Br. J. clin. Pharmac. (1987), **24**, 106–109

Placebo does not lower ambulatory blood pressure

A. G. DUPONT, P. VAN DER NIEPEN & R. O. SIX
Department of Internal Medicine, University Hospital, Vrije Universiteit Brussel, Laarbeeklaan 101, B1090 Brussels, Belgium

The effects of 4 weeks of placebo on clinic and on ambulatory blood pressure, measured non-invasively using the Remler M 2000 portometer, were studied in 46 hypertensive patients who were included in three consecutive double-blind randomized placebo-controlled trials with antihypertensive drugs. Placebo significantly reduced clinic blood pressure, but had no significant effect on ambulatory blood pressure.

Keywords placebo ambulatory blood pressure Remler M 2000 portometer

Introduction

The existence of the placebo effect in the treatment of a variety of diseases is a well-substantiated phenomenon, which can be measured both subjectively and objectively (Benson & Epstein, 1975). The frequency of occurrence and the magnitude of the placebo effect are such that placebo control has routinely been incorporated into the design of therapeutic experiments. It is a well-established fact that in most hypertensive patients clinic blood pressure falls in response to placebo (Montsos *et al.*, 1967; Doyle, 1983). In contrast, Gould *et al.* (1981) observed no placebo-induced reduction when blood pressure was monitored intra-arterially in ambulatory patients.

There has been increasing interest in recent years in the use of non-invasive ambulatory blood pressure monitoring for the accurate diagnosis of hypertension and for the evaluation of antihypertensive treatment (Brunner *et al.*, 1985a; Pickering *et al.*, 1985). We examined retrospectively the effect of placebo on ambulatory blood pressure measured non-invasively with the Remler M 2000 portometer, a semi-automatic device, in patients included in placebo-controlled trials with antihypertensive drugs. The results were compared with those obtained with standard measurement of blood pressure in the outpatient hypertension clinic.

Methods

Patients

Forty-six untreated patients with mild to moderate essential hypertension, who were included in three consecutive double-blind randomized placebo-controlled clinical trials with antihypertensive drugs, were studied retrospectively. Their mean age was 59.7 years; 19 patients were female. They all had supine diastolic 'clinic' blood pressures, measured on at least three occasions over 1 week apart, between 95 and 115 mm Hg. None of them had secondary hypertension or evidence of organ damage due to hypertension. All previous antihypertensive treatment was withdrawn at least 3 weeks before entry into two of the trials, and at least 2 weeks in the third trial. The study protocols were approved by the local Hospital Ethics Committee and informed consent was obtained in each case.

Methodology

A placebo-period of 4-weeks duration was included in each study protocol; both, 'clinic' and 'ambulatory' blood pressures were measured in each patient at the beginning and again at the end of this placebo-period.

On the days of study, the patients attended the outpatient hypertension clinic and 'clinic' blood

Correspondence: Dr Alain G. Dupont, Department of Internal Medicine, A.Z. VUB, Laarbeeklaan 101, B-1090 Brussels, Belgium

pressure was measured with a standard mercury sphygmomanometer at 08.30 h. Clinic blood pressure was defined as the average of three readings taken after 10 min of supine rest (Korotkoff phase V was accepted as the diastolic level.) Ambulatory blood pressure was then measured non-invasively on the same day using the semi-automatic Remler M 2000 portometer (Remler Corporation, Brisbane, CA, USA), a portable blood pressure recording system. The details of the design of the apparatus have been published previously (Kain *et al.*, 1964). A microphone is taped over the brachial artery at the point of maximal pulsation above the antecubital fossa. The blood pressure cuff is applied in the usual position over the microphone, which plugs into the blood pressure recorder. The signal is recorded on a microcassette tape recorder. The subject inflates the cuff using a standard inflation bulb, and at a preset level, which is above the systolic pressure, the equipment is switched on, as indicated by a red light. The pressure leaks automatically as calibrating pulses and arterial sounds are recorded on magnetic tape, until the red light is extinguished when a low pressure pneumatic switch automatically turns off the recorder. The cycle is repeated for each pressure recording, and the signal is recorded on magnetic tape.

