Optimisation of antihypertensive treatment by crossover rotation of four major classes

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Summary

Background Most comparisons of antihypertensive drugs are undertaken in parallel groups. We undertook a crossover rotation of the four main classes of antihypertensive drugs, in untreated young hypertensive patients, to assess the response rate with monotherapy achieved by a systematic rotation.

Methods 56 patients, mean blood pressure 161/98 mm Hg, entered the rotation, of whom 36 received all four monthly cycles of treatment with an angiotensin-converting-enzyme (ACE) inhibitor (A), β-blocker (B), calcium-channel blocker (C), and diuretic (D). Each patient's best drug was then repeated to assess repeatability. Two measures of individual variability in response were used. First, the value of rotation was measured by the increased proportion of patients reaching target blood pressure on their best drug versus their first drug. Second, we assessed whether the responses to each drug were correlated with each other.

Findings Significant variability in response was found. 20 of the 41 patients reaching target blood pressure (≤140/90 mm Hg) failed to achieve this target on their first drug. Rotation increased from 22/56 (39%) to 41/56 (73%) the success of monotherapy (p=0·0001); in half the patients, blood-pressure on the best treatment was 135/85 mm Hg or less. There were significant correlations between the blood pressure responses to A and B (r=0·5, p<0·01), and C and D (r=0·6, p<0·001), but not between the other four pairings of treatments. The responses to the AB pair were, on average, at least 50% higher than those to the CD pair; this difference was highly significant by multivariate repeated-measures ANOVA.

Interpretation There is a marked variability in hypertensive patients' response to different antihypertensive drugs. The basis may be underlying variability in types of essential hypertension. Optimisation of treatment requires systematic rotation through several therapies; however, an "AB/CD" rule is proposed in which one of each of the two pairs of treatments is initially selected to abbreviate the rotation in routine practice.

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Introduction

Most studies of antihypertensive agents in unselected patients with essential hypertension have emphasised the similarity of the average response to the different drug groups,[1] despite the widely differing mechanisms of action. However, essential hypertension is a heterogeneous disorder, and it would be surprising if the variable pathogenesis did not cause detectable variability in individual responses to the different agents. A few investigators have observed such variability during crossover studies,[2–7] and systematic rotation through each class has been suggested as the most logical, if laborious, approach to treatment.[8,9] However, to our knowledge no prospective rotation study of the four main classes of antihypertensive drugs has previously been done.

Our study was of young hypertensive patients, in whom it was safe to have a wash-out period between each drug. Our main question was whether, and by how much, a systematic rotation of patients through the four drug classes would increase the proportion of patients reaching target and normal blood pressure. Changes in response rate were measured by comparing response to first and response to best drug for each patient. Our secondary aims were to find out whether a patient's best drug could be predicted by a range of baseline measurements and whether inter-individual variability in response was itself quantifiable.

A logistic obstacle to a four-way crossover study is that of masking. However, in a study concerned solely with individual responses to each drug, there is no systematic bias to be avoided and an open-label study has the advantage of testing a scheme for treatment initiation that could be readily adapted for routine practice.

Methods

Study design and participants

A four-way, open-label, crossover study, approved by the local research ethics committee, was done in 56 white patients from the East Anglia region of the UK, aged 22–51 years, with previously untreated essential hypertension. All patients gave written informed consent. Routine screening was followed by a 7-month rotation phase in which patients received sequentially each of the four main drug groups, angiotensin-converting-enzyme (ACE) inhibition (A), β-blockade (B), diuretic (D), and calcium-channel blockade (C), subject to the absence of contraindications. The efficacy and tolerability of each treatment was assessed after 1 month.[10] There was then a 1 month wash-out period. Each patient's most effective drug was repeated on completion of the rotation. If contraindicated by an adverse event, this drug was substituted by the most effective well-tolerated treatment.

In patients whose blood pressure was over 135/85 mm Hg on their best drug, a titration phase ensued during which extra treatment was added to lower the blood pressure to this target. If doubling the dose of the best single drug was ineffective, a second drug was selected according to an AB/CD rule, where the letters are the initials of the four drug classes. Patients received

Drug class	Drug name	Daily dose
ACE inhibitor	Lisinopril	20 mg*
β-blocker	Bisoprolol	5 mg
Diuretic	Hydrochlorothiazide+triamterene (Dyazide)	25 mg+50 mg
Calcium-channel blocker	Nifedipine (Adalat LA)	30 mg

The drugs were administered for 1 month each, in the order listed, with a quarter (14) of the patients starting the rotation on each of the four drugs.
*Titrated from an initial dose of 10 mg daily at 2 weeks.

