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A Comparison of the Effects of 1-Benzylpiperazine and Dexamphetamine on Human Performance Tests

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Summary. The effects of dexamphetamine (1 mg to 7.5 mg) and 1-benzylpiperazine (20 mg to 100 mg) on performance tests and cardiovascular responses were measured in two groups of 12 normal subjects. Drugs and dummy control were administered orally under double blind conditions at weekly intervals according to a balanced design. Significant ($p < 0.05$) improvement occurred in an auditory vigilance test following both drugs, and this test was sufficiently sensitive to detect the changes produced by dexamphetamine 1 mg at the time of peak drug action. Subjective effects were only detected by the subjects after dexamphetamine 7.5 mg and 1-benzylpiperazine 100 mg. Significant changes attributable to drug treatment were not found in tests of short duration such as tapping rate, hand steadiness and arithmetic. Both drugs produced significant increases in heart rate and systolic blood pressure. It was concluded that 1-benzylpiperazine has psychomotor stimulant activity similar to dexamphetamine and that this was most reliably detected by using a prolonged signal detection test. The effects of 1-benzylpiperazine eye-drops (2%) on pupil diameter was investigated in 6 subjects who had had one eye pretreated with guanethidine (5%) eye-drops. 1-Benzylpiperazine gave effects similar to tyramine but significantly different from methoxamine indicating an indirect sympathomimetic action.

Key words: Dexamphetamine, 1-benzylpiperazine, human psychomotor and vigilance tests.

While the effects of amphetamine and related compounds on normal and fatigued human subjects are well known and have been reviewed (Weiss and Laties, 1962), little information is available about the relative sensitivity of different tests used. Improvement of performance in a visual vigilance test was noted by Mackwoth (1950) and in an auditory vigilance test by Loeb, Hawkes, Evans and Aluisi (1965). The primary interest of both these groups of workers, however, lay in the psychological aspects of human performance, and the relationship between drug dosage and the size and duration of drug induced effect was not investigated. Wilkinson (1968), studying the effect of sleep deprivation has emphasized that impairment of performance occurs predominantly in tasks of a monotonous and repetitive nature. It seemed likely that tasks of this type might also be highly sensitive to the effects of amphetamine-like compounds. 1-Benzylpiperazine, a compound exhibiting antitetrabenazine activity in mice and rats was also observed to have some actions similar to dexamphetamine in these species by Miller, Green and Young (1971). The following experiments were designed to compare the relative sensitivities of various tests used for the detection of amphetamine-like activity, while investigating the pharmacodynamic activity of 1-benzylpiperazine in man.

Methods

Subjects

Twelve healthy paid volunteers, staff of the Wellcome Research Laboratories, were used in each of two separate trials. They were medically screened and their general practitioners were contacted. Trial 1 was conducted with 9 men and 3 women aged 21 to 46 years, and Trial 2 with 7 men and 5 women aged 21 to 47 years.

Tests

The test schedule used lasted 2 h and consisted of 105 min of tests followed by a 15 min rest. This began at 09.00 h and was repeated four times. The tests described in order were: (1) a 15 min period of addition of two digit numbers, arranged in groups of five pairs. The sums completed and number of errors were counted. (2) a hand steadiness test in which the subject held a metal stylus, 2 mm diameter, in a hole in a metal plate, 4 mm in diameter, using the preferred hand, the arm being supported only at the elbow. The number of contacts per minute were recorded. (3) a tapping test measured using a microswitch and the preferred hand. In Trial 1 a 1 min period was used and in Trial 2 a half min period. (4) an auditory vigilance test lasting 1 h and

devised by R.T. Wilkinson (1968), in which the subjects listen through headphones to a series of short tones 0.5 sec in duration, occurring randomly through the hour, but with ten signals every 15 min, to enable analysis of performance every quarter hour. The sound intensity of the tone was approximately 82 db and the background noise 76 db. On recognition of a signal a subject registered the detection and also a confidence rating, high, medium or low, by pressing buttons.

