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A COMPARISON OF THE EFFECTS OF CHLORPHENTERMINE, DIETHYLPROPION AND PHENMETRAZINE ON CRITICAL FLICKER FREQUENCY

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Substituted phenylethylamines, of which amphetamine is the parent compound, have marked central nervous stimulant actions. When taken to excess, amphetamine (Connell, 1958) and phenmetrazine (Bartholomew and Marley, 1959) produce a distinctive psychosis. Chronic consumption over long periods of time can also lead to dependence and addiction (Connell, 1966). Several amphetamine derivatives widely used as appetite suppressants may have a similar abuse potential to amphetamine. An investigation was carried out to compare the effect of four of these drugs on critical flicker frequency and on the modification of the critical flicker frequency by adaptation to intermittent light of varying frequencies (Alpern & Sugiyama, 1961 ; Turner, 1964, 1965a).

The critical flicker frequency is a sensitive test for assessing centrally acting drugs in terms of potency and duration of action (Roback, Krasno & Ivy, 1952 ; Holland & Gooch, 1962 ; Ideström & Cadenius, 1963 ; Turner, 1965b & c). Alkalinization of the urine, which reduces the urinary excretion of amphetamine (Beckett, Rowland & Turner, 1965) enhances and prolongs the stimulant effect of amphetamine on the critical flicker frequency (Smart & Turner, 1966).

METHODS

The technique used has been described elsewhere (Turner, 1964 ; Smart & Turner, 1966), and in principle involved exposing subjects to an intermittent light of 25 or 50 c/s, for 1 min before determining ascending or descending thresholds of critical flicker. Thus, at any one time, four determinations were made, namely ascending and descending thresholds after exposure to 25 and 50 c/s, with an interval of 2 min between each determination. The source was a neon lamp of luminance 12.5 ft. Lamberts viewed through a telescope in which a lens was mounted so that parallel light reached the eye through an artificial pupil of 2 mm diameter. The lamp was a rectangular pulse generator (Solatron Pulse Generator Type GO 1101.2), with a mark-space ratio of 1 : 1 (Fig. 1). The experimenter sat opposite the subject with the apparatus and a white screen between them, and he adjusted the flicker rate in 0.5 c/s steps. The subject closed his eyes during

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changes in flicker frequency. On opening them, he was instructed, without a limit on time, to look directly at the light and decide if it appeared to flicker or not. The critical flicker frequency was taken to be the fastest rate at which the source was considered to be flickering as opposed to being steady. This threshold was determined either by an approach from a lower to a higher frequency (ascending threshold) or vice versa (descending threshold).

The experiments were carried out in a room 4 ft×12 ft with grey walls and ceiling, with background illumination of 8 lm./ft.^{2}

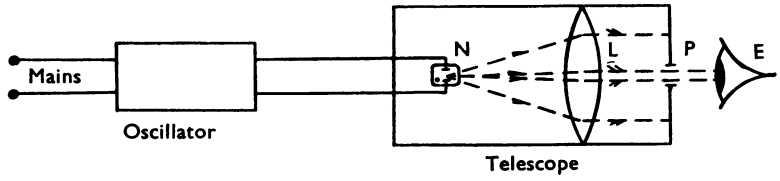

Fig. 1. Diagram of apparatus used to measure critical flicker frequency. N=neon lamp at focal point of lens (L), P=artificial pupil of 2 mm diameter, E=eye of subject.

Ten healthy subjects of both sexes aged between 22 and 32 yr were studied. At 9 a.m., 1.5 hr after a light breakfast, the four determinations of critical flicker frequency were made in random order. One of four drugs, chlorphentermine 25 mg, diethylpropion 25 mg, phenmetrazine hydrochloride 25 mg, and phenmetrazine theoclate 30 mg+phenbutrazate hydrochloride 20 mg or a placebo were then administered in a double-blind randomized procedure based on a latin-square design, and the four thresholds measured again at 3 and 6 hr after administration. Subjects abstained from tea, coffee and nicotine during the experimental period. All subjects received each treatment with an interval of 3–4 days between.

RESULTS

Table 1 shows the mean C.F.F. values obtained at 0 hr—that is, before administration of the drug—and at 3 and 6 hr after administration.

