Diagnosis Ex Juvantibus
Individual Response Patterns to Drugs Reveal Hypertension Mechanisms and Simplify Treatment

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SUMMARY Heterogeneity of response to antihypertensive therapy is a well-recognized clinical phenomenon. An agent that is antihypertensive in one patient may increase blood pressure in another or have no effect in a third. We believe that this variety of individual response to drug treatment can provide a new framework for the study of hypertensive subjects. Different patterns of response elicited by sequential trials of individual drugs with different mechanisms of action (diuretics, calcium channel blockers, \( \alpha \)-blockers, \( \beta \)-blockers, and converting enzyme inhibitors) should provide another means to classify hypertensive patients into biologically relevant groups. The documentation and analysis of this therapeutic heterogeneity in relation to renin profiling and to other physiological and demographic parameters may add a new dimension to the investigation of the pathophysiology of hypertension; it may serve as a basis for more appropriate stratification of participants in clinical trials and may ultimately contribute to a more rational approach to patient management. (Hypertension 12: 223-226, 1988)

KEY WORDS • hypertension treatment • antihypertensive agents • comparative studies • clinical trials • diuretics • converting enzyme inhibitors • calcium channel blockers • adrenergic receptor blockers

VARIATION in individual responses to antihypertensive therapy is a well-known phenomenon and is consistent with the clinical, physiological, and prognostic heterogeneity that characterize hypertensive patients. 1-4 Since the development of orally active antihypertensive agents in the 1950s, it has repeatedly been observed that patients' blood pressures respond differently to different drugs. 5-9 These clinical observations, though widely recognized by practicing physicians, have not been characterized systematically. They are supported, however, by studies in animal models. Thus, there are salt-sensitive and salt-resistant forms of hypertension; there are experimental models that respond to sodium depletion (e.g., deoxycorticosterone-salt and Dahl salt-sensitive hypertension) and others that do not (e.g., spontaneously hypertensive rat and two-kidney Goldblatt hypertension). 10

Individual differences in drug responses are not explained by differences in dose. They seem, rather, to reflect different mechanisms of blood pressure elevation. If this is so, one might expect that individual patients would exhibit characteristic patterns of response to different pharmacological agents that might expose different underlying pathophysiology.

To determine the relative effectiveness of specific agents in individual patients, we reviewed studies comparing the effectiveness of two or more antihypertensive agents. Through a MEDLARS search we identified 1486 separate reports in English published between January 1980 and December 1986 and classified these studies into three types. For studies in the first group, normalization of blood pressure was the goal, and drugs were added in series and as needed to achieve this goal. For studies in the second group, the objective was to compare blood pressure response to particular drugs. Subjects received, in parallel, only one of two or more drugs. In neither of these first two types of experiment was the same subject exposed systematically to all drugs studied, one at a time, or even to two drugs one by one. 223
The third, and far less common, form of trial used a crossover design in which the same subjects were exposed to single agents in series. This type of study usually involved a relatively small number of subjects and frequently lacked a placebo control group. Interestingly, in the second and third kinds of study, many subjects, in some cases a majority, failed to attain a substantial (variably defined) blood pressure fall: 10 to 59% of selected groups of subjects failed to respond to diuretics, and 12 to 86% did not respond to \( \beta \)-blockers. In addition, an identifiable fraction experienced a rise in pressure during the administration of almost every drug. Retractively, from our point of view, the data in such studies were usually presented in the aggregate. Only three studies actually reported the responses of individual subjects to two drugs of different classes. One was an open, randomized, crossover study of 18 subjects in which a slow calcium channel inhibitor (verapamil) was compared with a \( \beta \)-adrenergic blocker (propranolol). Even though final diastolic blood pressures were similar (82.6 mm Hg for propranolol vs 85.8 mm Hg for verapamil) and similar numbers responded to propranolol and verapamil treatment with a diastolic blood pressure below 90 mm Hg (13 vs 11 patients), these aggregate similarities masked substantial individual variation. In eight subjects, for example, there was more than a 10 mm Hg difference in final diastolic blood pressure between the two drugs, and in two subjects the difference exceeded 30 mm Hg. Although this study was not designed to address our question, its results are consistent both with our clinical perceptions and with our hypothesis that individuals respond differently to different classes of antihypertensive drugs.

