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Initial blood pressure as a predictor of the response to antihypertensive therapy

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1 The relationship between fall in systolic blood pressure and initial systolic blood pressure has been investigated in 255 mixed normotensive and hypertensive subjects given placebo or one of five types of antihypertensive drug (ACE inhibitors, calcium antagonists, direct vasodilators, α-adrenoceptor blocker, β-adrenoceptor blocker).

2 In all cases there was a significant correlation between the change in blood pressure and initial blood pressure. When Oldham's transformation was used (replacing the initial blood pressure by the mean of the initial and minimum pressures) the correlation coefficients were all reduced, although five out of six were still statistically significant.

3 In a subset of 43 hypertensive subjects given four antihypertensive agents, concentration-effect analysis was carried out. For three of the agents a linear model was used to relate effect to concentration; for the remaining agent a Langmuir type model was used.

4 For all four sets of data for which concentration-effect analysis was carried out, there was a significant correlation between the sensitivity of response and the initial blood pressure.

5 The observed relationships between initial blood pressure, change in blood pressure and sensitivity of response can be qualitatively explained by postulating a general form of dose-response relationship for all antihypertensive agents.

Keywords blood pressure hypertension antihypertensive therapy concentration-effect analysis

Introduction

It has been suggested from recent studies with calcium antagonists that these agents lower blood pressure to a greater extent in hypertensive patients that in normotensive subjects (MacGregor *et al.*, 1982). In contrast, a β-adrenoceptor blocker (propranolol) and an ACE inhibitor (captopril) reduced blood pressure to the same extent in both normotensives and hypertensives. It was also suggested that the calcium antagonist drugs were particularly appropriate for the more severe degrees of hypertension. This was based on the observation that the higher the initial (pre-treatment) blood pressure, the greater was the fall in response to a calcium antagonist. It has been further proposed that these observations were related to fundamental differences in the mechanisms of action, such that calcium antagonists had specific antihypertensive activity (MacGregor *et al.*, 1985a).

The statistical analysis which led to these conclusions has been subsequently criticised (Gill *et al.*, 1985), on the grounds that spurious correlations will arise if the initial blood pressure is correlated with the change in blood pressure, since the latter is calculated from the initial blood pressure and effectively the same variable appears on both axes.

To investigate further these various conflicting claims we have examined the relationship between the initial blood pressure and the change

in blood pressure following a range of antihypertensive agents. We have extended our observations, using concentration-effect analysis, to investigate whether there is a relationship in individual subjects between the initial blood pressure and the responsiveness to a drug, in terms of fall in blood pressure per unit of drug concentration.

Methods

Change in blood pressure vs *initial blood pressure*

The data used for this analysis were obtained from 30 double-blind, placebo-controlled single dose studies of antihypertensive drugs, a total of 255 mixed normotensive and hypertensive subjects. All the hypertensive subjects were suffering from essential hypertension but were otherwise normal on the basis of routine clinical examination, and routine screening of biochemistry, haematology and electrocardiography. They were on no other regular drug treatment and avoided over the counter preparations during the duration of the study.

All studies were undertaken under standardised and reproducible conditions in a dedicated clinical research laboratory with the same attendant nursing and medical staff and using directly comparable protocols and timings for the blood pressure recordings. An identical study day was specifically undertaken to examine the effects of blood pressure and heart rate of the administration of placebo in each individual subject. In the volunteer studies placebo was invariably administered as part of a random order design but in some of the patient studies the placebo was the first 'treatment' which was administered. In this latter type of study the patients had invariably been followed up on several previous occasions during a treatment-free period of not less than 6 weeks.

Placebo and five types of antihypertensive drugs were studied:

(a) ACE inhibitors (captopril, enalapril, cilazapril),
(b) Calcium antagonists (nifedipine, nisoldipine, nicardipine, amlodipine and verapamil),
(c) Direct vasodilators (endralazine and MDL899),
(d) α-adrenoceptor blocker (prazosin),
(e) β-adrenoceptor blocker (flusoxolol).

The protocols for all these various studies involved the frequent measurement of supine and erect blood pressure and heart rate (using an automated sphygmomanometer) over a period of at least 8 h. Analysis has been confined to supine systolic pressure during the first 8 h following administration of the drug or placebo. For reasons of brevity, in this section of the study supine systolic blood pressure is referred to simply as blood pressure.