Table 1: **The drugs used for the rotation**

their most effective drugs from the AB and CD pairs; this ensured that the combination was one of the four whose constituents are generally considered to have complementary and additive effects.[11,12] Blood pressure control was then monitored for at least 1 year, both at clinic visits and by 24 h ambulatory monitoring.

The principal entry criterion was a supine blood pressure on three or more occasions over 3 months of at least 140 mm Hg (systolic) or 90 mm Hg (diastolic), or both. All but one patient met both systolic and diastolic criteria. Patients with pressures in the range 140–159 mm Hg (systolic) or 90–94 mm Hg (diastolic), or both, had an additional clinical indication for treatment, such as evidence of target organ damage. Blood pressure and heart rate were measured in triplicate at each visit after 10 min supine and 2 min standing with the same Datascope 2100 (oscillometric) automated monitor (Datascope Medical Co, Huntingdon, UK). Blood samples were obtained after a minimum of 15 min supine rest for measurement of plasma catecholamines and renin activity.[13,14] Patients who had a standard contraindication to more than one of the drug groups, or in whom a cause of secondary hypertension was found, were excluded from the study. Non-pharmacological treatments (salt or alcohol reduction, weight reduction, exercise) were recommended when appropriate before recruitment.

The choice of drugs and doses (table 1) was based on our experience of assigning randomised treatment to more than 600 untreated patients from the same general practices during the past 10 years, with monthly titration of dose over 2 months.[15] Because study of more than one dose of each drug during the rotation was not practicable, our aim was to choose comparable rather than maximal doses, which might have caused either excessive hypotension or other adverse effect in some patients. Drug order during the treatment-rotation phase was allocated according to a Latin-square design[16] in which each patient started at the next available point in the cycle, but followed the same treatment sequence (ACE inhibition, β-blockade, diuretic, calcium-channel blockade). This was preferred to a randomised sequence so that we could select the order least likely to permit interactions between consecutive treatments. Patients with a contraindication to a drug group in the rotation proceeded to the next drug. Each drug was taken in the morning except for lisinopril, which was taken in the late evening where necessary to allow at least 4 h between dosing and monitoring. Visits were scheduled to be nearer to the time of peak than the trough response to each drug, to increase sensitivity for detecting differences between drugs, and visit time was constant for each patient. Adverse events were recorded by means of a standard questionnaire.

Statistical analysis

Order effects were studied by repeated-measures ANOVA, to check that the blood-pressure readings on treatment were not influenced by either the sequence of drugs, the starting drug, or position in the cycle. Repeatability was assessed as the coefficient of variation (SD/mean×100) for the pairs of blood-pressure readings measured after two separate cycles of each patient's best drug.

In the analysis of blood-pressure responses, percentage changes in blood pressure were calculated with Oldham's correction (corrected change in blood pressure=actual change divided by the average of pretreatment and post-treatment blood pressures).[17]

We planned to assess variability in blood-pressure response to each drug in two main ways. Our null hypothesis was that each patient would show the same response to all four drugs; an extreme, alternative hypothesis was that only one of the four drugs would be effective. The primary analysis, done on all patients entering the rotation, was a McNemar's test to determine whether rotation increased the proportion of patients

	Number of patients	Mean (SD) supine blood pressure (mm Hg)
Study entry	56	161 (12)/98 (8)
End of first wash-out	56	156 (13)/96 (9)
End of second wash-out	56	156 (12)/96 (9)
End of third wash-out	40	155 (13)/95 (7)

Table 2: **Mean supine blood pressure at study entry and at the end of the three wash-out periods**

