peak	-2	5 $\pm$ 7	0	+17	0	3	-5	14 $\pm$ 6	15 $\pm$ 0.3	-9	20 $\pm$ 3	19 $\pm$ 1
90 min	(40)	(28) C	(-)	(10)	(-) C	(10)	(64)	(52) C	(40)	(22)	(58) C	(70)
WA φ												
Peak	1	2 $\pm$ 1	3 $\pm$ 2	6	5 $\pm$ 3	2 $\pm$ 1	3	12 $\pm$ 3	8 $\pm$ 4	1	15 $\pm$ 4	10 $\pm$ 5
90 min	(52)	(64) C	(2)	(34)	(10)	(34)	(52)	(64) C	(2)	(46)	(58) C	(10)
CMD φ												
Peak	-19	3 $\pm$ 3	2 $\pm$ 2	-19	-6 $\pm$ 1	2 $\pm$ 3	-6	25 $\pm$ 3	22 $\pm$ 4	-14	16 $\pm$ 3	9 $\pm$ 5
90 min	(64)	(16)	(16)	(34)	(22)	(22)	(76)	(52)	(28)	(70)	(46)	(34) C
THB δ												
Peak	3	4 $\pm$ 6	8 $\pm$ 4	-5	-0.3 $\pm$ 2	3 $\pm$ 2	-6	7 $\pm$ 3	3 $\pm$ 1	-21	9 $\pm$ 6	10 $\pm$ 3
90 min	(39)	(39) C	(39)	(45)	(21)	(33)	(27)	(27) C	(3)	(33)	(33) C	(33)
Phenylephrine on third day after end of debrisoquine												
Phenylephrine on third debrisoquine day												
Supine												
Tilted												
AHS δ												
Peak	-16	24 $\pm$ 2	35 $\pm$ 4	-33	44 $\pm$ 4	34 $\pm$ 0.3	-	-	-	-	-	-
90 min	(42)	(81) C	(81)	(44)	(87) C	(87)	-	-	-	-	-	-
WA φ												
Peak	-3	7 $\pm$ 2	15 $\pm$ 3	-11	16 $\pm$ 2	11 $\pm$ 1	-1	4 $\pm$ 0.3	4 $\pm$ 2	-2	7 $\pm$ 4	5 $\pm$ 3
90 min	(4)	(64) C	(64)	(10)	(34) C	(34)	(4)	(64)	(64)	(10)	(58)	(34)
CMD φ												
Peak	-10	62	30	-22	46 $\pm$ 4	43 $\pm$ 10	-11	11 $\pm$ 1	9 $\pm$ 1	-32	0	4 $\pm$ 1
90 min	(16)	(26) C	(26)	(22)	(22) C	(22)	(28)	(28)	(40)	(34)	(-)	(34)
THB δ												
Peak	-15	18 $\pm$ 8	24 $\pm$ 2	-33	34 $\pm$ 5	29 $\pm$ 1	-11	-1 $\pm$ 1	10 $\pm$ 6	15	6 $\pm$ 7	5 $\pm$ 3
90 min	(40)	(40) C	(53)	(47)	(47) C	(47)	(57)	(35)	(57)	(26)	(63)	(27)

(Effects still present at 150 min)

(Phentolamine was given at the peak effect)

stants ranging from 5 to 15. They had then reverted to the normal range, though some were mildly hypertensive subjects (Table 3). The mean values for the slopes had changed little throughout, and Aminu (1972) concluded that debrisoquine alters the sensitivity of the baroreceptor reflex responses, but not the setting.

Similar slopes were examined for the four subjects of the present study. Unfortunately, regular slopes were not obtained, possibly because these subjects were tilted between each pair of recumbent blood pressure readings. In fact, the relationship between pulse interval and blood pressure went round a hysteresis loop in these subjects, a sudden fall in heart rate preceding the main rise in blood pressure in each case (Figure 2). The postural fall in blood pressure caused by debrisoquine disappeared during the hypertensive interaction (Figure 1).

Interaction in the iris

In each of the four subjects phenylephrine dilated the pupil, blanched the conjunctiva and widened the palpebral fissure. One subject (AS) developed a severe erythematous reaction to the drops, in conjunctiva and nearby skin, after four applications, but completed the eye experiments before this became severe.

During debrisoquine treatment in three subjects the pupil dilatation began some 20 min earlier and was increased (Table 4). The effects were more marked in bright than in dim light. The three

Fig. 2 Pulse interval (s) and supine systolic blood pressure (mmHg) in 3 debrisoquine-treated subjects given phenylephrine. The arrows indicate the time sequence of the results.

subjects who showed potentiation of phenylephrine effects were the same as those who experienced the increased hypertension after phenylephrine. In two subjects potentiation of phenylephrine was still seen four and six days after debrisoquine had been withdrawn.

Table 3 Baroreceptor sensitivity tests in debrisoquine treated subjects, adapted from Aminu (1972). *b*, regression slope; $\bar{y}$, means of R-R interval (s); $\bar{x}$, means of recumbent systolic blood pressure (mmHg). The slope *b* represents ms/mmHg blood pressure increase.