Table 2 shows the values of the differences (averaged over thresholds and frequencies, and adjusted for regression on the corresponding differences at 0 hr) between each of the four active drugs and the placebo at 3 and 6 hr. The values of these differences are derived from the means in Table 1. Table 2 also gives the values of the generalized distance, D^2, between the response to placebo and each drug for the 3-hr and 6-hr values separately and in combination; the values of D^2 are again corrected for regression on initial values. The calculation of these values, and the method of adjustment for regression, are discussed in the section on statistical analysis.

From the values of D^2 in Table 2 the following conclusions may be drawn:

For Drug A (phenmetrazine hydrochloride) there is a significant difference from the placebo at 3 hr ($0.01>P>0.005$) and at 6 hr ($0.005>P>0.001$). However, when the effect of using both measurements simultaneously is compared with the effect of each separately, it is found that $D^2_{3,6}$ is significantly greater than D^2_3 ($0.05>P>0.025$) but not significantly greater than D^2_6 ($0.1>P>0.05$). Thus, the difference between placebo and A is not determined with more precision by any combination of the two post-drug responses than is the case with the 6-hr value alone.

TABLE 1

FLICKER FUSION THRESHOLDS (c/s): MEANS OF 10 OBSERVATIONS

Threshold is specified by the conditioning frequency (25 or 50 c/s) and by ascending (A) or descending (D). Thus, for example, 50A indicates an ascending threshold measured after exposure of the subject's eye to light flickering at 50 c/s

Drug	Threshold	Time (hr) after drug		
		0	3	6
A	50A	47·65	47·60	47·10
	50D	44·90	46·10	45·20
	25A	43·50	44·60	44·80
	25D	43·60	43·50	43·55
B	50A	47·45	47·65	47·60
	50D	45·65	45·95	45·50
	25A	45·35	44·45	44·60
	25D	43·75	43·90	43·65
C	50A	47·00	48·15	46·25
	50D	45·35	46·35	44·45
	25A	44·40	44·40	44·00
	25D	42·70	44·15	42·90
D	50A	46·05	47·70	46·00
	50D	45·90	45·00	44·15
	25A	43·90	42·75	42·45
	25D	43·45	42·90	42·00
E	50A	46·25	46·45	45·45
	50D	45·10	44·80	44·15
	25A	44·00	42·80	43·15
	25D	42·70	42·20	42·70

TABLE 2

ADJUSTED DIFFERENCES BETWEEN PLACEBO AND ACTIVE DRUGS, AND CORRESPONDING VALUES OF D_2

Drug	d_3	d_6	D_3^2	D_6^2	$D_{3,6}^2$	Best discriminator
A	1·13	1·15	0·3549	0·4085	0·5780	d_6
B	0·76	1·10	0·1605	0·3738	0·4200	d_6
C	1·47	0·41	0·6006	0·0519	0·6011	d_3
D	0·32	−0·33	0·0285	0·0337	0·0916	Neither

For Drug B (phenmetrazine theoclate + phenbutrazate hydrochloride) a similar result is obtained, except that the difference at 3 hr is not significant ($0.1>P>0.05$). The difference at 6 hr is significant ($0.01>P>0.005$) and once again the distance obtained by combining the responses at 3 and 6 hr is not significantly greater than that derived from the 6-hr value alone.

For Drug C (diethylpropion) the situation is reversed; the value of D_3^2 is highly significant ($0.001>P$) while the 6-hr value is not significant ($P>0.2$), and the combination of the 3-hr and 6-hr values is not significantly better than the 3-hr value alone.

For Drug D (chlorphentermine) neither the 3-hr nor the 6-hr value indicates any significant difference between drug and placebo whether the responses are considered separately or in combination.

STATISTICAL ANALYSIS

In this experiment there were 20 treatment combinations (ascending and descending threshold measurements with 25 c/s and 50 c/s conditioning for each of five drugs). All the treatments were administered in a random order to each of 10 subjects and on each occasion measurements were made before administration of the drug and at 3 and 6 hr thereafter. There are thus 200 sets of three measurements on which to carry out an analysis.

