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Comparison of the Effects of Dexamphetamine and 1-Benzylpiperazine in Former Addicts

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Summary. The subjective, behavioural and autonomic effects of dexamphetamine 10 mg, 1-benzylpiperazine 100 mg and lactose dummy were compared in a group of 18 former amphetamine addicts. All subjects received the three preparations according to a balanced design under double blind conditions. 1-Benzylpiperazine and dexamphetamine produced indistinguishable subjective effects and both were liked. The effects of both compounds differed significantly from the effects following the dummy preparation. Increases in pulse rate and both systolic and diastolic blood pressure were similar following the two active compounds, but 1-benzylpiperazine produced pupillary dilation whereas no significant change in pupil size followed dummy or dexamphetamine. It was concluded that 1-benzylpiperazine is a compound liable to abuse by an addict population, and that this type of study might be of value in predicting abuse liability of other new drugs.

Key words: 1-Benzylpiperazine, dexamphetamine, prediction of drug abuse.

Reliable methods for the detection of amphetamine-like activity in compounds undergoing early clinical studies are of increasing medical and social importance because of the possible abuse by a susceptible population. Originally synthesised as a potential antihelminthic agent 1-benzylpiperazine was subsequently found to reverse the effects of tetrabenazine in rats and mice, indicating potential antidepressant activity of clinical importance (Miller, Green and Young, 1971). In addition, however, hyperactivity, involuntary head movements and a reduction of reaction time in shock avoidance studies in rats indicated that the compound had a similar type of action to dexamphetamine. It was therefore necessary to establish whether this compound produced amphetamine-like effects in man before proceeding with clinical trials in depressed patients.

Pharmacodynamic studies in man were reported by Munro-Faure, Peck, Pullin and Young (1971), and Bye, Munro-Faure, Peck and Young (1973), in which the effects of 1-benzylpiperazine and dexamphetamine on various aspects of human behaviour and autonomic function were compared, and close similarity between the two compounds was found. Two studies were each conducted on 12 healthy volunteers none of whom had any previous experience of amphetamine-like drugs. The effects of the two compounds on the heart rate and blood pressure were similar and both were shown to improve performance in the test of auditory vigilance described by Wilkinson (1968). Subjective effects assessed using the adjective checklist of Legge and Steinberg (1962) suggested stimulant activity when subjects received either 7.5 mg dexamphetamine or 100 mg 1-benzylpiperazine, the two highest doses used.

The present study compared both subjective and autonomic effects of dexamphetamine, 1-benzylpiperazine and a lactose dummy in a group of patients under the psychiatric care of one of us (M.E.), all of whom had had extensive experience of the effects of amphetamine and related drugs. Volunteers from a population prone to abuse drugs of this type had two major advantages over drug naive subjects when comparison of subjective effects is the chief aim. Firstly, the patient's previous knowledge of amphetamine effects enabled them to make a judgement on points of similarity or difference between these effects and those produced by the new compound. By including dexamphetamine and a placebo among the test preparations and assessing effects under double blind conditions a measure of both the reliability of the patients' reports and the validity of the method of assessment was obtained. Secondly, it was possible to obtain a measure of the patient's degree of liking for the preparations used in a way similar to that of Fraser, Van Horn, Martin, Wolbach and Isbell (1961). It was felt that this information obtained from a population prone to abuse of drugs of this type would have more relevance in predicting possible abuse of 1-benzylpiperazine than studies in normal volunteers.

Methods

Subjects

Eighteen physically fit volunteers who had had extensive experience of amphetamine were selected. They had not taken amphetamine for four weeks before the trial; no-one was taking any antidepressant drugs or major tranquillisers. The subjects were naturally divisible into two groups. The first group consisted of eight males and two females aged between 16 and 29 years, who had all had experience of multiple drug abuse, e.g. amphetamine, barbiturates, lysergic acid diethylamide and cannabis. The second group consisted of eight females aged between 34 and 50 years who had only abused amphetamine and related compounds.

The procedure of the clinical trial, including its double blind nature, was explained to the subjects prior to the commencement of the experiment. Subjects were told that they would receive an amphetamine-like drug and a new drug, and an inactive preparation, and that different preparations might be given to different subjects on one day. They were warned that they would be asked about any late effects of the drug. The importance of honest reporting was emphasized.

Preparations Used and Design of Experiment

The preparations used in this trial were dexamphetamine sulphate 10 mg, 1-benzylpiperazine hydrochloride 100 mg and a placebo of lactose made up to the same volume and placed in identical capsules. Each subject received all three of the preparations on separate occasions with an interval of at least one week between the separate parts of the trial.

