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The role of personality factors and suggestion in placebo effect during mental stress test

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The aims of this study were first of all to document a placebo effect on systolic blood pressure and heart rate during mental arithmetic induced stress and secondly to assess the role of suggestion in producing this effect. Two types of placebo were used, a simple placebo and a placebo with an implied therapeutic action. Both were compared with alprazolam. A placebo response was seen in just over half of the volunteers when the cardiovascular changes to mental arithmetic induced stress in healthy volunteers were measured. This response appeared to be unaffected by the suggested therapeutic effect. Dominant, independent subjects, identified using the Cattell 16 PF personality test were less likely to respond to placebo. Alprazolam (0.5 mg) did not prevent, to a significantly greater degree than placebo, the systolic blood pressure or heart rate increases provoked by the mental stress.

Keywords placebo alprazolam suggestion personality profile Catell 16 PF mental arithmetic blood pressure heart rate

Introduction

Over the last 50 years many papers have appeared in the literature discussing various aspects of the placebo phenomenon. There is no doubt that placebos work effectively in certain situations, yet few physicians will deliberately prescribe them. This reluctance stems, in part at least, from our ignorance on how placebos work.

Some authors feel that there is scant evidence to suggest that patients who respond to placebos have distinctive personality traits. However, Lasagna *et al.* (1954) report that placebo sensitive subjects have a tendency to be dependent and anxious. Tibbets & Hawking (1956) and Medvedev *et al.* (1984) also found them to be anxious. In two separate studies, McNair *et al.* (1979) and Pichot *et al.* (1967) found a correlation between a positive response and a tendency to acquiese. McNair *et al.* (1979) also found that non-specific somatic complaints prior to treatment predicted a response, however he considered the two tendencies to be independent of each other. Using a personality test, the Cattell 16 PF (Cattell, 19??) and the somatisation dimension of the SCL 90 R (Derogatis *et al.*, 1976), a psychological wellbeing self report questionnaire, we looked at the personality profiles of the placebo responder and of the persistent non-responder.

In a group of patients the desire to get better will vary in intensity; even with the same physician certain patients interact more positively than others and receive more reinforcement. To avoid these variables we used healthy volunteers and kept volunteer/physician interaction to a minimum. As some authors (Bernheim, 1910; Leslie, 1954) mention suggestion as a possible mechanism in the placebo response, we attempted to clarify its role.

To achieve these aims, we investigated the cardiovascular responses to mental stress during treatment with a benzodiazepine anxiolytic (alprazolam) and two types of placebo. The first placebo was given with no specific action implied by the experimenter, the second was administered with a clear suggestion of its therapeutic effect (simple and active placebos). The personality profiles of the placebo responders and non-responders were then compared.

Methods

The study was submitted to and approved by the Ethics Committee of Hôpital Necker—Enfants Malades and the Institut Pasteur, Paris V.

Thirty young healthy male (mean age 22 ± 1 years) volunteers participated. They gave no history of heavy alcohol consumption or drug abuse. No volunteer with a history of psychiatric illness was included and the principal items of the SCL(R) 90 (depression, anxiety, psychotism and global scores) were within normal limits for all 30 subjects. Informed written consent was obtained from each volunteer.

The study had a single-blind, cross over design. It

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included an initial baseline session followed by three randomised treatment sessions. All four sessions were carried out at weekly intervals. The treatments consisted of alprazolam (0.5 mg), 'simple placebo' and 'active placebo' and were given on one occasion only in each case. Psychological testing with Cattell 16 PF and SCL (R) 90 was carried out prior to main study. The results of these tests were unknown to physicians involved in the rest of the study.