The steadiness and tapping tests were then repeated. Subjective effects were assessed from a check list consisting of 41 adjectives given at the beginning of the second and third rest periods. Heart (radial pulse) rate and blood pressure, taken using a sphygmomanometer, were measured after ten minutes rest in a supine posture before the beginning of each rest period. All tests except heart rate and blood pressure, were conducted in a sound-proof air conditioned room at 70° F (21°C).

In the week before each trial a half day training session was given. No information on individual test performances was divulged at any stage. No tea, coffee or cigarettes were allowed on the experimental day and the subjects omitted breakfast. Subjects were fed during the second, third and fourth rest periods.

Drugs

Individual treatments were administered orally in identical soft gelatin capsules under double blind conditions during the first rest period at 10.45 h. Subjects received each of six treatments at weekly intervals in a balanced design based on two six-sided Latin squares. In Trial 1 the treatments were dexamphetamine sulphate 2.5, 5.0 and 7.5 mg, 1-benzylpiperazine hydrochloride 50 and 100 mg, and a lactose dummy. In Trial 2 a lactose dummy was used on two occasions, the other four treatments being dexamphetamine sulphate 1 and 2.5 mg, and 1-benzylpiperazine hydrochloride 20 and 50 mg.

Eye Studies

Six normal male subjects were used to test the effect of methoxamine, tyramine and 1-benzylpiperazine all at a concentration of 20 mg/ml, on the size of the normal pupil, and the pupil pretreated with guanethidine, 50 mg/ml, to produce adrenergic neurone blockade. One drop of guanethidine solution was instilled into the left conjunctival sac and one drop of normal saline into the right conjunctival sac 24 and 16 h before instillation of one drop of the sympathomimetic amine into both eyes. The three amines were tested at weekly intervals. Pupil size was recorded under standard lighting using a fixed focus 35 mm reflex camera before instillation of the amines, and after 15, 30, 45 and 60 min. Measurements were made by projection of the film giving a magnification of $\times 20$. Differences between the right and left pupil diameters were submitted to analysis of variance.

Analysis of Results

All measured variables with the exception of the subjective effects, were submitted to analysis of variance, enabling the effects of drug treatment to be assessed. Fisher's exact probability test for the double dichotomy situation was used in the analysis of the subjective effects recorded on adjective check lists. Values of d′ and β were calculated from the proportions of signals correctly detected, and proportions of non-signal tones eliciting false reports, using the Freeman Tables (Freeman, 1964), and were then submitted to a Friedman (1937) two way analysis of variance. Values of $p < 0.05$ were taken as statistically significant.

Results

Addition

In Trial 1 there were no significant differences in the number of sums completed following different treatments (Table 1). A significant increase was noted following both doses of 1-benzylpiperazine in Trial 2, after 4 h 30 min.

Hand Steadiness

No significant changes in hand steadiness occurred in either trial.

Tapping

A consistent small dose related increase in tapping rate followed administration of both dexamphetamine and 1-benzylpiperazine (Table 1). The effects, however, were not statistically significant except at 2 h 36 min and 4 h 36 min after 1-benzylpiperazine 50 mg in Trial 2.

Auditory Vigilance

In both trials there was a decrement in performance following the lactose dummy during each quarter of the one hour test with the exception of hour 3 in Trial 1 (Table 2) and also the initial performance fell with successive one hour tests with the exception of the final test. The performance pattern following the dummy was similar in both trials but

