An approach to realistic evaluation of antihypertensive regimes

RAYMOND CARLISLE
M.A., M.D., F.R.C.P.

U. BASILE*
M.D.(Roma), D.T.M. & H.

O. O. AKINKUGBE
M.D., D.Phil.(Oxon), F.R.C.P.

M. E. E. SOLAGBADE
S.R.N., S.R.M.

Department of Medicine, University College Hospital, Ibadan, Nigeria

Summary

Where practicable, all subjects found with onset-phase-four blood pressure of 90 mmHg or more after referral were allocated, on a random basis, to alternative antihypertensive regimes at a dosage related to response. Of those 110 receiving either guanethidine, methyl-dopa or debrisoquine, only the group on methyl-dopa had significantly reduced median blood pressure by two out of four criteria and after 6 months of therapy. It is nevertheless considered that by assessment of the total group more significant conclusions can be drawn for an eventual attempt to control hypertension on a community basis than by studies of highly selected groups treated under unusually favourable conditions.

Introduction

Significant reductions of high blood pressure have been attained hitherto in limited patient groups and with good facilities. This is true for population groups of both Negroes and Caucasians (Veterans' Administration, 1967; Stuart, MacIver and Nicholson, 1972). However, the problems facing community programmes have to be posed in different terms. Is it best to confine control measures within well appointed clinics with full diagnostic facilities; or to extend them over a wide segment of the population at risk but with some loss of individual care? Do measures, effective in small select groups of patients, retain their usefulness when applied on a community scale?

As a preliminary step in seeking answers to these and related questions, subjects for management of hypertension have been separated from medical out-patients of other types. By following specially designed case note sheets and using suitably trained ancillary staff, waiting time was reduced despite the higher frequency of follow-up visits (Carlisle, Akinkugbe and Basile, 1975).

* Deceased, March 1975.

Correspondence: Dr Raymond Carlisle, Northwick Park Hospital, Harrow, Middlesex.

Requests for reprints: The Registry, Department of Medicine, University College Hospital, Ibadan, Nigeria.

The study was intended to compare effectiveness of different antihypertensive agents but, rather than conduct drug trials of the conventional kind, results were examined for the total group of regular attenders who completed a treatment regime and thus artificial exclusion criteria were avoided.

Subjects

Generally, patients from clinics and wards of the hospital (U.C.H., Ibadan) were referred because of diastolic blood pressure readings of 100 mmHg or over; and they were accepted for management at a specially created BP Control Centre if diastolic blood pressure readings of 90 mmHg or over were recorded under the conditions of measurement described below. Additionally, issue of tablets was for those who would continue to attend regularly and comply with treatment. The subjects who were not issued with tablets were still encouraged to return, at an extended interval, for follow-up. The characteristics of all attenders, grouped according to their subsequent management, are set out in Table 1.

It can be seen that of 198 subjects accepted to the Centre, 129 completed at least 12 weeks' treatment; 110 of those are included in the analysis of response to the three alternative regimes which were successfully applied.

Data on radiographic cardiothoracic (CT) ratios for comparison were obtained from normotensives (systolic below 160 and onset-phase-four below 95 mmHg) in the hospital population who had presented because of complaints not referable to the cardiovascular system or chest. A stratified sample was taken, in ignorance of the results, to match for sex and age with the hypertensive subjects.

Methods

The reception and subsequent follow-up procedures in a centre for large scale management of hypertension have already been described (Carlisle *et al.*, 1975). Standardized initial assessment pro formas and record sheets were used.

TABLE 1. Characteristics of the subjects accepted for the study

Subject group	No.	Sex ratio M : F	Age in years (s.d.)	Socio-economic class		Pre-treatment diastolic BP in mmHg (s.d.)	Cardiothoracic ratio on X-ray	
				1, 2 (%)	3, 4, 5 (%)		≤0.54 (%)	≥0.55 (%)
1. Completed 12- or 24-week treatment period by time of analysis	129	0.84	48.9 (11)	27.5	72.5	111.9 (15)	47.2	52.7
2. Offered treatment under conditions of trial but not completing 12-week period	50	1.00	45.8 (12)	14.6	85.4	116.7 (20)	42.5	57.5
3. Accepted for follow-up but not offered treatment	19	1.71	48.9 (14)	27.3	72.6	113.1 (21)	38.5	61.6

FIG. 1. Change of blood pressure after 12 weeks' treatment from that at the second visit. Guanethidine is the treatment in this example. Blood pressure change is plotted as the abscissa in classes at intervals of 5 mmHg. The ordinate is the number of individuals in each class. The median is ringed.