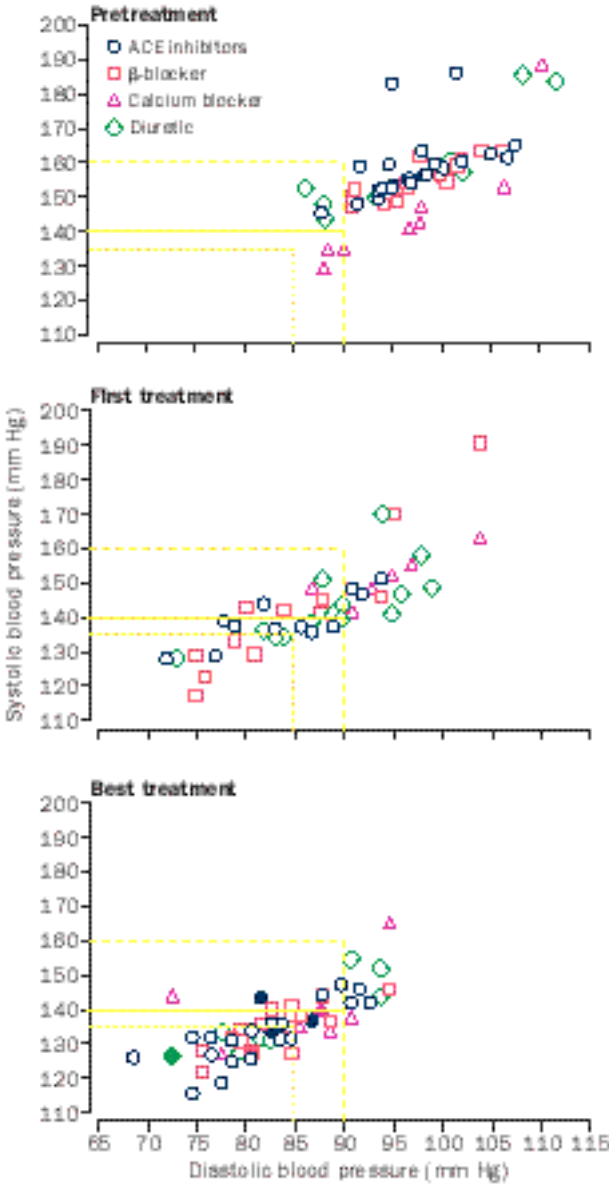

Figure 1: **Influence of rotation on blood-pressure reduction**
Pretreatment=means of four run-in measurements; first treatment=values at the end of each patient's first month of treatment; best treatment=values on each patient's best drug. The symbol used for each patient represents his or her best treatment in the pretreatment and best-treatment panels, and first treatment in the first-treatment panel. In the best-treatment panel, a closed symbol is used when a patient's best drug was also their first. The broken yellow lines represent the three blood pressure targets, as listed in the footnotes to table 3.