Table 1. *Performance in tapping, addition and steadiness tests*

Test	Time		Trial 1						Trial 2				
			Lactose dummy	Dexamphetamine			1-Benzylpiperazine		Lactose dummy	Dexamphetamine		1-Benzylpiperazine	
				7.5 mg	5.0 mg	2.5 mg	100 mg	50 mg		2.5 mg	1.0 mg	50 mg	20 mg
Tapping	Pre-drug	(a)	348	362	359	364	343	365	193	191	193	190	189
		(b)	337	345	341	348	340	343	187	182	184	186	185
Taps per	Post-drug												
60 sec	36 min	(a)	337	360	352	358	359	362	189	193	191	192	194
(Trial 1)	1 h 42 min	(b)	338	361	351	350	356	359	182	187	183	192	189
Taps per	2 h 36 min	(a)	357	370	359	356	367	366	187	190	191	194[a]	190
30 sec	3 h 42 min	(b)	341	349	348	345	347	353	185	188	186	188	180
(Trial 2)	4 h 36 min	(a)	355	364	352	355	352	357	185	189	183	194[b]	186
	5 h 42 min	(b)	338	356	354	349	353	342	188	187	185	189	184
Addition	Pre-drug		79	79	104	79	103	102	65	63	67	67	65
Total	Post-drug												
sums	30 min		104	109	85	83	83	105	68	68	68	71	68
completed	2 h 30 min		102	112	112	105	88	82	65	67	69	72	69
per	4 h 30 min		103	111	83	80	86	107	64	64	67	73[b]	69[a]
15 min													
Steadi-	Pre-drug	(a)	39	31	32	39	40	32	39	42	30	32	29
ness		(b)	23	26	28	22	26	31	31	30	21	26	29
	Post-drug												
	34 min	(a)	31	22	29	36	31	33	31	33	28	25	37
Contacts	1 h 40 min	(b)	19	21	22	32	29	23	30	22	20	25	23
per min	2 h 34 min	(a)	31	23	24	31	32	24	40	39	28	29	38
	3 h 40 min	(b)	32	19	24	34	26	22	33	30	31	27	27
	4 h 34 min	(a)	32	28	31	31	33	31	39	33	40	31	42
	5 h 40 min	(b)	33	27	28	30	39	30	35	30	37	33	34

Tests (a) were made before auditory vigilance testing, and tests (b) were made after auditory vigilance testing. Individual figures represent the mean value for 12 subjects. The statistical significance of differences following active treatments compared with performance following placebo are indicated by [a] ($p < 0.05$) and [b] ($p < 0.01$).

Table 2. *Performance in the auditory vigilance test*

Time		Trial 1						Trial 2				
		Lactose dummy	Dexamphetamine			1-Benzylpiperazine		Lactose dummy	Dexamphetamine		1-Benzylpiperazine	
			7.5 mg	5.0 mg	2.5 mg	100 mg	50 mg		2.5 mg	1.0 mg	50 mg	20 mg
Pre-drug												
Quarter	1	76.7	70.0	78.3	75.0	77.5	80.0	63.3	59.2	59.2	56.7	65.0
	2	57.5	63.3	60.0	67.5	57.5	57.5	43.8	44.2	42.5	41.7	48.3
	3	58.3	59.2	60.0	52.5	56.7	55.8	42.5	35.0	35.8	38.3	35.8
	4	47.5	50.0	56.7	55.8	56.7	53.3	36.7	32.5	35.8	47.5	38.3
Post-drug												
38 min	1	71.7	67.5	72.5	68.3	70.0	65.8	52.5	52.5	52.5	50.0	42.5
	2	58.3	67.2	61.7	62.5	58.3	67.5	36.3	42.5	50.8[a]	53.3[b]	45.8
	3	48.3	65.8	57.5	56.7	68.3	59.2	38.3	35.8	36.7	40.8	40.8
	4	36.7	57.5[b]	63.3[b]	49.2	56.7[b]	59.2[b]	27.5	35.8	31.7	44.2[a]	35.8
2 h 38 min	1	52.5	77.5[b]	75.0[b]	71.7[b]	79.2[b]	68.3[a]	37.9	52.5[b]	47.5[a]	55.8[b]	52.5[b]
	2	49.2	65.8[a]	65.0[a]	57.5	80.8[b]	64.2[a]	30.0	35.8	30.0	38.3	34.2
	3	44.2	56.7	58.3[a]	49.2	67.5[b]	51.7	25.4	23.3	30.0	33.3	30.8
	4	54.2	55.8	60.0[a]	55.8	69.2	67.5	29.2	32.5	29.2	40.8	38.3
4 h 38 min	1	63.3	77.5	72.5	60.0	64.2	63.3	43.8	49.2	46.7	50.0	45.8
	2	54.2	63.3	61.7	60.0	68.3	56.7	41.7	30.8	35.0	42.5	34.2
	3	38.3	52.5	47.5	53.3	61.7	50.0	27.9	27.5	27.5	34.2	31.7
	4	47.5	59.2	49.2	55.0	58.3	48.5	33.8	28.3	31.7	38.3	30.0

