Treatment for hypertension interrupted by placebo: the response of patients with high and low general health questionnaire scores

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SUMMARY. A study is described in which established treatment for hypertension was interrupted by placebo as part of a change to an alternative treatment.

The patients involved were divided into two groups according to their score on the general health questionnaire. All the patients showed an increase in diastolic pressure after the placebo phase of the change-over but the increase was greater for patients with a high score on the general health questionnaire than it was for patients with a low score. For the patients with a high score the diastolic pressure approximated to the level recorded when the diagnosis was first made, but for patients with a low score it was considerably lower than this initial reading.

The implication of this finding for the design of 'change-over' studies is discussed.

Introduction

THERE are a large number of preparations available for treating hypertension. A practitioner may prescribe a variety of preparations over the years, but at some point he may wish to rationalize his choice of treatment. This involves changing some medication and an outcome study should be carried out to ensure that the blood pressure control after the change is as good as or better than it was before.

An opportunity to perform an exercise of this nature occurred when the author's practice decided to take part in a premarketing study. The preparation under investigation was a single dose capsule containing atenolol (50mg) and nifedipine retard (40mg).

It was not possible to examine the efficacy of the individual original treatments because of their number. There were 15 different items, prescribed singly or in combination which could be grouped under four broad headings — thiazide diuretics, beta-blockers, methyldopa and others. This multiplicity of treatments was an important factor in the decision to rationalize the practice prescribing policy on hypertension. The number of preparations which are prescribed has now been reduced to four.

The use of a placebo in conditions such as hypertension raises an ethical question. Is it permissable to use an inactive preparation when a rise in blood pressure could precipitate a cerebrovascular accident or an episode of myocardial ischaemia? The dilemma was resolved to some extent by the Medical Research Council's trial which indicated that treatment for hypertension did not convincingly prevent major cardiovascular incidents.[1] Nevertheless this finding does not preclude the possibility that a sudden rise in pressure in a vascular system which is already under threat could cause some damage. It was decided to use a placebo but to use the opportunity to observe the response of the patients in detail, with the intention of developing guidelines which might be used in other similar circumstances.

Method

The 32 patients in the study had been receiving treatment for hypertension for at least one year. Review readings of blood pressure were taken at intervals of one month, using a Copal UA 215 electronic sphygmomanometer. Diastolic pressure was used as the criterion for the effect of the treatment.

Each patient had completed the 60-question version of the general health questionnaire as part of a parallel study. The patients were allocated to one of two groups using the criteria recommended for the questionnaire.[2] Those with a score of 11 or less were categorized as psychiatrically healthy (low scorers). Those with a score of 12 or more were considered to have an ongoing, non-affective, psychiatric disorder (high scorers).

Blood pressure readings were taken during the course of the change-over from the original medication to a randomized choice of either atenolol (50 mg per day) or a slow release form of nifedipine (40 mg per day). If the result in either case was unsatisfactory a combination of the two was prescribed.

A placebo was prescribed for one month prior to the change to the new drug to allow time for the original medication to be eliminated. Patients whose maintenance diastolic pressure had been 90 mmHg or less were given a six week course of the placebo.

The placebo was an orange capsule which was taken at night and morning. Each patient was told that the purpose of these capsules was to eliminate the previous treatment before changing to the alternative. This was essentially true, but it also suggested that a positive action was being taken and that the patient could expect his/her blood pressure to rise.

Blood pressure readings were recorded on four occasions:
1. At the consultation when the diagnosis was first made and the decision to start active treatment was taken (baseline).
2. At the final consultation prior to the start of the study (original treatment).
3. At the end of the placebo phase of the change-over (post-placebo).
4. After restabilization (alternative treatment).

The Wilcoxon signed rank test was used for all statistical comparisons made.

Results

The diastolic blood pressure readings at the four stages of the study are shown in Table 1 for the 21 low scorers and for the 11 high scorers. Baseline readings of diastolic pressure were used as the reference point and they were found to be similar for both high and low scorers.

The reductions in diastolic pressure on the original treatment were substantial for both groups. The mean diastolic pressure of the high scorers was higher than that of the low scorers on the original treatment but the difference between the groups (tested on ranked data) was not statistically significant.

Mean post-placebo readings of diastolic pressure were higher than the mean original treatment readings for both groups. For the high scorers the mean post-placebo reading equalled the

Table 1. Diastolic blood pressure readings at the four stages of the study for patients with low and high scores on the general health questionnaire (GHQ) ($n = 32$).