The study was designed to include all possible combinations of the order in which these three preparations could be administered and is illustrated in Table 1. Each of the subjects thus received each of the three preparations in turn on three separate days. Each preparation was administered to six subjects on the first occasion in which they were included in the trial, to six subjects on the second day of their inclusion in the trial, and to six subjects on the third day of their inclusion. On each day of the trial there were three subjects each of whom received a different preparation. The design therefore was a complete balanced block replicated three times.

The subjects were allocated at random to one particular sequence of preparations and the capsules were labelled with the subject's number and the day of the experiment. Neither the subject nor the physician were aware which preparation was being given to which subject and hence the study was double blind.

Procedure on the Day of Experiment

Three subjects reported to the ward at 8.30 a.m. not having had breakfast. Baseline observations were made of pulse, blood pressure, pupil size, mental state and each subject was scored on a psychiatric rating scale derived from that proposed by Malamud, Hoagland and Kaufman (1946). The capsules were administered orally by the physician, one to each subject at 15 min intervals. Observations were repeated at one, two and four hours after their administration and at these times questionnaires were completed by the subject and physician. The subjects were given breakfast 1½ h after taking the capsule and lunch after the termination of the experiment. On the second and third experimental days the same procedure was followed and in addition the subjects were asked to report any late effects they had observed from the previous test day, e.g. alteration in sleep pattern, mood or appetite. The physician was informed by post of any late effects following the third day. The breakfast menu was recorded for each subject on the first occasion and the same menu was provided on the two subsequent occasions.

Table 1. *Design of the experiment*

Subject No.	1st occasion	2nd occasion	3rd occasion
1	A	B	P
2	B	P	A
3	P	A	B
4	A	P	B
5	B	A	P
6	P	B	A

The treatments administered were: A = 10 mg dexamphetamine sulphate, B = 100 mg 1-benzylpiperazine hydrochloride, P = lactose.

This completely balanced block was replicated three times giving a total of 18 subjects. Subjects were allocated numbers at random.

Observations

All assessments were made by one physician.

a) Physical examination. The radial pulse rate, and blood pressure measured using a sphygmomanometer, were recorded after the subject had been lying supine for six minutes. Three readings of each were made at two minute intervals and the mean values were recorded. Pupil diameter was measured, using a transparent millimetre ruler, after the subject had been sitting for two minutes in a shuttered

sideroom with constant dim lighting. Other features, such as flushing, excessive sweating and tremor were observed and recorded.

b) *Psychiatric rating*. The psychiatric rating scale consisted of nineteen scales each of which was scored from one to six in two directions either to the right or to the left of a wide baseline. Baseline scores received a zero rating. The scores to the right indicated depression of functions and the scores to the left indicated excitation of functions. In the event nine out of the nineteen scales were useful in the trial and these were: motor activity, aggressiveness, socialisation, attention, speech, nutrition, sleep, mood and affect.

c) *Subject's questionnaire*. Six questions were asked:

(S1) Do you feel the effects of the drug?
(S2) Are the effects like amphetamines?
(S3) Do you like the drug?
(S4) Do you dislike the drug?
(S5) Are there any special effects you would like to comment on? Define each and score on 0—4 scale (vide infra).
(S6) Would you like to take the drug each day?

The questions were scored on a 0—4 scale as shown in Table 4.

d) *Physician's questionnaire*. The questions the physician answered were:

(P1) Is there any behavioural evidence of drug effect? This question was answered on a 0—4 scale as above.
(P2) Is the subject's behaviour like that seen after amphetamines? This question was answered 'Yes', 'No' or 'Doubtful'.
(P3) Do you think the subject liked or disliked the effect of the drug? This question was answered 'Liked', 'Disliked' or 'Doubtful'.

The physician also made a short clinical assessment of mental state, behaviour and attitude.

Results

The balanced design required that eighteen subjects should be seen on three separate occasions making 54 independent trials to complete the study. Fiftythree of these trials were successful but one subject was unable to attend for his third visit as he was sent to Cornwall as a condition of Probation. To preserve the balance the results for this missing experiment were estimated by the method of 'the missing plot' of Fisher (1935) which maintains the balance, does not introduce any bias to the trial but reduces the degrees of freedom by one in any test of statistical significance.