Statistical methods

The following notation has been used:

BP1 = Initial blood pressure
BP2 = Lowest blood pressure reached in the 8 h following drug administration
$\Delta BP = BP1 - BP2$

The correlation coefficient between BP1 and BP2 is denoted by ρ_1 and the correlation coefficient between ΔBP and BP1 by ρ_2. There is essentially an inverse relationship between ρ_1 and ρ_2, that is to say, as one increases the other decreases. In fact, if the variances of BP1 and BP2 are equal, it can be shown that

$$\rho_2 = \sqrt{\frac{1-\rho_1}{2}}$$

In the extreme case in which $\rho_1 = 0$ (i.e. no correlation between BP1 and BP2), then $\rho_2 = 0.707$. Conversely, if there is a perfect correlation between BP1 and BP2, i.e. $\rho_1 = 1$, then $\rho_2 = 0$. ρ_2 is thus an (inverse) measure of how well paired are the initial and minimum readings.

An alternative approach, sometimes referred to as Oldham's transformation, is to examine the relationship between ΔBP and (BP1 + BP2)/2 (Oldham, 1962). The relationship between these quantities is independent of any correlation that may exist between BP1 and BP2.

A further alternative approach which has been proposed (MacGregor *et al.*, 1985b), is to look directly at either the correlation between BP1 and BP2 or the correlation between log (BP1) and log (BP2). If f is the fractional drop in blood pressure, then these can be expressed as

$$BP2 = BP1 - f.BP1 = (1-f)BP1$$

and

$$\log(BP2) = \log(BP1) + \log(1-f)$$

Plotting BP1 against BP2 on a linear plot, a slope of about 1 with non-zero intercept would indicate that, on average, the fall in blood pressure did not depend on the initial pressure. On a plot of log(BP1) against log(BP2), a slope of about 1 but a non-zero intercept would indicate that the fall in blood pressure was simply propor-

tional to BP1, i.e. log(1 − f) was constant. A slope on the log–log plot which was significantly different from 1 would imply that the proportional change, f, was increasing with increasing BP1.

Concentration-effect analysis

The data used for this analysis were a subset of the total data and applied only to the hypertensive patients involved in four separate placebo-controlled studies with antihypertensive drugs: verapamil (12 subjects), endralazine (8 subjects), prazosin (15 subjects), and flusoxolol (8 subjects). These data were obtained from 10 h study periods, during which the pharmacodynamic measurements were obtained at the same times as the pharmacokinetic measurements (i.e. plasma drug concentrations). The pharmacodynamic response used was the erect systolic blood pressure. Since each patient received placebo and drug on separate study days, the responses were corrected for placebo effects by subtracting the changes in blood pressure on the placebo day from the changes in blood pressure on the day on which drug was administered. The aim of concentration-effect analysis is to relate the effect of a drug to its concentration in plasma or in a notional 'compartment' of a pharmacokinetic model. If the effect of a drug is not in phase with its plasma concentration, or the concentration in any of the conventional compartments of the pharmacokinetic model employed, the technique described by Sheiner *et al.* (1979) can be used. In this method a hypothetical 'effect compartment' augments the conventional compartmental model, without perturbing it. The resulting model, in the two compartment case, is shown schematically in Figure 1. The rate constant k_{eq} can be varied to enable the time of peak effect to be out of phase with the central and peripheral compartments. The next step is to express the effect as a function of drug concentration in the effect compartment, i.e. E = f(C). In this analysis two models have been applied:

1. A linear model: E = mC + i
   In this model the effect-concentration data were fitted to a straight line, where m = the slope of the line, effectively the sensitivity of response, and i = the intercept of the line on the effect axis.
2. A Langmuir equation of the form

$$E = \frac{E_{max}\, C}{C_{50} + C} + i$$

where E_{max} = maximum effect and C_{50} = concentration to achieve 50% of the maximum effect.

The choice of linear or Langmuir models was decided on the basis of a general linear test. The Langmuir model was considered the full model with four parameters (k_{eq}, E_{max}, C_{50}, i) and the linear model was the reduced model with 3 parameters (k_{eq}, m, i).

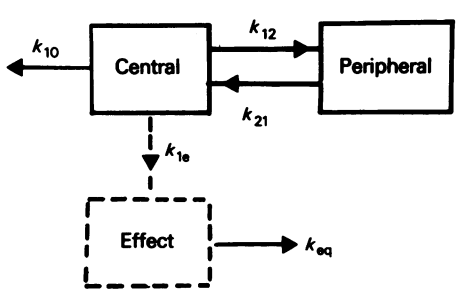

Figure 1 Schematic diagram of a two compartment pharmacokinetic model.