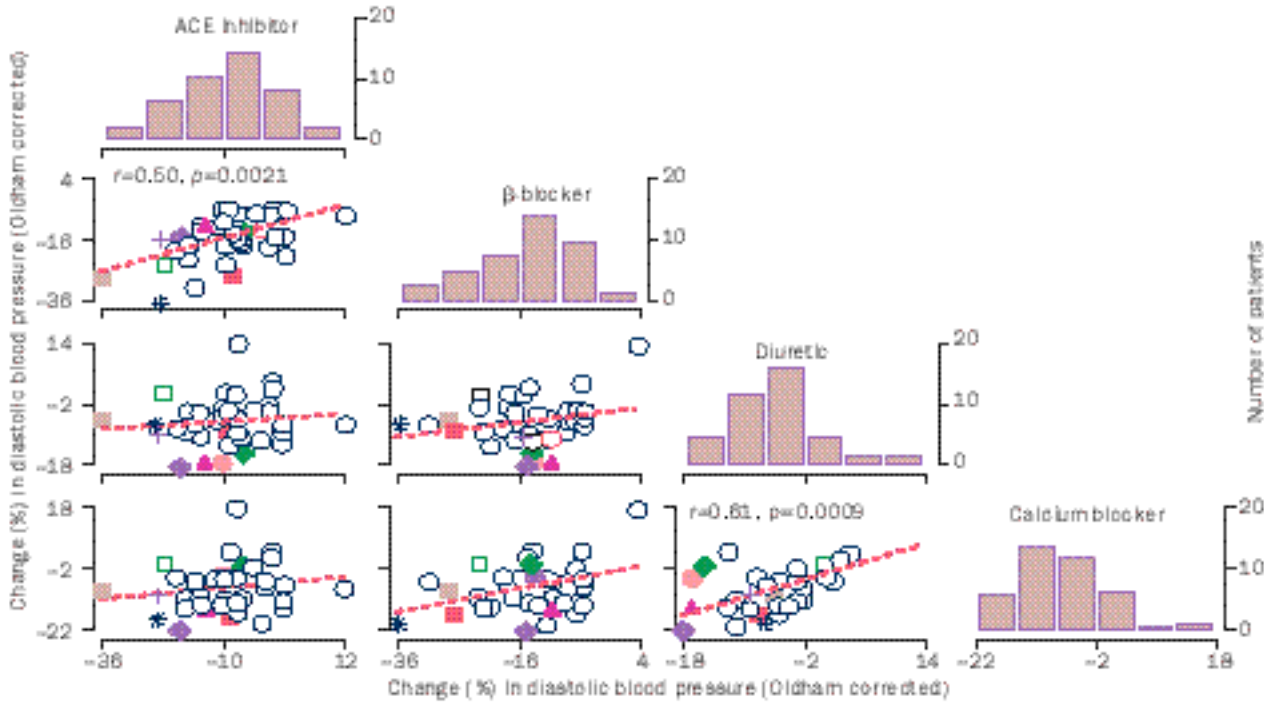

Figure 2: **Correlations between blood-pressure falls on four classes of antihypertensive drugs among 36 patients who completed rotation**

The figure shows (down the diagonal) the frequency plot for the Δcorrected change in diastolic blood pressure for each treatment, and (in the other six panels) the correlations between the corrected change in diastolic blood pressure on each drug pairing. Correlation coefficients are shown only for the two pairs for which significant correlations were observed. The corrected change in diastolic blood pressure values for patients showing one of the four best responses to any of the four treatments are shown in a unique colour-symbol combination, so that the responses for such patients to all four treatments can be compared.

reaching target blood pressures. In view of variations and changes in national guidelines, the data were examined for three different target blood pressures, with 140/90 mm Hg used for the primary analysis. The second test of variability was to find whether there was a significant correlation between the response to each pair of treatments; the null hypothesis would require all treatments to be correlated, whereas none would be correlated under the alternative hypothesis. Correlation analysis was done only on patients completing all four treatments, and was used also to investigate predictors of response. To allow for the two methods of analysis, the required p value in each case was set at less than 0·01.

We also planned a more qualitative question that could indicate whether treatment response reflects discrete differences in types of essential hypertension. Because patients responding well or badly to all drugs would still have a best drug, we defined a good response in the study as a response greater than the mean plus 1 SD of all patients' responses to all treatments; we then asked how many good responses each patient had. This question led to an unplanned repeated-measures ANOVA of the responses to the four drugs; this analysis was done because of a substantial difference in the number of good responses to one of the AB pair compared with CD pair of treatments.

We aimed to enter 56 patients into the rotation, of which around two-thirds would complete all four treatment cycles. The power of the primary analysis to compare success on the first with success on subsequent treatments would depend both on the difference we found between these, and on the proportion of non-contributory (non-discordant) patients—those controlled by all or none of the treatments. If the discordant proportion was 0·5, a sample size of 56 patients has 84% power (with a one-sided significance level of 0·01) to detect a difference in proportions of 0·3 (for instance, success rates of 40% *vs* 70%) with McNemar's test of equality of proportions. Additionally, in patients completing all treatments, the study was able to detect, at the 1% level of significance, a correlation between different treatments of 0·5. This figure was suggested by previous and pilot observations.[7]

Target (mm Hg)	Number achieving target on first drug	Number achieving target on any drug
<160/90 (BHS)	36 (64%)	49 (88%)*
<140/90 (JNCVI)	22 (39%)	41 (73%)†
≤135/85 ("normal")	11 (20%)	28 (50%)†

56 untreated hypertensive patients received in rotation either four (36 patients), three (19 patients) or two classes of antihypertensive. The success of rotation *vs* no rotation was compared by McNemar's test (*p<0·001, †p<0·0001). For each of the targets, one patient achieved this only on their first drug. BHS=British Hypertension Society;[18] JNCVI=Joint National Committee VI;[19] "normal"=mean+SD of 10 000 healthy individuals in general practice, aged 40–49 (median 44) years.

Table 3: **Comparison of response rates to each patient's first and best drug**

Results

Patients

36 men and 20 women were recruited. Their mean supine blood pressure, at the start of treatment, was 161/98 mm Hg (SD 12/8).