Table 2. *Mean value for eighteen subjects at each hour for each preparation*

Physiological variables	Preparation	Hour 0	Hour 1	Hour 2	Hour 4	Statistical significance of differences
Systolic B.P. mm/Hg	Dexamphetamine	122.4	134.8	138.6	132.2	p less than 0.001
	1-Benzylpiperazine	123.2	136.3	135.1	129.3	
	Placebo	125.8	126.3	128.1	125.2	
Diastolic B.P mm/Hg	Dexamphetamine	74.9	81.1	79.5	79.8	p less than 0.05
	1-Benzylpiperazine	74.9	82.4	78.3	78.3	
	Placebo	78.9	79.3	75.1	75.1	
Pulse rate beats/min	Dexamphetamine	77.1	82.3	88.4	87.1	p less than 0.001
	1-Benzylpiperazine	74.6	82.6	88.8	85.2	
	Placebo	75.6	77.7	81.9	78.1	
Pupil size mm	Dexamphetamine	6.08	6.22	6.22	6.17	p less than 0.001
	1-Benzylpiperazine	6.14	6.47	6.56	6.33	
	Placebo	6.03	6.28	6.28	6.08	

Each variable was then analysed by the method of 'Analysis of Variance' so that separate and independent estimates could be made of the statistical significance of any differences between the subjects, between the drugs or between the order of the days on which the trials were made.

1. Physiological Variables

The mean values of the physiological variables before and after administration of each drug are given in Table 2.

Systolic blood pressure: There was no statistically significant difference ($p > 0.05$) between the mean value of subjects' blood pressure before starting any of the three preparations. After all three preparations the mean systolic blood pressure rose during the first hour, remained high during the sec-

ond hour and had fallen again by the end of the fourth hour. In the pattern of this rise and fall there was a statistical difference between the mean values of systolic blood pressure observed after the administration of the different preparations ($F = 9.86$; $p < 0.001$). This difference was entirely due to the difference between either of the two active preparations and the placebo, there was no significant difference between the two active preparations themselves.

Diastolic blood pressure: Again there was no statistical significance in the difference observed between the subjects before administration. The two active preparations both gave a greater rise than the placebo but the level of statistical significance was lower than that found for systolic blood pressure ($F = 3.82$; $p < 0.05$). There was no significance in the difference between the active preparations. The observed significance was entirely due to the difference between the placebo and the other two preparations.

Pulse rate: The pulse rate of all subjects rose during the first two hours of the trial and had fallen after the subsequent two hours. This increase was significantly greater after administration of either of the active preparations than after the placebo ($F = 18.17$; $p < 0.001$). The difference between the active preparations was not statistically significant ($p > 0.05$).

Pupil size: The mean pupil size tended to increase during the first two hours after all three preparations and to decrease during the subsequent two hours. This increase was significantly greater after the administration of 1-benzylpiperazine than after either dexamphetamine or the placebo $F = 10.85$; $p < 0.001$). There was no significant difference in mean pupil size after either dexamphetamine or the placebo.

2. *Psychological Variables*

The mean score for these variables after each drug at each point of observation are given in Table 3.

a) Psychiatric rating scale. Excitation Score: The excitation score after all three drugs behaved in a manner similar to that of the systolic blood pressure, there was a rise during the first hour which was sustained during the second and which was followed by a fall during the next two hours. There was a greater rise in the excitation score after administration of either of the two active preparations compared with the placebo ($F = 9.86$; $p < 0.001$). The difference between the two active preparations was not significant.

Table 3. *Mean reading for 18 subjects at each hour for each preparation*

Variables	Preparation	Hour 1	Hour 2	Hour 4	Statistical significance of the differences
Excitation Score	Dexamphetamine	1.3	1.4	0.7	p less than 0.001
	1-Benzylpiperazine	0.6	1.1	0.4	
	Placebo	0.2	0.2	0.0	
Depression Score	Dexamphetamine	0.0	0.3	0.0	Not significant
	1-Benzylpiperazine	0.1	0.5	0.1	
	Placebo	0.1	0.1	0.3	
Physician's	Dexamphetamine	1.0	1.2	0.7	p less than 0.001
Amphetamine	1-Benzylpiperazine	0.8	1.0	0.8	
Score	Placebo	0.3	0.2	0.1	
Subject's	Dexamphetamine	0.9	1.0	0.8	p less than 0.001
Amphetamine	1-Benzylpiperazine	1.2	1.2	1.0	
Score	Placebo	0.4	0.4	0.2	

Excitation and depression scores refer to the psychiatric rating scale modified from Malamud *et al.* (1946)