Results

Change in blood pressure vs *initial pressure*

Figure 2 shows a graph of the change in blood pressure (ΔBP) plotted against the initial blood pressure (BP1) for ACE inhibitors. The correlation coefficient is 0.74. Figure 3 shows the same data set, but this time with Oldham's transformation applied, that is ΔBP plotted against (BP1 + BP2)/2. Clearly the correlation coefficient is not as high in this case. Table 1 shows the correlation coefficient obtained with and without Oldham's transformation, for each type of antihypertensive agent investigated. Table 2 shows the results of linear regression analysis of

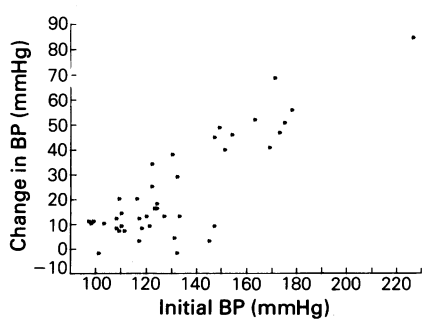

Figure 2 Graph of change in blood pressure plotted against initial blood pressure in 43 subjects given single doses of ACE inhibitors.

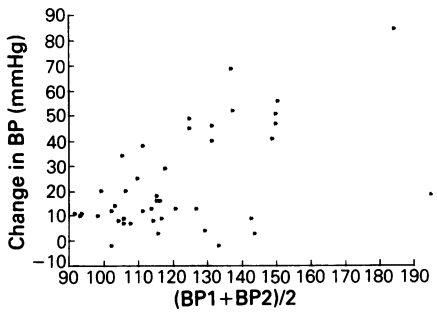

Figure 3 Graph of change in blood pressure plotted against mean of initial and minimum pressure in 43 subjects given single doses of ACE inhibitors.

log (BP2) *vs* log (BP1), i.e. log (BP2) as the y variable. It is apparent from these data that in all cases the slope is significantly different from one. One problem with this regression analysis is that it assumes negligible errors in the x variable (ln (BP1)). Also shown in Table 2 are the best estimates of the slope if it is assumed that ln BP1 and ln BP2 have equal variance. All the slopes remain below 1.

Concentration-effect analysis

For only one of the data sets (flusoxolol) was the Langmuir model found to be superior to the linear model. For this data set only, therefore, we investigated the relationship between E_{max} and BP1; for the remaining data sets we investigated the relationship between m and BP1. Figures 4 and 5 are graphs of the sensitivity parameter (m) plotted against the initial blood pressure (BP1) for verapamil and prazosin respectively. Table 3 shows the correlation coefficients for all four sets of data.

Discussion

A statistically significant correlation between the initial blood pressure and the change in blood pressure was shown with all treatments, including placebo. With Oldham's transformation, the correlation coefficients were much smaller, as might be expected; although most are statistically significant, it should be remembered that a correlation coefficient of 0.5 only explains 25% of the variability in the data. Turning to the

Table 1 Coefficients of correlation between (i) change in blood pressure and initial blood pressure and (ii) change in blood pressure and mean of initial and minimum blood pressures for five antihypertensive agents and placebo

Drug	*Number of subjects*	*Correlation coefficient for BP* vs *BP1*	vs *(BP1 + BP2)*
α-adrenoceptor blocker (prazosin)	24	0.78	0.52**
Calcium antagonist	64	0.68	0.50*
ACE inhibitors	55	0.74	0.49*
Direct vasodilators	35	0.77	0.43**
Placebo	69	0.64	0.35**
Flusoxolol	8	0.89	0.58

*$P < 0.001$, **$P < 0.01$.

Table 2 Results of linear regression analysis of log (minimum pressure) *vs* log (initial pressure) for five antihypertensive agents and placebo

Drug	*Number of subjects*	*Intercept (mean ± s.d.)*	*Slope (with ln (BP2) as y variable) (mean ± s.d.)*	*Best estimates of slope assuming ln (BP1) and ln (BP2) have equal variance*	*Correlation coefficient*
α-adrenoceptor blocker (prazosin)	24	2.53 ± 0.62	0.44 ± 0.13	0.74	0.59**
Calcium antagonists	64	0.71 ± 0.33	0.81 ± 0.07	0.96	0.84*
ACE inhibitors	55	1.93 ± 0.42	0.57 ± 0.09	0.70	0.67*
Direct vasodilators	35	2.57 ± 0.8	0.43 ± 0.16	0.37	0.43**
Placebo	69	1.74 ± 0.35	0.61 ± 0.01	0.84	0.72*
Flusoxolol	8	4.8 ± 1.4	0.02 ± 0.27	0.06	0.03

*$P < 0.001$, **$P < 0.01$.

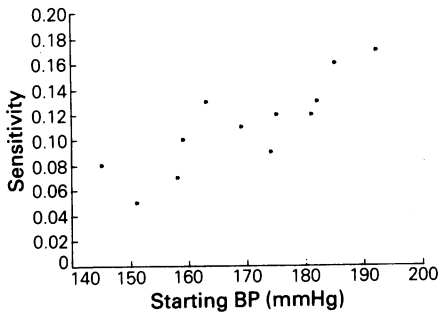

Figure 4 Graph of the sensitivity parameter (m) obtained from concentration-effect analysis plotted against the initial blood pressure in 12 subjects given single doses of verapamil.