Efforts were made by routine questioning to check that the tablets had been taken as directed. If side effects were complained of, then specific symptoms were queried as follows: constipation, diarrhoea, fainting, giddiness, headache, impotence (in men), anorexia, vomiting, nausea, rash, sleeplessness, tiredness, blurred vision.

Blood pressure readings for systolic (onset of phase one) and diastolic (onset of phase four) were dictated, in ignorance of earlier values, after the subject had rested supine for 5 min and again after 1 min standing. Space was also provided on the record sheets for prescription of tablets, given free of charge. Active treatment was started on the second visit to the Centre. During the initial interval of, generally, 2 weeks the subjects with a diastolic pressure of below 120 mmHg had placebo tablets but those with a higher pressure continued the existing treatment until the second visit. All attenders with a diastolic BP of 90 mmHg or more were given one of four antihypertensive agents by random allocation. The alternatives were guanethidine, methyl dopa,

debrisoquine and bethanidine. Supplies of bethanidine became exhausted, however, and propranolol was substituted; so the results for the fourth group were not included in the analysis.

The antihypertensive was prescribed on a twice or thrice daily schedule, starting at low doses and building up until either the diastolic blood pressure remained below 90 mmHg or side effects necessitated change of treatment. If so, and in any case after completion of 6 months on one drug, another antihypertensive was employed in the sequence guanethidine—methyl dopa—debrisoquine—bethanidine/propranolol—guanethidine.

Blood pressure readings after treatment periods were subtracted from the corresponding reading at the second visit. From Fig. 1 it can be seen how subjects were ranked according to the change which occurred over the 3- and 6-month periods and, for each treatment, the median change was identified.

Results

Table 1 indicates that, as compared with the total group of subjects, the fully treated group shows no considerable difference in age or pre-treatment diastolic pressure.

Lower socio-economic class (three, four or five), which could be expected to make travelling to the centre relatively expensive, is most frequent among those who failed to complete treatment. The group not offered treatment had most male members and most enlarged hearts (CT ratio was 0.55 or more in 61.6%).

Of those completing at least 3 months' treatment, all but one were Nigerians of indigenous Negro descent. There were considerably larger numbers of attenders, especially women, having radiographic cardiomegaly as compared with the normotensives who showed 85.0% with cardiothoracic ratio 0.54 or less and 15.0% with 0.55 or more.

The median blood pressure changes are illustrated in Fig. 2 and it is apparent that, of the three antihypertensive agents satisfactorily tested, methyl dopa

FIG. 2. Change of median values of blood pressure after 12 weeks' and after 24 weeks' treatment. Results from each of the drugs tested and for each of the four measurement criteria are shown. The small numerals give the size of the treated groups. * = Significance by the Wilcoxon Matched-Pairs Signed-Ranks Test at the 0.05 level; ** = significance at the 0.01 level.

yielded statistically significant evidence of pressure reduction and that only after 6 months and for the erect position. The data were therefore re-examined using the more traditional arithmetic mean change but then showed no significant evidence of pressure reduction in any group.

The median daily dose being administered at the end of the 3-month periods was 100 mg of guanethidine, 1000 mg of methyldopa and 80 mg of debrisoquine. The amounts after the 6-month periods were 150 mg, 1500 mg and 100 mg respectively.

Cross correlation of CT ratio with blood pressure reading by each criterion at onset, at 3 months and at 6 months of treatment; variability; fall and rise in reading for all the treated patients gave linear coefficients of generally less than 0.20. Blood urea similarly showed no marked correlations with blood pressure or change of blood pressure ($r = 0.19$).