Individual figures are mean values for 11 subjects of the % signals detected during the quarter hour periods of the tests. Hours after drug refers to the time of commencement of the lh test. The statistical significance of differences in the % of signals detected following active treatments compared with the performance following dummy treatment is given by [a] and [b] indicating $p < 0.05$ and $p < 0.01$ respectively.

approximately 10% lower at all points during Trial 2. Following dexamphetamine 5.0 and 7.5 mg the initial performance did not fall during the later tests. The performance decrement during each one hour test was reduced by dexamphetamine, with significant improvement occurring at the end of hour 2 and the beginning of hour 3. Trial 2 confirmed the effect of dexamphetamine 2.5 mg at the beginning of hour 3 and also showed that a statistically significant improvement occurred at this time following dexamphetamine 1.0 mg. Mean values of signals detected were higher for up to 5 h 30 min after dexamphetamine administration but were not statistically significant.

Table 3. *Cardiovascular effects*

Variable	Time	Trial 1						Trial 2				
		Lactose dummy	Dexamphetamine			1-Benzylpiperazine		Lactose dummy	Dexamphetamine		1-Benzylpiperazine	
			7.5 mg	5.0 mg	2.5 mg	100 mg	50 mg		2.5 mg	1.0 mg	50 mg	20mg
Heart rate (per min)	Pre drug	63	63	64	65	62	64	62	61	62	63	61
	Time post drug											
	1 h 54 min	59	69[b]	66[b]	64[a]	66[b]	66[b]	59	61	61	66[b]	63[a]
	3 h 54 min	65	73[b]	73[b]	72[b]	72[b]	73[b]	66	69[a]	68	72[b]	71[b]
	5 h 54 min	65	76[b]	74[b]	72[b]	76[b]	71[b]	68	69	69	72	70
Systolic B.P. (mm Hg)	Pre drug	109	107	112	111	112	110	110	108	111	107	110
	Time post drug											
	1 h 54 min	110	119[b]	115	118[b]	126[b]	120[b]	108	110	111	112	111
	3 h 54 min	112	116	116	117[a]	121[b]	116	111	112	113	114	115
	5 h 54 min	115	120	119	115	121[a]	119	114	116	115	116	115
Diastolic B.P. (mm Hg)	Pre drug	71	71	71	71	74	72	67	67	66	65	64
	Time post drug											
	1 h 54 min	71	75	72	76	80[b]	73	65	69	67	67	65
	3 h 54 min	66	71	69	71	70	68	61	61	61	63	66
	5 h 54 min	69	69	69	68	71	69	63	64	64	63	64

The statistical significance of the differences in each variable following active treatments compared with dummy is given by [a] and [b] indicating $p < 0.05$ and $p < 0.01$.

1-Benzylpiperazine 50 mg and 100 mg produced similar changes to dexamphetamine in Trial 1. Significant improvement occurred during the final quarter of hour 2 and the first three quarters of hour 3. Trial 2 confirmed the effects of the lower dose.

The confidence scores obtained arbitrarily by giving high, medium and low confidence reports values of 3, 2 and 1 respectively, following drugs differed significantly from the dummy only when a similar difference was apparent in the percentage of correct detections. The mean confidence scores for each detection did not change significantly following administration of either drug.