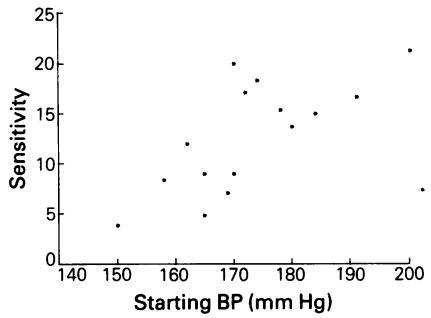

Figure 5 Graph of the sensitivity parameter (m) obtained from concentration-effect analysis plotted against the initial blood pressure in 14 subjects given single doses of prazosin.

relationship between log (BP1) and log (BP2) all the data sets have a slope less than one. It is therefore reasonable to conclude that subjects who have a higher initial blood pressure generally show a greater response to antihypertensive drugs. In this respect there is nothing unique about calcium antagonists, or any other group of antihypertensive agents, and a similar effect also occurs with placebo. It seems unlikely that several pharmacologically different antihypertensive drugs, and placebo, all affect the fundamental mechanism underlying raised blood pressure in a similar manner. However, it may not be necessary to invoke a common pharmacological mechanism to explain this relationship; instead it can be postulated that in hypertension the response to any blood pressure lowering effect has a sigmoid form. This point is discussed further in the context of concentration-effect analysis.

The statistical problems of interpreting apparent relationships between changes in blood pressure and initial values of blood pressure clearly do not permit us to be dogmatic about mechanisms of blood pressure control. It is, however, worth bearing in mind that the relationship between change in blood pressure and the initial pressure is important from the practical, predictive point of view, because the initial blood pressure is of course the only quantity known before treatment has started.

The results of concentration-effect analysis show a clear relationship between the responsiveness to a drug and the initial blood pressure. It seems most unlikely that this relationship could be due to a statistical artefact, as the data not only are placebo subtracted but also incorporate independent information on the individual pharmacokinetics. As before, the relationship appears to hold for several different types of antihypertensive drug, rather than being a property of any particular one, and accordingly it can again be postulated that it is a function of the hypertensive state rather than a property attributable to the drug treatment. A simplistic way of explaining this would be to imagine that a typical dose-response curve to *any* antihypertensive agent is as shown in Figure 6. It seems intuitively reasonable that the curve is sigmoid—since many dose-response curves have this form—and clearly there will be a minimum below which the blood pressure cannot fall. The lateral position of this curve will depend on the characteristics of the individual being studied, and of course on the particular drug being used. We might imagine that a very hypertensive subject would start at a

Table 3 Coefficients of correlation between m and E_{max} and initial blood pressure for four antihypertensive agents

Drug	*Number of subjects*	*Model*	*Variables correlated*	*Correlation coefficient*
Verapamil	12	Linear	m *vs* BP1	0.82**
Endralazine	8	Linear	m *vs* BP1	0.82†
Prazosin	15	Linear	m *vs* BP1	0.74**
Flusoxolol	8	Langmuir	E_{max} *vs* BP1	0.81†

**$P < 0.01$, †$P < 0.05$.

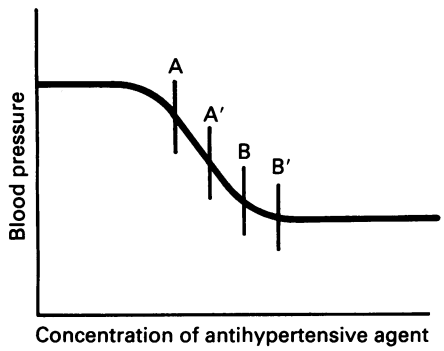

Figure 6 Hypothetical form of the dose-response relationship for antihypertensive agents.

higher point (say A) of the curve than a less hypertensive subject (say B). If a linear concentration-effect model is used, the sensitivity parameter (m) corresponds to the slope of that portion of the curve following from the starting point, i.e. A–A′ in the case of our hypothetical subject with the higher blood pressure, and B–B′ for our subject with lower blood pressure. Clearly the slope of the segment BB′ is less than that of AA′. This is consistent with the data shown in Figures 4 and 5.

The form of the curve shown in Figure 6 would also explain qualitatively the results presented in the first section of this paper. For a given increment of drug concentration a subject starting at point A of the curve is likely to have a larger drop in blood pressure than a subject starting at point B of the curve.

In summary therefore, the higher the blood pressure before treatment, the greater the response to treatment. This relationship can be inferred from straightforward blood pressure data but emerges convincingly from concentration-effect analysis. Moreover, the relationship applies to several types of antihypertensive agent and therefore may be more likely to reflect the form of the concentration-response curve for hypertension itself.

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