Giddiness was commonly reported by subjects on all drugs, as was expected of present-day agents which reduce erect pressure more than supine (see Fig. 2). Constipation was reported for guanethidine and methyldopa, although the incidence was not high. Other symptoms were fainting, in two subjects on debrisoquine; headache in five and weakness in seven subjects on guanethidine.

Serum from those receiving methyldopa showed Coombs-type red cell antibodies in only one individual.

The impression, on accumulating the reports of symptoms following treatment and testing them for

degree of confirmation by circumstantial evidence (Bagshawe, Maina and Mngola, 1974), was that genuine side effects apart from giddiness have not obtruded nor led to significant failure to follow the prescribed treatment. The incidence of sexual difficulty, though, is probably much higher than appears.

In the BP Control Centre, on-the-spot dispensing eliminated the risk of the prescription being unfilled (Carlisle *et al.*, 1975). The routine questioning on tablets taken and consistent checking of the data of attendance against the period of previous prescription ensured that the compliance of attenders in taking prescribed medication was at least as high as in the out-patient clinics generally; the follow-up rate markedly improved (34.8% losses compared to 53.1% in the antecedent cardiac and renal clinics).

Discussion

In trials of antihypertensive agents there is as yet no generally accepted measure of effectiveness. Some authors assess the proportions of responders and non-responders, variably defined; others report mean blood pressure reduction only for rigorously pre-selected patients. It seemed best to avoid the use of unrealistic admission criteria, as indicated above, and also to avoid as far as possible arbitrary levels of blood pressure as cut-off points between responders and non-responders. Instead, the changes of pressure have been studied and an attempt made to relate these to treatment. For purposes of admission to a therapeutic trial, however, one is bound to have some fixed criteria and these become relevant in the assessment of results.

Diastolic pressure has been used here in preference to systolic (which is more variable) or to a mixed criterion using both (because of the findings of Kannel, Gordon and Schwartz, 1971, that prognosis is no better correlated).

A diastolic pressure of 100 mmHg was found to be the usual minimum criterion for referral and a minimum of 90 mmHg on the second visit was adopted as a criterion of acceptance. The decision to continue existing treatment if the initial reading was 120 mmHg or more was made on ethical grounds and will have influenced the magnitude, but not validity, of the observed change for an individual. The overall changes are less affected since the median was derived rather than the arithmetic mean. The median involves no assumption of normal distribution which, as in the case of the data of Fig. 1, was generally unjustified.

The variation between groups 1, 2 and 3 of Table 1 was noted to concern sex and socio-economic class: but there is nothing to suggest that the response is correlated. CT ratio was shown not to influence response. The high prevalence of cardiomegaly in

African populations has been noted by participants at a WHO meeting of investigators (Fejfar, 1968) and termed 'idiopathic'. Although cardiomegaly was present also among the controls, the association with hypertension which is demonstrated here suggests that undiagnosed, transient hypertension may be the cause. The absence of clear correlation of blood pressure variability with CT ratio showed that no reverse effect is apparent over 6 months, however, and the same result also occurred for a 1-year study period.

Figure 2 shows that guanethidine gave some, statistically insignificant, response at 3 months but that therapeutic tolerance developed subsequently. Methyldopa eventually produced less tolerance but was slower to exert its optimal effects, owing partly at least, to the large number of tablets required. Significance was attained for two criteria, as mentioned above. There was no appreciable effect with debrisoquine.

The dominant impression gained from the results as a whole is of failure to obtain a satisfactory response. In view of a deliberate increase in number of subjects and of the adoption in the centre of more rigorous methods, this was surprising and led to a rethinking of both the described procedures and of currently accepted ideas.

There are several possible reasons for a poor result.

(1) The objective of conventional intensive drug trials is generally to promote maximum compliance in order to make a valid statement on the efficiency and side effects of any drug under study. However, measures were here avoided which are impracticable on a large scale, such as high rejection rate of less compliant patients as in the trials by the Veterans' Administration (1967, 1970); excessive prescription with counts of returned tablets; direct supervision of administration; and testing for drugs in serum. A certain amount of low compliance is one reality of the present-day situation and must be accepted in assessing the place of the self-administered oral medication in out-patient interventions. Other possible explanations for a poor result relate to the cut-off for accepting subjects, a diastolic pressure of 90 mmHg being lower than for the majority of clinical studies of anti-hypertensives.