Diuretics, converting enzyme inhibitors, \( \alpha \)-adrenergic and \( \beta \)-adrenergic blocking agents, and calcium channel blockers are classes of drugs that have quite distinct mechanisms of action. A priori, it seems unlikely that sequential testing would reveal a uniform pattern of response. From the biological perspective, patients who exhibit the most egregious responses to various drugs may be the most informative (i.e., a dramatic correction as opposed to a total lack of response or even a pressor effect). Our own unpublished experience with 736 mildly to moderately hypertensive patients who for first treatment were randomly allocated to either a diuretic or a \( \beta \)-blocker regimen was that 8% of both treatment groups had an initial (within 2–4 weeks) rise in diastolic pressure that exceeded 5 mm Hg. The full range of outcomes was observed among patients treated with either agent, including a sharp blood pressure decline, no apparent effect, and a rise in pressure.

In fact, blood pressure response to a drug most likely reflects the summation of one or more pharmacological actions and physiological reactions. How these contending forces play out in individual patients must surely reflect different underlying pathophysiology. In the case of nonresponders to diuretics, for example, the loss of sodium and volume may be perfectly counterbalanced by an activated renin-angiotensin system. This effect has been documented. It has also been verified by the demonstration that such nonresponders do respond promptly to the addition of a converting enzyme inhibitor. Thus, it appears that patients responding successfully to a diuretic are those whose appropriate compensatory and conservatorial responses to an imposed deficiency of salt are blunted (e.g., low-renin patients). In the normotensive subject, blood pressure homoeostasis is maintained in the face of a diuretic challenge by a perfect balance of opposing forces involving, in particular, a full reactive response of the renin system. Hypertensive individuals, in contrast, display a range of outcomes that presumably reflect the power of the physiological forces unleashed by the pharmacological stimulus as well as the underlying pathological state.

An interplay of opposing forces can also be expected in response to \( \beta \)-blocker therapy. Will the fall in plasma renin with a reduced cardiac output produce a blood pressure decline? Or will the counterbalancing effect of unopposed \( \alpha \)-adrenergic tone result in a canceling of the \( \beta \)-blocker effect and no change in blood pressure? Or will unopposed \( \alpha \)-adrenergic tone in the presence of an already suppressed renin actually cause a rise in pressure? All three outcomes occur, and they undoubtedly express a different balance between pharmacological effect and reactive control mechanisms.

The same range of possible outcomes attends the use of calcium channel blockers. In some patients, perhaps those in whom angiotensin is the major factor driving blood pressure, calcium antagonists fail to produce a blood pressure decline. Conversely, a number of reports now indicate that these drugs are especially effective in patients with low renin. Perhaps for the same reason, in response to superimposed sodium restriction or added diuretic therapy, an induced reactive renin rise may actually be associated with a blunted
anti hypertensive effect in patients receiving calcium antagonists. This seemingly paradoxical effect of sodium depletion already suggests a sodium-calcium interplay in low-renin hypertension.

It takes little imagination to recognize the rich variety of individual patterns of response that might be revealed and defined by a sequential testing process using different anti hypertensive agents in which non responders are given equal analytical attention. Such a classification of hypertensive subjects into subgroups will almost certainly produce new clues concerning the underlying mechanisms of blood pressure control.

At the very least, we need to get a feeling for the numbers in each category of response for each of the various types of drugs. It is unlikely to be the same individuals who respond, fail to respond, or get a pressor response to every drug type. With this information in hand, we can begin the exciting project of examining the demographic, clinical, biochemical, and pathophysiological profiles of subjects in the different subgroups. These modern drugs, with their greater specificity of action, could thus be fully exploited as probes to reveal different pressor mechanisms at work in different subjects. Identification and analysis of therapeutic heterogeneity, particularly when combined with an awareness of the underlying associated biological mechanisms, should contribute a new dimension to the investigation of the pathophysiology of hypertension and should perhaps serve as a basis for more appropriate stratification of participants in clinical trials, ultimately leading to more rational patient management.

The heterogeneity of individual responses to drug treatment could provide a new framework for the study of hypertensive subjects, independent of their blood pressure, that can be seen as the pharmacological analogy to the classification of subjects by analysis of their renin-sodium profiles. Just as the quantification of the contribution of renin to blood pressure control has proved such a productive tool for investigating human hypertension, so might a process using different antihypertensive agents offer another paradigm for patient management. And as understanding improves, many patients may be brought closer to the primary goal of all long-term drug therapy—to achieve, for as many as possible, a long-term program involving the fewest number of drugs given in the lowest possible amount and frequency.

References


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