Calcium-channel blockade and ACE inhibition were not contraindicated for any patients; 13 patients were excluded from receiving β-blockade and three from receiving diuretic therapy. 40 patients were eligible for, and 36 completed, all four cycles.

Mean blood pressure for all patients at the first visit and the three subsequent wash-out phases are shown in table 2. The repeated measures ANOVA showed no effect of order, or starting point in the cycle, on treated blood pressure; the average blood pressures at the end of the four cycles were almost identical, in the range 144–145/87–88 mm Hg.

Variability of blood-pressure responses

Figure 1 shows the range of individual blood-pressure values for all patients, comparing the average of their untreated readings with the blood pressures on patients'

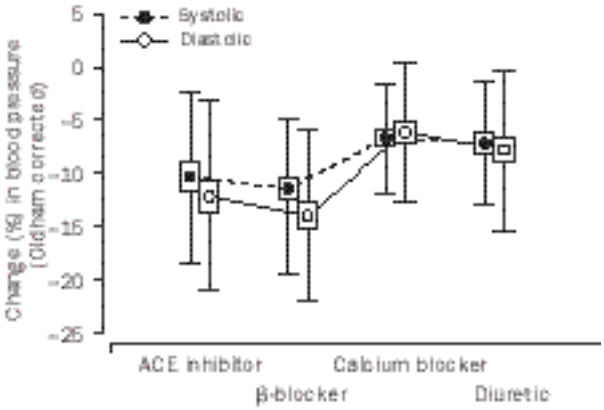

Figure 3: **Comparison of mean blood-pressure responses to four classes of antihypertensives in a Latin-square crossover study**
Values=mean, SD (bars), and SE (boxes) of the means, in 36 patients.

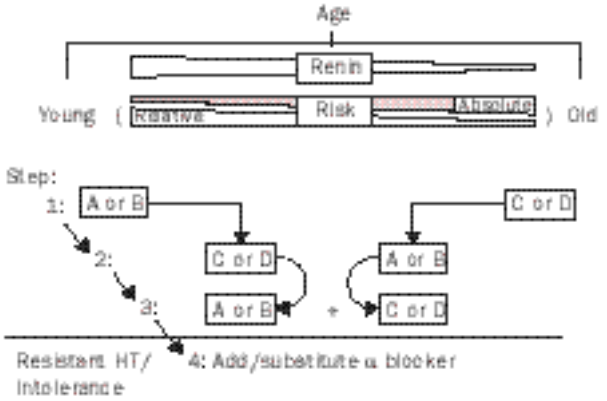

Figure 4: **Cambridge AB/CD rule for optimisation of antihypertensive treatment**
The schema represents the recommendations of the text. Steps one and two are monotherapy, with the order influenced by the patient's renin status. This is partly determined by the patient's age and ethnic group, permitting initial selection of treatment without actual renin measurement. Steps three and four are combination treatment. Progress to each step is indicated by failure to meet the treatment target. Decisions to treat hypertension are guided by overall cardiovascular risk assessment. The young are less likely than their peers to reach target age of 70 years (relative risk); older patients have protection factors, but have reduced 5-year survival (absolute risk).[34] A,B,C,D are the initials of the main drug classes, which either block (AB) or stimulate (CD) the renin system.

first and best treatments. The proportion of patients who reached target blood pressure on either their first or best drug is shown in table 3. Despite the almost identical average blood pressures at each treatment stage in the cycle, there were highly significant, progressive increases in the proportion of patients reaching any of the target blood pressures as a consequence of rotation.

A good response—predefined as one greater than the mean plus 1 SD of all responses in the study—was 17% for systolic blood pressure and 19% for diastolic blood pressure. 15 of the patients had only one good response, and there were 34 such responses in 24 patients. As is also apparent from figure 1, the good responses were not evenly distributed among the classes, being 16 to ACE inhibition, ten to β-blockade, four to calcium-channel blockade, and four to diuretic.

Many patients responding well to one drug responded poorly to another. Between four of the six possible pairs of treatment responses, there was no significant correlation. There were, however, two exceptions, namely ACE inhibition with β-blockade, and calcium-channel blockade with diuretic. The data for diastolic blood pressure are shown in figure 2, and a similar picture was observed for systolic blood pressure.

Although overall comparison of the four classes was not one of the prior objectives of the study, a repeated- measures ANOVA was done in view of the obvious difference in proportion of good responders to each class (figure 3). Univariate and multivariate analysis confirmed the significance of the 50–100% greater responses to either ACE inhibition or β-blockade, on the one hand, than to calcium-channel blockade or diuretic on the other, with no difference between the two treatments within the AB or CD pairs.