(2) The mechanism could be as suggested by Dollery (1973), that most doctors are satisfied to see a diastolic blood pressure reduced to below 100 mmHg.

(3) The 'regression toward the mean' phenomenon (see below) operates negatively in reducing apparent response for the individuals with lesser degrees of hypertension.

(4) Reduction of blood pressure may be more difficult for individuals with the milder degrees of hypertension. There may be a long term 'equi-

librium point' (Guyton *et al.*, 1972) which is less susceptible to therapy than shorter term mechanisms of more severe hypertension.

The decision on minimum severity for treatment was taken in the light of current concepts such as the definition of hypertension by the World Health Organization (1962) and that employed by the Veterans' Administration (1970) for their multi-centre trials. Although the place of treatment in mild hypertension is still a matter for debate (Proger, 1972; Short, 1974) there is little doubt that cardiovascular risk is still appreciably graduated by blood pressure in the 'borderline' range, for North American males (Kannel and Dawber, 1974) at least.

(5) The avoidance of full discontinuation of treatment in establishing baselines for severe (diastolic pressure of 120 mmHg or more) hypertensives is unlikely to have affected the overall results (mentioned above).

(6) It was also considered whether the blood pressure would have risen, without treatment, owing to natural progression of the condition, so as to contrast with the results on treatment.

Some evidence on this question from randomized placebo treatment of mild hypertension is presented by Stuart *et al.* (1972) in the report quoted earlier. Examination of their published data from an average follow-up of 26 months indicates a median change of only +8 mmHg in onset-phase-five blood pressure for all inclusions in the placebo group: although severe hypertensives, mean resting pressure onset-phase-five of over 115 mmHg with age adjustment, were not included in the randomization. The Veterans' Administration reports (1967, 1970) give results of 4 months' follow-up which, correspondingly, indicate a 6 mmHg rise; but for the more severe group a median 2 mmHg fall can be calculated. The effect in halting natural progression is thus unlikely to be detectable in this study.

(7) Finally, inquiries must be directed to the efficiency of the drugs employed. They were among the best accepted antihypertensives available at the time but under these circumstances were hardly measuring up to the description. Numerous clinical reports for each of the agents used may be relied upon to indicate that under specified conditions and in selected patients they do indeed work: but the generally low potency, low therapeutic ratio and short duration of action of agents presently available should be recognized.

The reasons ascribed to a general optimism, or overoptimism, in most reported out-patient antihypertensive trials are: (i) concentration of effort and resources on to the trial subject is usually out of keeping with those generally available; (ii) exclusion of subjects from trials in the interests of reducing extraneous factors makes the results unrepresenta-

tive of the total group; (iii) selection by single or short-term pre-treatment blood pressures produces a bias, because of natural fluctuations, in favour of downward progression over a period of about 10 weeks subsequently: as can be seen from the publication by the Hypertension-Stroke Co-operative Study Group (1974). Dollery (1973) has termed this a 'regression towards the mean' and it is well illustrated when pressure changes are ranged in terms of the initial value, as in Fig. 2 of his article; (iv) control procedures and statistical assessments are frequently not fully valid or are entirely lacking. As already indicated, the arithmetic mean of blood pressure, where not normally distributed over the population of subjects selected for treatment, seems inappropriate; especially if one considers the ease with which a positive response can be obtained for the group by including a few individuals who have very high pre-treatment pressures; (v) negative results go mostly unreported. This fact alone can produce a considerable bias.

A subsidiary conclusion drawn from the results described in this paper is that the ranking of different agents according to apparent effectiveness is of limited value. The order of preference may readily change; even during the course of one study, as here. It can also be expected to depend on slight modifying factors—dosage schedules, tolerance of side effects, and so on.