There were no significant changes in the number of false detections attributable to drugs in either trial. The incidence of occurrence of false detection was however very low, between zero and 0.25% of the non-signal tones. The numerical indices d′ and β have been postulated by Swets, Tanner and Birdsall (1961) and Broadbent and Gregory (1963) to distinguish changes in subject's ability to detect signals from the subject's willingness to report a signal. Values were calculated from the relative frequency of signals correctly detected and the frequency of false reports, using tables prepared by Freeman (1964). Because false reports were rare the indices for the combined 3 h period following drug administration were calculated. Values for d′ following the placebo ranged from 2.122 to infinity and for β from 48.043 to infinity. The values for each subject were ranked and submitted to the Friedman two-way analysis of variance. Mean values of d′ were higher and values of β were lower following both drugs compared with the values following lactose, but these changes were not significant.

Subjective Effects

Any or all of five of the 41 adjectives on the check list, alert, elated, quickwitted, stimulated and talkative, were arbitrarily selected as indicating a stimulant effect. Subjects were divided on each occasion into those showing evidence of a stimulant effect and those without. A significant increase in the proportion of subjects experiencing stimulant effects occurred only following the two highest doses of either drug, dexamphetamine 7.5 mg, and 1-benzyl-

piperazine 100 mg, compared with the proportion occurring following lactose.

Cardiovascular Effects

In Trial 1 heart rate was significantly increased by all doses of both drugs 1 h 54 min, 3 h 54 min and 5 h 54 min after the drug administration as shown in Table 3. Systolic blood pressure was raised by all drug treatments, except dexamphetamine 5.0 mg. No changes occurred in diastolic blood pressure. Trial 2 confirmed the increases in heart rate following dexamphetamine 2.5 mg, and 1-benzylpiperazine 50 mg. No significant changes in sytolic or diastolic blood pressure occurred in Trial 2.

Effects on the Pupil

Table 4 shows the mean differences in diameter of the pupils of the two eyes before and after instillation of methoxamine, tyramine and 1-benzylpiperazine into both conjunctival sacs. The guanethidine treated pupil was always smaller. Methoxamine reduced the difference between the two eyes by producing dilation of the left pupil, whereas tyramine and 1-benzylpiperazine did not.

Table 4. *Differences in diameter between the normal (right) pupil and the guanethidine treated (left) pupil before and after instillation of sympathomimetic amines*

	Baseline difference		15 min difference		30 min difference		45 min difference		60 min difference	
	(mm)	F	(mm)	F	(mm)	F	(mm)	F	(mm)	F
		3.62		0.74		2.48		5.94		10.95
Methoxamine	1.14		1.03		0.63		0.21		0.03	
Tyramine	1.22		1.16		1.27		1.30		1.30	
1-Benzylpiperazine	0.77		0.95		0.93		0.89		0.87	

Significant differences were found between treatment with methoxamine and tyramine after 45 min ($p < 0.05$), and 60 min ($p < 0.01$); and between 1-benzylpiperazine and methoxamine after 60 min ($p < 0.05$). F has 2 and 10 degrees of freedom in each instance. Six subjects each received all treatments.

Discussion

The results reported show that 1-benzylpiperazine and dexamphetamine produce similar effects in man. Numerous studies have suggested that prolonged and monotonous tests are more suitable for detection of amphetamine-like activity than tests of short duration, and this work confirms this. In general significant changes in performance using tests of short duration have only followed the administration of relatively high doses of stimulant drug. Thus Legge and Steinberg (1962) and Dickins, Lader and Steinberg (1965) failed to produce significant ($p < 0.05$) increases in tapping rate over 1 min or arithmetic over 2 min by administration of amphetamine 15 mg orally to 12 subjects. Similarly Goldstein, Searle and Schimke (1960) found no significant changes in a series of short tests after administration of dexamphetamine 10 mg to 8 subjects. By using a dose of 20 mg of amphetamine, Thornton, Holk and Smith (1939) reduced the reaction time and increased tapping speed in 3 subjects, and Lehman and Csank (1957) using doses of 12.5 to 15 mg of dexamphetamine produced significant changes in these tests in groups of subjects varying from 13 to 18.

