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

JOHN H. LARAGH, BERNARD LAMPORT, JEAN SEALEY, AND MICHAEL H. ALDERMAN

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, α-blockers, β-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. 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. 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).

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.
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, sometimes 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. Regrettably, 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 that it is the same 50 to 60% of persons who respond to every drug. This would require that a reciprocal 40 to 50%—again the same 40 to 50%—invariably fail to respond to all antihypertensive drugs. Such uniformity of response not only is inconsistent with clinical experience but seems inconceivable in view of the varied mechanisms of action of each drug. For example, it has been demonstrated repeatedly that, as a group, patients with high levels of plasma renin activity respond well to \( \beta \)-blockers or converting enzyme inhibitors but frequently are resistant to the hypotensive effects of a low sodium diet or a diuretic. Patients with low renin levels, on the other hand, are especially sensitive to thiazide or spironolactone diuretics or to a low sodium diet and to the newer calcium antagonists. However, as a group they respond poorly to \( \beta \)-blockers or angiotensin converting enzyme inhibitors.

A more likely outcome of sequential testing of individual drugs would be a heterogeneous 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 conservational responses to an imposed deficiency of salt are blunted (e.g., low-renin patients).

In the normotensive subject, blood pressure homeostasis 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
antihypertensive 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 antihypertensive agents in which nonresponders 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 quantitation of the contribution of renin to blood pressure control has proved such a productive tool for investigating human hypertension, so might a classification of hypertensive subjects according to their individual pattern of response (or lack of it) to pharmacological agents offer another paradigm through which fundamental mechanisms of blood pressure control could be examined. In a sense, this approach reflects an attempt to diagnose by treating (diagnosis ex juvantibus), a clinical strategy once widely used but no longer in favor.

Recent evidence suggests that, at long last, investigators are beginning to evaluate antihypertensive drugs with these considerations in mind. And already the clinical fruitfulness of this approach is becoming apparent. Two articles from a recent issue of Hypertension are examples. In one, Ménard et al. described a workable crossover design with a 15-day washout between each active drug trial that offered to each subject the possibility of individualized treatment with the most effective agent. In the second report, Bidiville et al. demonstrated that a calcium antagonist or an angiotensin converting enzyme inhibitor given alone in the same individuals produced different responses. Some subjects responded to one drug, some to both, and some to neither, without revealing any basis for this heterogeneity. More extensive trials along these lines are badly needed. Because the results of such a study are likely to focus and reduce the range of indications for most drugs to particular subgroups, it is unlikely that the pharmaceutical industry would support such research. Notwithstanding, ultimately, no single agent will be indicated for all patients with hypertension. Each single drug will be indicated only for those in whom it can be shown to be especially beneficial.

Meanwhile, pending the availability of more complete and precise information regarding comparative patterns of individual response to particular drugs, the practicing physician might prudently pursue blood pressure control by sequentially testing and withdrawing single agents from among the five major types of antihypertensive drugs rather than by adding second and third drugs to previously unsuccessful therapy. Such an approach would lead to a more parsimonious, rational, and safer strategy 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

Diagnosis ex juvantibus. Individual response patterns to drugs reveal hypertension mechanisms and simplify treatment.
J H Laragh, B Lamport, J Sealey and M H Alderman

doi: 10.1161/01.HYP.12.3.223

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/12/3/223

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/