Since measurements taken from the same subject at comparatively short intervals of time may be assumed to be correlated, it is desirable to use a method of analysis which allows for such correlation. We have, therefore, performed an analysis of dispersion (Rao, 1952). This technique is the multivariate analogue of the analysis of variance; the major difference between the two techniques being that, in the analysis of variance, we are concerned to subdivide a sum of squares, and to test the significance of sources of variation by means of variance ratios, whereas in the analysis of dispersion we are concerned to subdivide a matrix of sums of squares and products, and to test the significance of sources of variation by means of ratios of the determinants of the resultant matrices.

In the present example there are three variables, namely the values of the C.F.F. at 0 hr and at 3 hr and 6 hr after taking the drug. If we refer to these as χ_0, χ_3 and χ_6 respectively, then the sum of squares or products for any variable or pair of variables may be defined as

$$\chi_{ij} = \Sigma(x_i - \chi_i)(x_j - \chi_j)$$

where i and j can take any of the values of 0, 3 or 6. We thus obtain a 3×3 matrix which can be subdivided into matrices associated with treatments, subjects, etc.; and since the matrices are symmetric we can effect a substantial saving of space on the page by presenting the upper triangle of each matrix as a single line. Thus the figures in the "Total" line of Table 3 represent the upper triangle of the matrix

2712.84	2710.19	2353.51
2710.19	3636.52	2875.74
2353.51	2875.74	3061.19

Table 3 shows the analysis of dispersion for all three variables. The rows for "Subjects" and "Days" are of no intrinsic interest, but, as in the analysis of variance, the variation due to these two factors must be removed from the residual Sums of Squares and Products (SSP) matrix if tests of significance are to have maximum precision.

It is also necessary, before testing for significant differences between treatments, to examine the effect of variations in the control values χ_0 on the post-drug values χ_3 and χ_6. The matrix of SSP attributable to the regression of χ_3 and χ_6 simultaneously on χ_0 is obtained from the matrix equation

$$\mathrm{R} = \begin{bmatrix} \chi_{0,3} \\ \chi_{0,6} \end{bmatrix} \begin{bmatrix} \chi_{0,0} \end{bmatrix}^{-1} \begin{bmatrix} \chi_{0,3} & \chi_{0,6} \end{bmatrix}$$

where the χ_{ij} are obtained from the "Residual" line of Table 3. The analysis is shown in Table 3a.

The regression is tested for significance by means of Wilks' Λ-criterion (Rao, 1952). The determinant of the "Error" matrix is

$$\begin{vmatrix} 597.26 & 182.66 \\ 182.66 & 537.39 \end{vmatrix} = 287596.8758$$

and the determinant of the matrix for "Error plus Regression" is

$$\begin{vmatrix} 870.66 & 337.46 \\ 337.46 & 625.03 \end{vmatrix} = 430309.3682$$

The value of Λ is therefore 0.668349, which leads to a variance ratio of 40.688 with 2 and 164 D.F. ($P<0.001$). The regression is thus highly significant and must be taken into account in subsequent calculations.

A further refinement of the analysis is to subdivide the SSP matrix for "Treatments" (which is associated with 19 D.F.) into 19 separate matrices, each associated with 1 D.F., by means of appropriate sets of orthogonal factorial coefficients. The 19 contrasts thus produced represent the effects of thresholds and frequencies on the one hand, and the effects of differences between drugs on the other, together with the interactions between the two groups of effects. Table 3b shows the result of the subdivision.

The first four lines of Table 3b call for special comment. Since the four active drugs are not related to one another in any obvious way, there is no convenient way of comparing their effects in this part of the analysis; the obvious procedure of comparing each drug in turn with the placebo does not, unfortunately, yield an orthogonal set of contrasts. One D.F. of the four associated with differences between drugs is associated with the contrast between placebo on the one hand and the average response to all four drugs on the other; and this contrast is represented in the first line (P) of Table 3b. The three lines A, B and C represent, respectively, the contrasts (A vs. the average of B, C and D), B vs. the average of C and D) and C vs. D). These contrasts are orthogonal but not very informative. However, the interactions between these contrasts and the effects of frequency (F) and threshold (T) are of interest, since any interaction between either T or F and any contrast between drugs (even a somewhat arbitrary one) would, if statistically significant, indicate that one or more of the drugs was producing different effects according to the combination of frequency and threshold used to measure the effect of the drugs. As it happens, none of the interactions between drugs and frequency or threshold is significant, and the problem, fortunately, does not arise.