The Cattell 16 PF is comprised of 187 questions which are divided into 16 essentially independent bipolar scales e.g. reserved/open, modest/authoritative. Four secondary factors with broader dimensions derived from weighted combinations of the primary factors are also used: introversion/extroversion (Q 1); adaptation/anxiety (Q II); emotivity/ dynamism (Q III); submission/independence (Q IV). The somatisation dimension of the SCL 90 R, for which there are 12 questions was also taken into account as part of the study. Each question is rated on a 5 point scale of distress from 'not at all' to 'extremely'. The tendency to somatise psychological distress is measured in this section of the questionnaire.

During each of the four experimental sessions a standard procedure was followed. Subjects were tested on each occasion at the same time of day and were asked to remain recumbent, but alert, for 150 min. Systolic blood pressure (SBP) and heart rate (HR) were measured automatically at the beginning of the session ($t0$) and at 60, 100, 110, 120, 125, 130, 135 and 150 min. After $t0$ measurement on treatment days the 'medication' was administered. On the days when alprazolam and the simple placebo were given, the subjects were asked to take the tablet and were informed that an 'effect would be seen in due course'. On the active placebo day the subjects were told that the tablet 'would reduce the effect of the stress on their blood pressure and heart rate.' Further conversation was kept to a minimum.

During each session, after a period of rest and at the time which corresponded with the peak action of alprazolam (120 min) the mental stress test was carried out over 5 min. This consisted of repeated ordered subtractions e.g. 3000 less 7 equals 2993, 2993 less 7 equals 2986 etc., different starting numbers having been randomised to each subject for each session (e.g. 2500 less 8, or 5000 less 11). To increase the element of stress the subjects were asked to calculate as quickly and as accurately as possible, the number of subtractions and errors being counted. SBP and HR were measured at the beginning ($t120$) and end of test ($t125$).

To continue to take part in the study the volunteers had to respond adequately during the baseline condition to the mental stress. Our criteria were strict and only an increase in SBP or HR of at least 20% between the resting value at $t100$ and the maximum stress value (either $t120$ or $t125$), was considered a positive response. On the other hand, during subsequent sessions, a positive treatment/placebo response was regarded as an absolute variation of systolic BP *and* heart rate of *less* than 10% between $t100$ and maximum stress value.

In the statistical analysis, a two-way analysis of variance (ANOVA) was used to study SBP and HR responses within the different treatment/order conditions, and the Student's unpaired t-test to investigate psychological testing in placebo responders and non-responders. In the case of an overall significant factor in the ANOVA results, post-hoc comparisons were performed by Duncan's test. All significant differences were assessed for a significance level within the limit of 0.05.

Results

Twenty-three volunteers (76.6%) responded positively to the stress test at baseline and continued in the study.

Twelve (53.2%) of the remaining volunteers responded to at least one of the placebo situations, with an absolute variation of both SBP and HR of less than 10% between $t100$ and t_{max}, and 11 did not: five volunteers responded to the active placebo alone, four to the simple placebo alone and three responded to both.

A rise in SBP and HR of less than 10% during stress was seen in nine subjects taking alprozolam, seven of whom also responded to one of the placebo situations. Mean SBP and HR at each time interval were compared (ANOVA) for the three treatment conditions and no significant differences were found (Table 1). For the group of 23 stress responders a significant stress reaction, both in SBP and HR, was found for each treatment when a comparison of values at $t110$ and t_{max} was made (alprazolam $P < 0.001$, simple placebo $P < 0.001$ and active placebo $P < 0.01$). No significant treatment/sequence interaction was found (ANOVA).

Table 1 Pulse rate and systolic blood pressure

Mean pulse rate and s.d. (beats min^{-1}) for 23 'stress reactors' at different time periods for each treatment

	Time (min)					
Treatment	*100*	*110*	*120*	*125*	*130*	*135*
Active placebo	65.5 (5.7)	64.9 (6.1)	74.6 (9.1)	66.0 (8.2)	66.3 (6.2)	65.2 (6.3)
Simple placebo	65.1 (6.1)	65.0 (7.2)	77.0 (13.9)	69.0 (8.1)	66.6 (6.4)	65.7 (7.7)
Alprazolam (0.5 mg)	66.6 (7.3)	64.9 (6.7)	76.4 (12.9)	67.1 (8.6)	68.0 (6.5)	65.6 (6.3)