Repeatability of individual blood-pressure responses

On completion of the rotation phase, all but three patients repeated a month of one of the treatments used during the rotation phase. The mean (SD) supine blood pressure was 137/82 mm Hg (10/8) during the rotation phase and 137/82 mm Hg (14/9) during the repeat month of therapy. The coefficient of variation for systolic blood pressure ranged from 0–13% with a median of 2·5%; and for diastolic blood pressure from 0–15% with a median of 3·3%.

Achievement of target blood pressure during the titration phase

Three patients withdrew after the rotation phase. 50 of the patients remaining in the study reached the target supine blood pressure (≤135/85 mm Hg). 23 patients achieved this value on a single drug with acceptable tolerability; 21 of the remaining 27 patients reached the target on a combination of one drug each from the AB and CD pairs. ACE inhibition was substituted by angiotensin blockade, with similar efficacy in seven patients; poor tolerability or efficacy of other drugs led to substitution or addition of an α-blocker, respectively.

Prediction of response

Prediction of the mean blood pressure responses to each of the four classes was analysed by multiple regression analysis into which age, body mass index, logarithm of plasma renin activity, plasma norepinephrine, and baseline blood pressure were entered. Plasma renin activity weakly predicted the response to ACE inhibition ($r=-0{\cdot}40$, p=0·005). Baseline blood pressure significantly predicted diastolic blood-pressure response only to calcium-channel blockade ($r=-0{\cdot}48$, p=0·001).

Tolerability

Eight patients experienced adverse events that were definitely or probably related to treatment and resulted in early discontinuation of therapy, by patient or physician. Nifedipine was not tolerated by six patients, two of whom also experienced problems with triamterene-hydrochlorothiazide. Lisinopril and bisoprolol were each discontinued by single patients.

Discussion

We found significant variability in the response of most patients to the four main classes of antihypertensive agent. This variability was such that only a minority of patients were likely to receive their best drug first, or to reach a conventional target for blood-pressure treatment, without the process of systematic rotation. By contrast, such a target or better was reproducibly achieved in most patients on at least one treatment during rotation. With our predefined assessment of good response as a fall in blood pressure greater than the mean plus 1 SD, most

patients had only one such treatment, which was unlikely to be the first drug prescribed. There were no baseline measurements that were significantly predictive to permit significant improvement in the success of an initial treatment, except plasma renin activity and, indirectly, age.

The existence of variability as such may initially seem unsurprising, and consonant with everyday clinical experience. The challenge to us was how to measure such variability between individuals rather than the more usual comparison of average responses between groups. However, on closer inspection our results are at variance with most current guidelines, and surveys of current practice, both of which point to a stepped-care approach except when there is no fall in blood pressure after the first treatment is started.[18,20] The usual design of parallel-group comparison of antihypertensive agents cannot, of course, provide any measure of variation in each patient's response to the drugs, and the similarity in average response to the main classes of antihypertensive agents[1] may further deflect attention away from the scope for individual variation in response.

The practical implications of our findings are considerable. In our study of over 6000 hypertensive patients treated in general practice[15] we found that 31% of patients were receiving at least two drugs (26% of those aged less than 50 years), despite which only 35% of patients had a blood pressure of 140/90 mm Hg or less. There have been several published surveys showing the paucity of well-controlled hypertensive patients, the proportion being below 50% in many studies.[21–23] By contrast, the rotation strategy resulted in almost twice as many more patients being controlled on a single drug than on their first drug. With 140/90 mm Hg as the target for blood-pressure reduction, our findings suggest that monotherapy can be the aim in all but a few patients; where stiffer targets are introduced, the findings have a more dual-edged implication—that half the patients can still be controlled by one drug, but targets will not be achieved nationally unless half the patients are receiving combination therapy. It is difficult to compare our findings exactly with surveys of everyday practice. We can comment, however, that 49 of the 56 patients have had their blood pressure remeasured 1 year after reaching target, during which only two patients have required any adjustment to their treatment to maintain blood pressure at or below 140/90 mm Hg. Our open-label design (in which patients paid standard UK prescription charges) abolished one of the main differences between everyday and trial practice, and the reduction in the number of drugs required will itself probably be an important contributor to better compliance.