The various components of the Treatments SSP matrix were tested for significance by means of the Λ-criterion. In every case the 2×2 matrix based on χ_3 and χ_6 was adjusted for regression on χ_0 as described above, and the test of significance performed using the determinants of the adjusted matrices.

The P contrast was found to be statistically significant ($0.025>P>0.01$). The T and F contrasts were both highly significant, but being averaged over all drugs including the placebo, do not provide any information about differences between drugs. As mentioned above, no significant interactions between drugs and frequency or threshold effects were found.

The existence of a significant P effect indicates that one or more of the drugs is producing a significant effect on CFF. The effect of each drug, averaged over thresholds and frequencies (as is proper in the absence of interactions between T or F and drugs) was compared with the placebo by means of the generalized distance D^2.

TABLE 3
ANALYSIS OF DISPERSION

Source of variation	Degree of freedom	Sums of squares and products					
		$x_{0,0}$	$x_{0,3}$	$x_{0,6}$	$x_{3,3}$	$x_{3,6}$	$x_{6,6}$
Total	199	2,712·84	2,710·19	2,353·51	3,636·52	2,875·74	3,061·19
Treatments	19	424·25	459·54	385·15	641·36	493·81	443·71
Subjects	9	1,528·59	1,702·57	1,645·89	1,943·33	1,863·71	1,862·64
Days	4	103·22	124·39	82·59	181·17	130·77	129·82
Residual	167	656·79	423·69	239·89	870·66	337·46	625·03

TABLE 3a
REGRESSION ANALYSIS

Source of variation	Degree of freedom	Sums of squares and products					
		$x_{0,0}$	$x_{0,3}$	$x_{0,6}$	$x_{3,3}$	$x_{3,6}$	$x_{6,6}$
Residual	167	656·79	423·69	239·89	870·66	337·46	625·03
Regression	1	—	—	—	273·40	154·80	87·64
Error	166	—	—	—	597·26	182·66	537·39

TABLE 3b

SUBDIVISION OF SSP MATRIX FOR TREATMENTS

Source of variation	Degree of freedom	Sums of squares and products					
		$x_{0,0}$	$x_{0,3}$	$x_{0,6}$	$x_{3,3}$	$x_{3,6}$	$x_{6,6}$
P	1	8·82	21·16	13·02	50·75	31·23	19·22
A	1	0·83	−0·85	−3·50	0·88	3·59	14·70
B	1	13·30	5·89	24·72	2·60	10·94	45·94
C	1	0·03	0·88	0·56	27·61	17·63	11·25
T	1	77·50	72·83	81·86	68·45	76·93	86·46
F	1	286·80	360·45	264·05	453·01	331·85	243·10
TF	1	3·25	8·93	6·06	24·50	16·63	11·28
PT	1	0·01	0·01	0·11	0·03	0·25	2·42
PF	1	0·06	−0·10	0·29	0·17	−0·47	1·36
PTF	1	1·36	0·72	0·21	0·38	0·11	0·03
AT	1	0·08	0·12	0·15	0·19	0·24	0·30
AF	1	1·30	−0·76	−1·30	0·44	0·76	1·30
ATF	1	15·77	−7·88	−2·36	3·94	1·18	0·35
BT	1	3·38	−0·12	1·07	0·00	−0·04	0·34
BF	1	1·43	1·93	−0·15	2·60	−0·21	0·02
BTF	1	0·23	−0·66	0·06	1·84	−0·18	0·02
CT	1	9·45	−1·72	2·06	0·31	−0·38	0·45
CF	1	0·53	−0·89	−1·54	1·51	2·61	4·51
CTF	1	0·08	−0·41	−0·22	2·11	1·14	0·61

In order to calculate D^2 we require the matrix of error variances and covariance of χ_3 and χ_6; this matrix is obtained by dividing the values in the "Error" line of Table 3a by the appropriate number of D.F., namely 166. The resultant matrix is