Depression Score: There was no statistically significant difference between the mean values of these scores after the administration of any of the preparations.

b) Subject's and physician's questionnaires. Amphetamine Score: The replies to the question "Are the effects like amphetamine?" were scored on a 0—4 scale and a mean value calculated for each group of 18 subjects at 1 h, 2 h and 4 h after taking the preparations. This mean value was called the subject's amphetamine score. Similarly the replies by the physician to the question "Is the subject's behaviour like that seen after amphetamine?" were also scored and mean values calculated. These scores are given in Table 3. The values were analysed as if they were a continuous variable and it was found that for the subjects' amphetamine scores there was a significant difference between either of the two preparations and the placebo ($F = 35.9$; $p < 0.001$). There was a dif-

ference between the two active agents ($t=4.0$; $p<0.001$) in that the subjects considered that the action of 1-benzylpiperazine had a higher amphetamine rating than had dexamphetamine itself. Similarly the physician's amphetamine score distinguished between the three preparations ($F=45.0$; $p<0.001$) but there was no difference between the two active drugs.

The answers to the subjects' questionnaires at the end of the second hour after taking the various preparations are shown in Table 4. This was the time at which the active drugs were most effective. For the first three questions S1, S2 and S3, there was significant difference in the replies after the three treatments ($p<0.05$) using the Kolmogorov Smirnov Procedure and in each case the replies indicated that on average the subjects could detect an active agent but could not distinguish between them, they felt that these effects were like those of dexamphetamine and they liked the effects. For none of these questions was there a statistical significance in the difference between the active preparations but it is interesting that more subjects, 14 out of 18 (78%), thought that the action of 1-benzylpiperazine was like that of dexamphetamine than did so after dexamphetamine itself, 10 out of 17 (59%). There was no statistical significance in the answers to questions S4—S6.

The replies by the physician to questions P1, P2 and P3 (two hours after taking the capsules) are shown in Table 5. The physician was able to detect a behavioural effect in the subjects even more certainly than they could themselves. The differences between the three groups is statistically significant ($p<0.005$) and again this difference is due entirely to that between the two active agents and the placebo. She was not able to detect a difference between the agents although pupil dilation was a possible clinical sign to identify the 1-benzylpiperazine but this association was not understood until the code was broken.

In reply to P3 the physician considered that 14 out of 18 (78%) liked 1-benzylpiperazine and that 11 out of 17 (65%) liked the dexamphetamine and only 3 out of 18 (17%) liked the placebo.

c) Additional clinical observations. The physcian also made certain observations on the state of the subjects at 1 h, 2 h and 4 h after taking the preparations. Flushing was observed on eight occasions after 1-benzylpiperazine, on nine occasions after dexamphetamine and only twice after the placebo. Sweating was observed on four occasions after 1-

Table 4. *Number of subjects in the different reply categories of the subjects' questionnaire two hours after drug administration*

Question	Answer	1-Benzyl-piperazine	Dexamphetamine	Placebo
S1	0	3	7	11
Do you feel the effects	1	8	4	6
of the drug?	2	5	4	0
	3	2	2	1
S2	0	4	7	13
Are the effects like	1	8	4	4
amphetamine?	2	4	5	0
	3	2	1	1
S3	0	4	7	13
Do you like the	1	6	3	4
drug?	2	6	3	0
	3+4	2	4	1
S4	0	14	11	8
Do you dislike the	1	4	5	8
drug?	2	—	1	1
	3	—	—	1
S5	0	4	7	11
Are there any special	1	8	4	6
effects?	2	3	2	1
	3+4	3	4	—
S6	0	7	6	13
Would you like to take	1	3	3	4
the drug every day?	2	5	3	—
	3+4	3	5	1

0 = Not at all, 1 = Slightly, 2 = Moderately, 3 = A lot, 4 = An awful lot.

benzylpiperazine, on eight occasions after dexamphetamine and not at all after the placebo.

d) Effect of sequence of preparations. As a consequence of the complete balance of the design of this trial it was possible to identify the effect of the preparations themselves. The only factors which demonstrated a significant temporal change were the subjects' pulse rate and the response to questions S1 and P1. The pulse rate was significantly higher on the first day in which a subject took part in an experiment and showed a higher rise on that day irrespective of what preparation was used.

Similarly both the subjects and the physician gave a higher amphetamine rating to the preparation used on the first day than would have been justified from the drug effect alone. None of the other factors showed a significant difference in the mean score at the different sessions.