Mean systolic blood pressure and s.d. (mm Hg) for 23 'stress reactors' at different time periods for each treatment

	Time (min)					
Treatment	*100*	*110*	*120*	*125*	*130*	*135*
Active placebo	115.0 (10.8)	114.0 (11.6)	121.9 (11.6)	120.3 (9.7)	116.3 (10.5)	112.9 (11.0)
Simple placebo	115.0 (10.9)	115.1 (11.5)	122.5 (13.8)	120.5 (10.5)	117.5 (11.5)	117.0 (9.9)
Alprazolam (0.5 mg)	110.4 (10.1)	109.6 (10.6)	119.1 (11.5)	113.1 (9.3)	113.6 (11.1)	112.0 (11.7)

Table 2 Side effects. Number of volunteers reporting side effects after each session

	Simple placebo	*Active placebo*	*Alprazolam (0.5 mg)*
Drowsiness	17	10	18
Nausea	–	–	1
Headache	–	–	2
Dizziness	–	–	2
Other	–	–	2

A univariate analysis was made comparing, one by one, the scores obtained by the placebo responders and non-responders on the Cattell 16 PF (first and second order factors). Factor E, which measures submission *versus* dominance was significantly ($P < 0.01$) higher in the non-responding group, this group being more authoritative and aggressive. The second order factor Q IV score, which has a wider dimension than Factor E, was also significantly ($P < 0.01$) higher (placebo responders = 5.8 *versus* placebo non-responders = 8.1, $P < 0.01$) in this group. It takes into account measures of ascendancy and dominance not being independent of Factor E, however it also measures independence and conservatism. No significant differences were found in relation to the other Cattell 16 PF factors.

A similar comparison was made using the somatisation dimension of the SCL(R) 90 and no difference was found between the two groups.

Side effects (Table 2) occurred almost as frequently during the simple placebo condition as with alprazolam. They did not occur more frequently in the group which responded to suggestion than in the non-responders.

Discussion

Just over half of the volunteers responded positively, according to our criterion, to a placebo on at least one occasion. This criterion may be considered correct as a variation under baseline conditions of SBP and HR together of less than 10% was observed in only one subject. The number of placebo responders is similar to that found with patients (5) but is higher than that generally found with healthy volunteers (11). This finding may be explained by the fact that there were two placebo sessions and only three subjects responded to both.

The role of suggestion did not appear very important as almost as many volunteers reacted to the simple placebo situation as to the other. When we were deciding on the phrase to imply suggestion, in the active placebo situation, we tried to be neither too subtle nor too obvious and probably erred towards the former situation. The suggestion was only given on one occasion, at the time of drug administration, all other verbal interraction being kept to a minimum. In a clinical situation or in a longer study, suggestion would be reinforced on an ongoing basis. The volunteers taking part in this study were aware, from the consent form that they signed, that at least one placebo session was involved. It would appear therefore, that their personal interpretation of the situation, based on prior expectations in addition to physical symptoms on the day, played a more major role than the external suggestion coming at one point in time even though it came from a person in authority.

As the placebo responder group turned out to be rather heterogeneous with no sub-group sufficiently large to compare with the non-responder group we focused on the more uniform non-responding subjects to see if certain personality characteristics emerged. This group of subjects, who did not respond to placebo on any occasion, were more authoritative and aggressive than their counterparts. They did not differ in terms of mean anxiety scores on the Cattell 16 PF, so the continued stress effect would not appear to be due to the fact that this group were more anxious from the start. In fact, there is no evidence in the literature that the stress of mental arithmetic is normally significantly extinguished with well spaced repetition. On the contrary, Faulstich *et al.* (1986) found temporal stability in his study on various stress tests including mental arithmetic of this type. A different figure was given on each occasion in our study to avoid any possibility of a practise effect over the four sessions. It is true that some numbers could appear more difficult than others, however numbers of a similar degree of difficulty were randomised beforehand for each session. The comparison made between $t100$ and t_{max} for the three conditions showed a significant difference on each occasion, demonstrating that overall the stress reaction did continue throughout the study. In the majority of cases for each treatment the t_{max} corresponded with t_{120}.