3.5980	1.1004
1.1004	3.2373

The elements of the variance–covariance matrix, being derived from the error line of Table 3a, are already adjusted for regression. The differences between drug and placebo means must also be adjusted; the procedure is discussed by Cochran & Bliss (1948). In the present notation, let d_3 and d_6 be the differences between drug and placebo means at 3 and 6 hr respectively, and let d_0 be the corresponding difference at 0 hr. Then the adjusted differences d_3^1 and d_6^1 are given by the expression

$$\begin{bmatrix} d_3^1 \\ d_6^1 \end{bmatrix} = \begin{bmatrix} d_3 \\ d_6 \end{bmatrix} - \begin{bmatrix} b_{3,0} \\ b_{6,0} \end{bmatrix} \begin{bmatrix} d_0 \end{bmatrix}$$

where $b_{3,0}$ and $b_{6,0}$ are the coefficients of regression of χ_3 and χ_6 on χ_0. The regression coefficients are derived from the expression

$$\begin{bmatrix} b_{3,0} \\ b_{6,0} \end{bmatrix} = \begin{bmatrix} \chi_{0,3} \\ \chi_{0,6} \end{bmatrix} \begin{bmatrix} \chi_{0,0} \end{bmatrix}^{-1}$$

where the χ_{ij} are derived from the "Residual" line of Table 3.

Since there are two variables (χ_3 and χ_6) we may calculate three values of D^2, one based on d_3^1 one based on d_6^1 and one based on both simultaneously. The method of calculation and tests of significance are given by Rao (1952). In the present case we obtain

$$D_3^2 = \frac{(d_3^1)^2}{v_{3,3}}; \quad D_6^2 = \frac{d(_6^1)^2}{v_{6,6}}; \quad D_{3,6}^2 = \begin{bmatrix} d_3^1 d_6^1 \end{bmatrix} \begin{bmatrix} v_{3,3} v_{3,6} \\ v_{3,6} v_{6,6} \end{bmatrix}^{-1} \begin{bmatrix} d_3^1 \\ d_6^1 \end{bmatrix}$$

where D_3^2 is the distance based on χ_3 alone, D_3^2 is the distance based on χ_6 alone, and $D_{3,6}^2$ is the distance based on both values simultaneously. $v_{3,3}$, $v_{6,6}$ and $v_{3,6}$ are the adjusted error variances and covariance of χ_3 and χ_6 derived as described above.

DISCUSSION

Tests of sensation in man show considerable random variation even when carried out under strictly controlled conditions. This may produce significant differences in control readings when several drugs are compared on different days, even though the order of administration may be randomized to eliminate order effects. While it is possible to ignore these variations and simply compare changes in sensory threshold from the control over time following drug administration, possible interrelationships between drugs, subjects and times of testing both before and after drug administration will be lost, with a corresponding reduction in the sensitivity of discrimination between them. For this reason, an analysis of dispersion is best suited to such experimental data. All threshold values after drug administration are adjusted to take account of the scatter of mean control values.

The results of this investigation demonstrate that phenmetrazine hydrochloride 25 mg produced significant elevation of the mean critical flicker frequency at 3 and 6 hr, phenmetrazine theoclate 30 mg + phenbutrazate hydrochloride 20 mg at 6 hr, diethylpropion 25 mg at 3 but not at 6 hr compared with a placebo, while chlorphentermine 25 mg did not produce a significant effect at these times.

The effect of phenmetrazine hydrochloride is not unexpected, in view of its known central stimulant actions both in man and animals (Evans, 1959; Duncan, Rose & Meiklejohn, 1960; Knoll, 1961). Animal studies (Hengen & Siemer, 1955; Hengen, 1957) suggested that phenbutrazate hydrochloride modified the effect of phenmetrazine theoclate on the central nervous and cardiovascular systems and they were, therefore, introduced together in an attempt to reduce these unwanted side-effects of anorectic treatment. Although it is an effective appetite-suppressant agent (Heine & Turner, 1963), this combined preparation was shown to elevate the critical flicker frequency in four subjects between 1 and 3 hr (Turner, 1965b) and in this experiment elevation was present at 6 hr. This difference in time of action may depend on differences in rates of absorption and excretion in the subjects studied. Urine pH is known to be particularly important in determining the rate of excretion and duration of action of amphetamine and its related amines (Beckett *et al.*, 1965; Smart & Turner, 1966). Clinical experience (Practitioner, 1961; Turner, unpublished observations) has shown that this preparation has effects on the central nervous system which are probably similar to other phenmetrazine derivatives.