The blood pressure data recorded on the microcassette cartridge are later analysed through a separate M 3000 decoding unit into a permanent graphic display on chart paper, from which the blood pressure level is measured. The pressures corresponding to the first and last sounds are recorded as the systolic and diastolic endpoints, respectively. As weaker sounds may not deflect the pen in the decoder, an observer listens to the tape during decoding and marks on the pressure tracing the position of the first and last sounds. Pen deflections caused by artefacts can be excluded at the same time. The system had proved to be reliable and accurate for the non-invasive measurement of daytime ambulatory blood pressure (Fitzgerald *et al.*, 1982; Gould *et al.*, 1984); furthermore, ambulatory blood pressure measurements with this apparatus are reproducible (Fitzgerald *et al.*, 1984).

The patients left the hospital after they were fitted with the device; they were instructed to inflate the cuff every 30 min between 09.00 h and 18.00 h. The choice of interval of 30 min has been validated by comparison with the continuous beat-to-beat intra-arterial recording (Di Rienzo *et al.*, 1983). The rate of deflation of the cuff was set at 10 mm Hg per period of 1.5 s. The tapes were then evaluated using the Remler M 3000 decoding unit and systolic and diastolic blood pressure were defined for each pressure recording. All systolic and diastolic ambulatory blood pressures measured during one recording session were then averaged.

Analysis of results

Values obtained at the end of the placebo-period were compared with those obtained before the administration of placebo using the Wilcoxon matched-pairs signed-ranks test. A significant difference was accepted at a two-tailed $P < 0.05$.

Results

The results are shown in Table 1. In agreement with previous findings (Dupont *et al.*, 1986), average systolic and diastolic ambulatory blood pressure levels were significantly (both $P < 0.01$) lower than the corresponding clinic blood pressures; they were overestimated by 10.3% and 6.6%, respectively. Reduction of blood pressure after 4 weeks of placebo, as measured by standard sphygmomanometry in the outpatient clinic was highly significant for both systolic and diastolic pressures ($P < 0.001$). In contrast, concomittant assessment by non-invasive monitoring in the same subjects showed no significant effect of placebo on ambulatory blood pressure. After placebo, the disparity between clinic and ambulatory blood pressure was reduced to 4.4% and 2.3% for systolic and diastolic blood pressure, respectively.

Discussion

In this study, we retrospectively analyzed the effect of placebo on 'clinic' blood pressure and on ambulatory blood pressure measured on the same day, in 46 patients with mild to moderate essential hypertension, participating in drug trials. The semi-automatic recorder used, has found

Table 1 BP before and after placebo (mean ± s.e. mean; *$P < 0.001$, as compared with baseline; †$P < 0.01$ as compared with clinic blood pressure)

	Baseline	*Placebo*
Systolic (mm Hg)		
clinic	174.6 ± 8.1	161.8 ± 7.6*
average ambulatory	158.3 ± 6.8†	154.6 ± 7.1†
Diastolic (mm Hg)		
clinic	109.8 ± 3.9	104.2 ± 4.1*
average ambulatory	103.0 ± 3.6†	101.8 ± 4.1

wide acceptance and was shown to be reliable and accurate for the measurement of ambulatory blood pressure during the daytime period (Pickering *et al.*, 1985). Furthermore, it has the advantage of being non-invasive and less time consuming than direct intra-arterial blood pressure monitoring, which is confined to a small number of patients and which is not completely free of complications.

The disparity observed between baseline clinic and ambulatory blood pressures had been noticed previously (Sokolow *et al.*, 1966; Floras *et al.*, 1981; Dupont *et al.*, 1986). This disparity is probably, at least in part, due to the pressor effect of the presence of a physician, often referred to as 'white coat hypertension' (Mancia *et al.*, 1983). The lower pressure obtained with a Remler recorder appears to be more consistently related to the presence and extent of organ damage than clinic cuff blood pressure measurements (Sokolow *et al.*, 1966). As recently reviewed by Brunner *et al.* (1985b), evidence has indeed accumulated suggesting that, in the individual patient, cardiovascular complications are more accurately predicted from the blood pressure recorded in the ambulatory state.

Our data show a difference in the effect of placebo, administered during 4 weeks, between the two methods of monitoring blood pressure. In agreement with previous reports (Gould *et al.*, 1981; Doyle, 1983), clinic blood pressures, in the group as a whole, were significantly reduced by placebo; this can probably be attributed to a combined effect of placebo and the orienting reflex (Gould *et al.*, 1981). In contrast, non-invasive intermittent ambulatory blood pressure in the patient's normal environment with the Remler recorder was not influenced by placebo. Accordingly, the disparity between clinic and office blood pressure was reduced by placebo. These findings with non-invasive blood pressure monitoring are in agreement with those previously reported with intra-arterial monitoring (Gould *et al.*, 1981). The absence of placebo-effect on ambulatory blood pressure measured with the Remler Portometer, further concurs with the reproducibility of the method as reported by Fitzgerald *et al.* (1984).