N.H. Mackworth (1950) demonstrated the ability of amphetamine 10 mg to improve performance significantly in the monotonous "clock test", which lasted 2 h. Twentyfour subjects each received amphetamine, dummy treatment or no treatment according to a Latin square design. J.F. Mackworth (1965) emphasized the necessity of recording false alarm data. From the percentage of signals heard and the percentage of false alarms it is possible to derive a value β which indicates the subject's willingness to report signals, and a value d′ which indicates the subject's ability to distinguish signals from noise. Analysis of signal detection theory has been fully discussed by Swets, Tanner and Birdsall (1961), and Broadbent and Gregory (1963).

The effects of dexamphetamine 10 mg on performance of 24 subjects in an auditory vigilance test 1 h in duration was studied by Loeb, Hawkes, Evans and Alluisi (1965) using a cross over type of design. The performance decrement following the placebo was abolished by dexamphetamine, but neither β nor d′ changed significantly. In the present study the percentage of signals detected at the beginning of the first test following drug administration was not increased, but the initial performance during the second post drug test was significantly improved by both drugs. The performance decrement was re-

duced by both drugs and this trend could be seen for up to 5.5 h. The sensitivity of the test to this type of drug is indicated by the significant improvement in correct detections following dexamphetamine 1 mg in Trial 2, and dexamphetamine 2.5 mg in both trials. It is possible that sensitivity of the test was underestimated because the time of peak drug action may well have occurred during the hour between the second and third tests. In both trials the rarity of false alarms prevented significant conclusions being drawn from the indices β and d'.

Throughout Trial 2 correct detections are approximately 10% lower as compared with Trial 1. This may have been due to a fortuitous difference between the two groups of subjects, but could have resulted from the effects of drugs and the design of the investigations. In Trial 1 on the first occasion 10 of the 12 subjects received doses of stimulant drug subsequently shown to improve performance. Carry over effects might have raised the performance level following subsequent dummy treatments. In Trial 2, 8 of the 12 subjects received active drug on the first occasion and 4 of these were low doses. Any carry over effects would be expected to be smaller, and occur in fewer subjects.

In marked contrast to the vigilance test the short duration performance tests and subjective effects were less sensitive to drug effects. Consistent dose related trends towards improvement occurred in hand steadiness and tapping rate increased following both drugs, but did not reach significance levels. A significant increase in the proportion of subjects, experiencing stimulant effects only occurred after the highest doses of each drug, indicating that the auditory vigilance test is capable of detecting changes in performance produced by dosages of these compounds which fail to produce any subjective effects.

Both drugs produced tachycardia and increases in systolic blood pressure. The size and dose response relationship of these increases was usually small and this is probably due to the low doses of drugs selected for the purpose of examining the sensitivity of the vigilance test. Martin, Sloan, Sapira and Jasinki (1971) gave intravenous dexamphetamine 7.5 mg, 15 mg, and 30 mg, per 70 kg body weight to a group of 12 subjects and from the effects of these large doses on heart rate and systolic blood pressure it can be seen that 7.5 mg is approaching the lower end of the dose response curve. Only small drug induced changes would be expected from doses used in the present study, and the relative effects produced by these doses would be less than those seen from doses of dexamphetamine 7—5 mg or more. The fact that the small changes measured in the present study were statistically significant emphasizes the importance of highly standardised environmental conditions. It was concluded from the effects on the cardiovascular and central nervous system, together with the similarity to tyramine on the pupil, that 1-benzylpiperazine is an indirectly acting sympathomimetic amine similar to dexamphetamine.

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