Diethylpropion produced a significant increase in critical flicker frequency at 3 but not at 6 hr. This is of interest in view of the infrequency with which patients complain of central side-effects from this drug. Seaton, Duncan, Rose & Scott (1961), Cunningham (1963) and de Ramos (1964) found no such effects in a total of 101 patients. Silverstone and Solomon (1965) found that only 3 of 32 patients complained of giddiness or increased tension. Studies in mice, rats and dogs (Martin, 1959; Melander, 1960) confirm that this compound lacks the stimulant effects on the central nervous system found with amphetamine. Our unexpected findings may be due to the fact that the experiment was concerned with the effect of acute administration of a single dose, while these investigators were dealing with chronic administration, when tolerance might develop to these effects. It is also possible that side-effects were present, but like the elevation

of critical flicker frequency, passed off between 3 and 6 hr and so failed to produce troublesome symptoms, particularly insomnia.

Chlorphentermine, like diethylpropion, has been claimed to be free of side-effects of central stimulation (Levin, Trafford, Newland & Bishop, 1963; Seaton, Rose & Duncan, 1964; Russek, 1965) and unpublished data distributed by the manufacturers (William R. Warner & Co. Ltd.) contain results of a comparison of this drug with amphetamine on critical flicker frequency which showed elevation after the latter but not after chlorphentermine. No other experimental details of this investigation are given. The results of our experiment indicate that at 3 and 6 hr chlorphentermine does not differ from a placebo in its effect on critical flicker frequency.

Other experiments (Turner, 1965c; Smart & Turner, 1966) have shown that amphetamine significantly increases critical flicker frequency at 3 hr and dexamphetamine reverses the depressant effect of amylobarbitone on this threshold at 2 and 4 hr. It would appear, therefore, that the stimulant effect of these appetite suppressant drugs on critical flicker frequency can be demonstrated more satisfactorily at 3 than at 6 hr, and that it is unlikely that additional discriminative information will be obtained from the 6 hr reading. It may, however, give information on duration of action which the 3 hr reading alone will not provide.

The absence of other significant interactions in the analysis suggests that none of the drugs tested influences the adaptation of critical flicker frequency by flickering light of different frequencies which is a stable phenomenon (Turner, Patterson & Smart, 1966), or the difference between ascending and descending thresholds (Turner, 1964). The fall in mean critical flicker frequency after the placebo is a consistent finding with the method described and appears to be due to the adaptation procedure (Turner, Sneddon & Smart, in press). Its reversal by these central stimulant drugs suggests that it may represent a fatigue effect.

It is becoming increasingly evident that drugs which produce central nervous stimulation are capable of abuse. Amphetamine decreases fatigue with subjective feelings and objective evidence of increased efficiency (Weiss & Laties, 1962). The "rebound" depression which is an after-effect of the drug may reinforce drug-taking behaviour leading to chronic abuse. The pattern is familiar with amphetamine and, to a lesser extent, phenmetrazine and it is a real or potential danger in amphetamine derivatives in which facilitation of central nervous mechanisms can be demonstrated by objective testing such as the critical flicker frequency.

SUMMARY

1. The effects of four anorectic drugs on the critical flicker frequency of 10 normal subjects were compared with a placebo under double-blind conditions using an analysis of dispersion.

2. Phenmetrazine hydrochloride 25 mg produced a significant increase at 3 hr and 6 hr, phenmetrazine theoclate 30 mg + phenbutrazate hydrochloride 20 mg at 6 hr, and diethylpropion 25 mg at 3 hr. Chlorphentermine 25 mg did not significantly alter the critical flicker frequency at 3 hr or 6 hr.

3. None of these drugs influenced the modification of critical flicker frequency by intermittent light of varying frequency.

4. The results demonstrate the value of an analysis of dispersion in discriminating drug effects at various times when there is significant variation in resting values of the sensory modality tested.

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