Alprazolam has been studied by Stratton & Halter (1985) in relation to its effects on systolic BP and HR after an exercise stress (treadmill test). They found that in comparison to baseline (stress with no prior medication) no effect was seen after alprazolam in relation to systolic BP, however the HR was slightly but significantly lower during the exercise period, although the exercise induced increase in HR was not significantly different. Similarily, in this study comparing alprazolam with placebo no significant differences were found at any point in relation to SBP or HR. Prescribing a benzodiazepine anxiolytic such as alprazolam for stress induced rises in blood pressure would therefore appear to have little rationale.

In conclusion, no definite effect of suggestion was seen in a group of healthy volunteers. It may play a more important role in patients. A dominant, independent type of subject, identifiable using the Cattell 16 PF is less likely to exhibit a placebo effect when stress induced changes in cardiovascular parameters are being measured. Alprazolam (0.5 mg) does not control, to a significantly greater degree than placebo, systolic BP or HR increases provoked by mental stress.

References

Bernheim, H. (1910). *Hypnotisme et Suggestion.* Paris: Doin.

Cattell, R. B. (1974). *Manual d'application.* Paris: Centre de Psychologie Appliquee.

Derogatis, L. R., Richels, K. & Roch, A. F. (1976). The SCL 90 and the MMPI, a step in the validation of a new self-report scale. *Br. J. Psychiat.*, **128**, 280–289.

Faulstich, M. E., Williamson, D. A., McKenzie, S. J., Duchman, E. G., Hutchinson, K. M. & Blouin, D. C. (1986). Temporal stability of psychophysiological responding: a comparative analysis of mental and physical stressors. *Int. J. Neurosci.*, **30**, 65–72.

Haynel, A. & Pasini, W. (1984). *Abrege de Medicine Psychosomatique.* Masson. 2nd edition, d'apres Scheller 1980.

Lasagna, L., Mosteller, F., von Felsinger, J. M. & Beecher, H. (1954). A study of the placebo response. *Am. J. Med.*, **16**, 770–779.

Leslie, P. (1954). Ethics and practice of placebo therapy. *Am. J. Med.*, **16**, 854–856.

McNair, D. M., Gardos, G., Haskell, D. S. & Fisher, S. (1979). Placebo response, placebo effect and two attributes. *Psychopharmacology*, **63**, 245–250.

Medvedev, V., Zavyalova, E. K., Ovchinnikov, B. V. & Posokhova, S. T. (1984). Functional structure of the placebo response. *Fiziologiya Cheloveka* (translation), May-June, **10**, 458–464.

Pichot, P., Barucand, D. & Perse, J. (1967). L'attitude de l'aquiescement comme détirminant de l'effet placebo. In *Hypnosis and Psychosomatic Medicine.* Amsterdam: Springer Verlag.

Pichot, P. (1961). A propos de l'effet placebo. *Rev. Med. Psychol.*, **3**, 37–40.

Rickels, K., Csanalosi, I., Greisman, P., Cohen, D., Werblowsky, J., Ross, H. A. & Harris, H. (1983). A controlled clinical trial of alprazolam for the treatment of anxiety. *Am. J. Psychiat.*, **140**, 82–85.

Stratton, J. R. & Halter, J. B. (1985). Effect of a benzodiazepine (alprazolam) on plasma epinephrine and norepinephrine levels during exercise stress. *Am. J. Cardiol.*, **56**, 136–139.

Tibbets, R. W. & Hawking, J. R. (1956). The placebo response. *J. Ment. Sci.*, **102**, 60–66.

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