During debrisoquine			After withdrawal of debrisoquine					
<i>b</i>	$\bar{y}$	$\bar{x}$	Less than seven days after			More than seven days after		
			<i>b</i>	$\bar{y}$	$\bar{x}$	<i>b</i>	$\bar{y}$	$\bar{x}$
1.78	1.34	189.5	2.42	0.81	154.8	10.75	0.92	139.5
1.27	1.29	213.0	2.54	0.80	158.0	13.07	0.93	119.8
2.47	0.79	131.8	2.39	0.75	130.4	6.83	0.88	137.1
2.69	0.80	132.1	2.22	0.77	130.5	7.18	0.76	188.9
1.26	—	—	8.88	0.91	162.0	4.98	0.74	188.9
1.53	—	—	8.10	0.89	162.0	9.63	0.80	157.8
			2.82	0.92	202.0	15.07	—	—
			3.22	0.93	202.2	10.2	—	—
			7.27	0.85	125.4	15.2	—	—
			7.61	0.87	125.9	12.3	—	—
			4.04	0.81	145.7	9.63	—	—
			4.30	0.82	122.3			
			4.10	0.82	122.0			
			2.27	0.80	122.0			

Table 4 Mean mydriasis (mm) to phenylephrine eye drops (10%), expressed as difference from saline control in four subjects, $n = 2$. Results were obtained before (a), during (b) and after (c) debrisoquine treatment.

Subject		Time (min)			
		0	20	40	60
AHS δ	a	0	0	1.5	2.5
	b	0	1.1	3.2	4.25
	c	0	0.75	3.0	3.75
WA η	a	0	0	0.8	1.5
	b	0	0.3	1.6	2.4
	c	0	0.5	1.9	2.3
CMD η	a	0	0	1.3	1.75
	b	0	0.3	1.3	1.95
	c	0	0	0.6	1.2
THB δ	a	0	0	0.5	0.5
	b	0	0.25	0.875	1.75
	c	0	0	1.2	2.2

Discussion

Debrisoquine potentiates phenylephrine; the pupil size results indicate that stimulation of α receptors is a component of this response. Why it should occur, and why only 2 out of 10 observed interactions should be precipitated and hazardous, is less easy to understand. Debrisoquine is a weak inhibitor of monoamine oxidase (Pletscher, 1966; Pettinger, Korn, Spiegel, Solomon, Pocelinko & Abrams, 1969; Solomon, Ashley, Spirt & Abrams, 1969; Giachetti & Shore, 1967; Malmfors & Abrams, 1970). Phenylephrine is a monoamine oxidase substrate in some animal preparations (Trendelenburg, Draskoczy, Graefe & Hennemann, 1969).

Hence it is possible that the intestinal absorption of phenylephrine is substantially increased by debrisoquine, or, less probably, that its metabolism after neuronal uptake is blocked. Very small increases in absorption could account for the effects observed. Similar effects on blood pressure were observed by Aminu (1972), from 450 μg of phenylephrine given to one subject intravenously. Alternatively, uptake of phenylephrine into inactivating sites may be hindered by debrisoquine which may compete with it successfully for the amine uptake systems. However, the four subjects reported in detail here had received debrisoquine for only three days. Debrisoquine in higher doses causes hypertension at first; Luria & Fries (1965) described this and were unable to find elevation of

plasma catecholamines during the response in the same way as with guanethidine. This effect was shown by two of the present subjects (Table 1). It could be that phenylephrine effects potentiate this early hypertensive response to debrisoquine. However, Aminu's (1972) patient who developed severe hypertension had taken debrisoquine for six months, hence an early effect cannot be the whole explanation. If debrisoquine is acting only as a monoamine oxidase inhibitor it would not be expected to potentiate a directly acting pressor substance. However, if debrisoquine blocks re-uptake mechanisms in a manner similar to cocaine or imipramine, an interaction could be confidently expected (Barar, Boakes, Benedikter, Laurence, Pritchard & Teoh, 1971). Certainly the failure of potentiation of phenylephrine after withdrawal of debrisoquine shows that it cannot be a persistent enzyme depleter like tranylcypromine. Its more persistent effect in the eye may be due to intraocular cumulation similar to that of atropine (Herxheimer, 1958).

Attention should be drawn to the prolonged duration of the interaction, a second peak being seen in several cases (Table 2, Figure 1). This adds greatly to its potential hazard.

The most likely explanation seems to be that phenylephrine is slowly absorbed from the gut, and rapidly uptaken into tissue from plasma and metabolized. Very low plasma concentrations would then result. Anything which blocks the uptake mechanism, which is normally not the rate limiting process, would then lead to a rapid rise in plasma phenylephrine concentration. Why the effect varies so much from person to person cannot be explained, though it could be a purely pharmacokinetic phenomenon. Further work is needed to elucidate this.

Aminu (1972) has shown that satisfactory estimates of baroreceptor sensitivity and setting could be obtained in subjects who do not develop exaggerated hypertension whilst taking phenylephrine with debrisoquine. The further observations given here show that when a marked interaction did occur the ordinary regular reflex pulse response is not seen and valid baroreceptor sensitivity slopes cannot then be measured.

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