It is widely accepted that some of the reduction of blood pressure that is seen when patients are first started on medication may be due to a placebo effect, hence, the widespread use of placebo in controlled clinical trials of any new medication. In every day clinical practice, it is not possible to tell whether a reduction of blood pressure observed in the clinic is due to a placebo effect or to the pharmacological effect of the drug. Our findings suggest that this problem would be solved by using non-invasive ambulatory blood pressure monitoring to evaluate this response. Furthermore, they suggest that this method might render the use of placebo control in clinical trials with antihypertensive drugs unnecessary.

We thank Mrs Karina Heyvaert for secretarial help.

References

Benson, H. & Epstein, M. D. (1975). The placebo effect. A neglected asset in the care of patients. *J. Am. med. Ass.*, **232**, 1225–1227.

Brunner, H. R., Waeber, B. & Nussberger, J. (1985a). Clinical use of non-invasive ambulatory blood pressure recording. *J. Hypertension*, **3** (suppl. 2), 513–517.

Brunner, H. R., Waeber, B. & Nussberger, J. (1985b) Blood pressure recording in the ambulatory patient and evaluation of risk. *Clin. Sci.*, **68**, 485–488.

Di Rienzo, M., Grassi, G., Pedotti, A. & Mancia, G. (1983). Continuous intermittent blood pressure measurement in estimating 24-hour average blood pressure. *Hypertension*, **5**, 264–269.

Doyle, A. E. (1983). Response to placebo treatment in hypertension. *Hypertension*, **5** (suppl. III) III-3–III-4.

Dupont, A. G., Vanderniepen, P., Volckaert, A., Finne, E. & Six, R. O. (1986). Non-invasive ambulatory monitoring of blood pressure in essential hypertension: effect of age on variability and disparity. *J. clin. Hypertension*, **3**, 278–284.

Fitzgerald, D. J., O'Callaghan, W. G., McQuaid, R., O'Malley, K. & O'Brien, E. (1982). Accuracy and reliability of two indirect ambulatory blood pressure recorders: Remler M 2000 and Cardiodyne Sphygmolog. *Br. Heart J.*, **48**, 572–579.

Fitzgerald, D. J., O'Malley, K. & O'Brien, E. T. (1984). Reproducibility of ambulatory blood pressure recordings. In *Ambulatory blood pressure monitoring*, eds Weber, M. A. & Drayer, J. I. M., pp. 71–74. New York: Springer-Verlag.

Floras, J. S., Hassan, M. O., Sever, P. S., Jones, J. V., Osikowska, B. & Sleight, P. (1981). Cuff and ambulatory blood pressures in subjects with essential hypertension. *Lancet*, **ii**, 107–109.

Gould, B. A., Hornung, R. S., Kirso, H. A., Altman, D. G., Cashman, P. M. M. & Raftery, E. B. (1984). Evaluation of Remler M 2000 blood pressure recorder. *Hypertension*, **6**, 109–115.

Gould, B. A., Mann, S., Davies, A. B., Altman, D. G. & Raftery, E. B. (1981). Does placebo lower blood pressure? *Lancet*, **ii**, 1377–1381.

Kain, H. K., Hinman, A. T. & Sokolow, M. (1964).

Arterial blood pressure measurement with a portable recorder in hypertensive patients. *Circulation*, **30**, 882–892.

Mancia, G., Bertinieri, G., Grassi, G., Parati, G., Pomidossi, G., Ferrari, A., Gregorini, L. & Zanchetti, A. (1983). Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet*, **ii**, 695–698.

Montsos, S. E., Sapira, J. D., Scheib, E. T. & Shapiro, A. P. (1967). An analysis of the placebo effect in hospitalised hypertensive patients. *Clin. Pharmac. Ther.*, **8**, 676–683.

Pickering, T. G., Harshfield, G. A., Devereux, R. B. & Laragh, J. H. (1985). What is the role of ambulatory blood pressure monitoring in the management of hypertensive patients? *Hypertension*, **7**, 171–177.

Sokolow, M., Werdegar, D., Kain, H. K. & Hinman, A. T. (1966). Relationship between level of blood pressure measured casually and by portable recorders and severity of complications in essential hypertension. *Circulation*, **34**, 279–288.

(Received 29 January 1987, accepted 16 March 1987)