The disappointing blood pressure reduction when present-day agents are administered to carefully managed subjects has some disturbing implications. Poor prospects for the average hypertensive outpatient, as currently identified in Ibadan—and probably outside Ibadan—must be admitted if one bears in mind the unusual scale and intensity of this study. The dangers are predominantly those of gross undertreatment. Dosage needs continuous adjustment if blood pressure reduction is to be both achieved and maintained but hypertensive subjects frequently escape medical surveillance altogether. The goal of effective community control of hypertension seems even more remote: and it remains to be shown how much long-term reduction of clinically-assessed blood pressure is necessary in preventing complications, especially for non-Western communities.

Acknowledgments

The study was financed by University of Ibadan Senate Research Grants No. 6/207/05 except where Roche, Burroughs-Wellcome and ICI Pharmaceuticals, all of U.K.,

donated drugs and the WHO, through the Ibadan Cardiac Registry and Mrs G. A. Kayode, supported the work of data collection. Professor L. A. Salako and Dr M. A. O. Soyannwo gave help and advice. Professor A. O. Lucas and Mr O. Ayeni of the Department of Preventive and Social Medicine, University of Ibadan, provided assistance with the calculations and we are also indebted for advice to Mr P. Walker, statistician, of Rothamsted Experimental Station, U.K., and to Professor E. Topley, Ibarapa Project, University of Ibadan. Professor S. K. Reddy, now of the Liverpool School of Hygiene and Tropical Medicine, arranged for the accommodation of the centre in the General Outpatient Clinic, University College Hospital, Ibadan. Miss J. Rawlinson and Mr P. 'Dayo Saduwa typed the manuscripts. The Medical Illustration Unit, University College Hospital, have prepared the figures.

References

- BAGSHAW, A.F., MAINA, G. & MNGOLA, E.N. (Editors) (1974) *The Use and Abuse of Drugs and Chemicals in Tropical Africa*, p. 621. East African Literature Bureau, Nairobi.
- CARLISLE, R., AKINKUGBE, O.O. & BASILE, U. (1975) Blood pressure control centre in Nigeria: feasibility study. *Tropical Cardiology*, Abidjan, 1, 51.
- DOLLERY, C.T. (1973) Adrenergic drugs in the treatment of hypertension. *British Medical Bulletin*, 29, 158.
- FEJFAR, Z. (1968) Idiopathic cardiomegaly. *Bulletin of the World Health Organization*, 38, 979.
- FRY, J. (1974) Natural history of hypertension. A case for selective non-treatment. *Lancet*, ii, 431.
- GUYTON, A.C., COLEMAN, T.G., COWLEY, A.W., SCHEEL, K.W., MANNING, R.D. & NORMAN, R.A. (1972) Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *American Journal of Medicine*, 52, 584.
- HYPERTENSION-STROKE CO-OPERATIVE STUDY GROUP (1974) Effect of antihypertensive treatment on stroke recurrence. *Journal of the American Medical Association*, 229, 409.
- KANNEL, W.B., GORDON, T. & SCHWARTZ, M.J. (1971) Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham Study. *American Journal of Cardiology*, 27, 335.
- KANNEL, W.B. & DAWBER, T.R. (1974) Hypertension as an ingredient of a cardiovascular risk profile. *British Journal of Hospital Medicine*, 2, 508.
- PROGER, S. (1972) Antihypertensive drugs: praise and restraint. *New England Journal of Medicine*, 286, 155.
- SHORT, D. (1974) Diagnosis and treatment of hypertension. *Lancet*, ii, 645.
- STUART, K.L., MACIVER, C. & NICHOLSON, J.A. (1972) Out-patient treatment trial of mild and severe hypertension. *British Medical Journal*, 2, 21.
- VETERANS' ADMINISTRATION (1967) Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mmHg. *Journal of the American Medical Association*, 202, 1028.
- VETERANS' ADMINISTRATION (1970) Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 90 through 114 mmHg. *Journal of the American Medical Association*, 213, 1143.
- WORLD HEALTH ORGANIZATION (1962) Arterial hypertension and ischaemic heart disease preventive aspects. *WHO Technical Reports Series*, No. 231.