The subjective effects as measured by a simple questionnaire and a psychiatric rating scale were also similar for the two drugs and differed from that of the response to the placebo. In addition the subjects expressed a similar liking for the effects of both active drugs which they, as former addicts, recognised as being like that of amphetamine. The fact that ten of the subjects expressed dislike of the placebo probably reflects disappointment on failing to receive an anticipated drug experience. At doses of 100 mg of 1-benzylpiperazine and 10 mg dexamphetamine the scores were slightly higher for the 1-benzylpiperazine which suggests that the effective potency of the two drugs was approximately in the ratio of 10 to 1.

Table 5. *Number of subjects placed in the various categories by the physician two hours after drug administration*

Question	Answer	1-Benzyl-piperazine	Dexamphetamine	Placebo
P1	0	3	3	14
Is there any behavioural	1	7	6	3
evidence of drug	2	7	6	1
effect?	3	1	2	—
P2	No	5	4	15
Is the subject's	Slight	7	5	2
behaviour like that seen after amphetamine	Positive	6	8	1
P3	Disliked	1	—	3
Do you think the subject	Doubtful	3	6	12
liked the drug?	Liked	14	11	3

Discussion

These results show that at the doses used in this trial 1-benzylpiperazine produces effects similar to dexamphetamine upon a group of patients who were former addicts. The objective effects on behaviour and physiological effects on pulse rate and blood pressure were similar for the two drugs and differed significantly from the responses observed after a placebo. Heart rate and both diastolic and systolic blood pressure, taken under basal conditions, were higher for the group of former addicts than for the healthy volunteers studied by Bye, Munro-Faure, Peck and Young (1973). These differences may be ascribable to the previous medical history of the former addicts, but might be due to a greater age range, degree of physical fitness, a hospital environment, and different observers.

There was one marked difference between the two active drugs in that 1-benzylpiperazine caused pupillary dilation, but dexamphetamine did not.

Fraser, Van Horn, Martin, Wolbach and Isbell (1961) investigated the subjective effects of amphetamine and similar drugs in former addicts, and extension of this work resulted in The Addiction Research Center Inventory comprising 550 questions, 38 items of which Haertzen (1966) found particulary useful in detecting subjective effects of amphetamine-like drugs. Martin, Sloan, Sapira and Jasinski (1971) used this questionnaire to study subjective effects of other amphetamine-like stimulant drugs in former addicts. Götestam and Gunne (1971) in a double blind trial with a cross over studied the effect of two anorectic drugs, fenfluramine and AN448, together with a placebo in 22 subjects who were dependent upon amphetamine; they showed that AN448 gave subjective effects similar to amphetamine, whereas the fenfluramine did not differ from the placebo. They did not publish statistical details and they did not administer amphetamine, so consequently the reliability of their subjects in recognising amphetamine was not

validly tested. The present investigation was designed to see if amphetamine-like activity could be detected in a new drug employing a simple questionnaire. The validity of this questionnaire was assessed by inclusion of dexamphetamine in the treatments.

In our study at the time of peak drug action, 7 out of 18 subjects thought they had received an active drug following the placebo, while 7 out of 17 failed to recognise subjective effects of dexamphetamine. Of the placebo reactors, 6 out of the 7 registered only the lowest rating for the action of the drug and of those, three had received the placebo on their first administration of treatment. Joyce (1959) studied placebo response in healthy medical students and while it is difficult for us to make exact comparisons with his study due to differences in design, it seems probable that only one of our 18 subjects would have been classified by Joyce as a reactor, whereas one fifth to a quarter of his medical students who were not experienced drug takers, were placebo reactors.

We considered carefully the risk of reactivating amphetamine abuse in this group, but assessed this risk to be small because all the subjects selected were well known to the investigators, one of whom (M.E.) was responsible for their psychiatric care, and volunteered to take part with enthusiasm. The subjects have now been followed-up for two years subsequent to the study and no clinical problems attributable to this trial have been detected. It is therefore suggested that an investigation of this type in which a small number of subjects selected from a population prone to drug abuse and in whom the drug effect is validated, might be useful to test new psychoactive compounds preventing clinical use of new amphetamine-like stimulants. We recommend that this type of investigation should be undertaken more extensively at an early stage in the development of new drugs. On the basis of these results the Wellcome Foundation Ltd. decided against proceeding with further clinical studies on 1-benzylpiperazine. Supplies of 1-benzylpiperazine are, however, freely available from commercial chemical companies and it is advisable in view of this work that it should be placed under statutory control similar to those regulating the use of amphetamine.

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