GHQ score	Mean diastolic blood pressure (range) (mmHg)			
	Baseline	Original treatment	Post-placebo	Alternative treatment
Low (⩽11) ($n = 21$)	116 (100–160)	96 (78–127)	102 (84–119)	93 (82–109)
High (⩾12) ($n = 11$)	116 (102–146)	101 (86–112)	115 (96–133)	93 (82–104)

Table 2. Comparison of post-placebo diastolic pressure with baseline diastolic pressure for patients with low and high scores on the general health questionnaire (GHQ) ($n = 32$).

GHQ score	Number of patients	
	Post-placebo >baseline	Post-placebo ⩽baseline
Low (⩽11)	2	19
High (⩾12)	6	5

Fisher's exact test: one-tailed $P<0.05$; two-tailed $P<0.05$.

mean baseline reading. The low scorers showed a smaller increase, and for this group the difference between the baseline and post-placebo readings was still statistically significant ($P<0.01$). The difference in the post-placebo reading between the two groups was also statistically significant ($P<0.01$).

The post-placebo diastolic pressure of six high scorers and two low scorers was higher than the baseline diastolic pressure. This difference between the two groups was statistically significant (Table 2).

By the end of the stabilization period on the alternative treatment, the mean diastolic pressure for both high and low scorers was slightly lower than on the original treatment, but the difference between these two stages was not significant.

Discussion

Hypertension is currently considered to be a biophysical phenomenon.[3] The hypothesis that it may be due, at least in part, to emotional stress has been discredited.[4] Therefore it would be expected that the effect of interrupting treatment with a placebo would be independent of the patient's psychological (or psychiatric) state.

The observations reported here do not confirm this expectation. If the original treatment had been completely eliminated by the end of the placebo phase, the diastolic pressure should have reverted to baseline levels in most cases. If psychiatric considerations are to be discounted, the fact that the group obtaining low scores on the general health questionnaire did not experience such a reversion suggests that either the preparations concerned were eliminated more slowly than anticipated, or that the various compensatory mechanisms involved had not readjusted to a drug-free state. These considerations should be equally applicable to the high scorers.

It is well-known that blood pressure readings are sensitive to momentary moods but the general health questionnaire identifies a background state of mind. When the placebo was issued, it was described as a preparation 'which would wash out the previous treatment': that is to say a specific action and effect were suggested to the patient. It is to be expected that high scorers would be more open to suggestion than low scorers, but the difference reported here would imply that the psychiatric state of the patient should not be disregarded in these circumstances.

It is possible that the high scorers were frightened about the anticipated adverse effects at the end of the post-placebo phase of the study, while the low scorers were still responding to the reassuring effect of medical attention, as demonstrated in the MRC trial.[4] The differences might also reflect the way these groups of patients view the practitioner, the high scorers being less trusting and more suspicious than the low scorers.

This study has practical implications for the design of 'change-over' studies using a placebo at an intermediate stage. It appears that fears concerning the use of a placebo may be exaggerated for low scorers on the general health questionnaire but not for high scorers.

The problem might be resolved if routine use of the general health questionnaire were included as part of the preliminary investigation before introducing patients to such a trial. High scorers could be excluded completely, or the use of a placebo avoided in their case. They could be transferred immediately to the new preparation but in order to ensure that the original treatment was not still exerting an influence, a longer period would be allowed to elapse before evaluating the effect of the change-over. However, the possibility of drug interaction or unwanted synergistic effects would still exist. The alternative would be to abandon the use of placebos and simply interrupt medication. In this case, the patient's blood pressure would have to be measured at shorter intervals and the use of new treatment delayed until the patient's blood pressure had risen to a level at which it was felt that interference was necessary in the interests of the patient's safety.

References

1. Medical Research Council Working Party. MRC trial of treatment for mild hypertension: principal results. *Br Med J* 1985; **291:** 97-104.
2. Goldberg DP. *The detection of psychiatric illness by questionnaire. Maudsley monograph no. 22.* Oxford University Press, 1972.
3. Peart WS. Concepts in hypertension: the Croonian lecture. *J R Coll Physicians Lond* 1980; **14:** 141-153.
4. Mann A. Hypertension: psychological aspects and diagnostic impact in a clinical trial. *Psychol Med* 1984; Suppl. 5: 1-35.

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Travel sickness in the elderly

A survey of 172 patients attending a geriatric day hospital revealed that 33 patients (19%) suffered travel sickness at some time. Sixteen (49%) of these patients also had a past history of travel sickness, while only 10 (7%) of those who were not sick gave a positive past history. The use of emergency vehicles for transporting patients may have increased the level of travel sickness. Seven (4%) of the patients had defaulted or considered defaulting on attendance because of the fear of travel sickness. Patients commenced on drug therapy for sickness responded well and experienced few side-effects and no interference with rehabilitation.

Source: Stokoe D, Zuccollo G. Travel sickness in patients attending a geriatric day hospital. *Age Ageing* 1985; **14:** 308-311.