There has been one previous rotation study with a similar number of patients, which used a single-blind design, but in that case only three drugs were compared, there was no titration phase, and no assessment of the number of patients controlled.[7] Our open-label design facilitated a more extensive rotation, and permitted us to evaluate rotation as a feasible method for optimising treatment in everyday practice. The design is thus somewhat different from that of "n of 1" trials; this term has been applied to comparisons of drugs with each other or placebo in individual resistant patients, referred to a specialist centre.[24]

Comparison of drugs usually requires a dose titration to ensure that maximum efficacy is compared. The scope for titration is limited in a crossover trial—especially a multiple crossover such as our trial. However, our aim was not to compare the drug groups but to discover whether the relative response to these varied among individual patients; we aimed to maximise tolerability rather than efficacy so as to maximise the number of patients completing the crossover. Our doses would generally therefore be regarded as submaximal in each class; they are equivalent in most cases to those used in the crossover study of three drug groups reported by Attwood and colleagues.[7] In particular, the 30 mg dose of nifedipine (Adalat LA) is equivalent to the dose of 20 mg twice daily of the shorter-acting formulation used in that study. Our previous data from older patients suggested that the one group for which dose titration was required was the ACE inhibitors. In the event, the data and conclusions from the young patients in this study would be almost identical if we had used the 2-week data from the ACE-inhibitor phase, when patients were receiving only 10 mg lisinopril daily. Despite these caveats about doses and masking, the difference we found between the classes is likely to be real, reflecting the low average age of our patients and the view that diuretics work better in low-renin hypertension and β-blockade works better in high-renin hypertension.[25,26] A lower response to diuretics has previously been seen in young patients,[27] whereas a review of six trials in elderly hypertensive patients found a greater effiacy of diuretics than β-blockade in this older age-group.[28] The studies showing similar efficacy of calcium blockade have generally been in older patients than in our study. All our patients were white, reflecting the local population, and the results would probably have been different in other ethnic groups.[29]

The significant correlations within the AB and CD pairs of drugs in the rotation might suggest a minimum practical strategy of comparing one drug from the two pairs: ACE inhibition or β-blockade and calcium-channel blockade or diuretic. We might tentatively propose an extension of the AB/CD rule we formulated for choosing drug combinations. This rule arose from the recognition that drugs are more likely to be additive when their actions are complementary, particularly on the renin system,[11,12] all four possible combinations of AB and CD are indeed the four that are now licensed as fixed-dose products for hypertension. Similarly, our study provides evidence that a patient whose blood pressure responds poorly to a drug that stimulates the renin system may respond better to one that inhibits the system (and vice versa). A provisional recommendation may be that patients younger than 50 years start on one of the AB pair and switch to one of the CD pair if target blood pressure is not achieved; patients aged over 60 years would proceed in the reverse order. If target blood pressure is not reached on either pair, further rotation may be undertaken, and forestall in some patients the need to proceed to a combination of the best drug from the AB and CD pairs (figure 4).

One of our interests in studying drug response has been its possible use as an intermediate phenotype in the search for the genetic loci responsible for the inherited component of essential hypertension. The theoretical interest in the documentation of variability of response is the support it offers for the expectation of distinct syndromes within the umbrella of essential hypertension. Our study does not exclude a pharmacokinetic component to the variability of response, although only

nifedipine among our drugs is known to show any marked variability in metabolism.[30] On the other hand, we have already shown a weak predictive effect of polymorphism in the renin-angiotensin and sympathetic system on the response to ACE inhibition and β-blockade, respectively.[31,32] Most of the secondary and monogenic causes of hypertension have a best drug, such as amiloride for Liddle's syndrome.[33] If essential hypertension proves to be polygenic in most patients (ie, requiring a contribution from alleles at several independent genetic loci), we are likely to need measurement of several of these before achieving sufficient predictive power in any individual patient.

Contributors

Claire Dickerson undertook all clinical measurements, and shared responsibility for study design and writing. Aroon Hingorani recruited patients and provided clinical cover, including the decisions on drug or dose titration and management of adverse effects. Michael Ashby did plasma catecholamine analyses. Chris Palmer advised on statistical aspects of study design and analysis, and contributed to the writing. Morris Brown conceived and planned the study, and undertook data analysis, presentation and some writing. All authors approved the final version.

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