Variability in Response to Antihypertensive Drug Treatment

Barry J. Materson

One of the definitions of the word pragmatic is “practical as opposed to idealistic.” Many of the controversies regarding the issue of the use of race to any degree whatsoever in medical decision-making may be more of a result of tensions between pragmatic and idealistic positions on the issue.

The biological determinants of human intraarterial pressure are such that there is no precise cutpoint that can be defined for what can be considered to be “normal.” Certainly, the statistical population norm is not a satisfactory cutpoint, because it is skewed to the right by those people whose blood pressures are biologically abnormal. How do we know that they are biologically abnormal? Here is another point of tension. We must make that determination based on the best epidemiological data on target organ consequences of elevated intraarterial pressure that we can gather. Reducing intraarterial pressure appears to be more important than the means by which it is reduced.1 Currently, a systolic pressure of <120 mm Hg and a diastolic pressure of <80 mm Hg defines normal, but there is growing evidence that <115 mm Hg systolic and <75 mm Hg diastolic should be the cutpoint.2–4

As if this were not enough uncertainty, add the fuel of measurement, physiological, geographic,5 and treatment variability of blood pressure to the philosophical fire. It is this variability within individuals and the overlap of group responses that is the central point of the study by Mokwe et al reported in this issue of Hypertension.6

In brief, the authors used data from the Quinapril Titration Interval Management Evaluation (ATIME) study on 533 African American and 2046 white patients to evaluate the influence of race and other factors on blood pressure response to quinapril. They also assessed the degree to which nonrace factors influenced the apparent racial differences. As a group, the African Americans responded less well by 4.7/2.4 mm Hg compared with the whites. When multiple nonrace factors were considered, this difference was reduced to 2.3/1.9 mm Hg. They concluded that the response variability was within, and not between, racial groups.

Measurement variability is well known to the readers of Hypertension. Investigators reduce this to the extent possible by careful training and certification of clinic personnel, using when possible validated equipment that eliminates observer bias, such as digital preference, by using the average of multiple readings as the visit blood pressure and, when practicable, using 24-hour automated blood pressure monitoring equipment to minimize “clinic” hypertension. Flack et al7 did not report the exact method of blood pressure determination for the ATIME study, but they do report that the last of 3 clinic visits was used as the baseline blood pressure. These are experienced investigators, and I suspect that the details were deleted for reasons of manuscript space.

Physiological variation in blood pressure is also well known. Some examples include factors such as time of day and time of year, ambient temperature, recently consumed drugs such as caffeine, nicotine, or medications that raise or lower blood pressure either by design or as a side effect, and the patient’s emotional state. Experienced investigators control for these variables to the extent possible. Basic measures include scheduling appointments for the same time of day, constancy of procedure and clinic personnel, having the patients bring all medications, herbal remedies, and the like to each clinic visit, and asking the patients not to smoke or consume coffee or alcohol before the visit. Again, I assume that these measures were taken in the ATIME trial.

Variability in response to treatment is one of the main observations of the article by Mokwe et al. In 1931, David Ayman6 commented on the difficulties that blood pressure variability created for assessment of response to antihypertensive treatments. The classic 1967 article by Dr Edward D. Freis8 that reported the results of treating severely hypertensive patients included a display of the distribution of systolic and diastolic blood pressure response for patients randomly allocated to treatment with placebo or active triple therapy. The systolic blood pressure response to placebo administration varied from an increase of 28 mm Hg to a decrease of 76 mm Hg; response to the active drugs ranged from an increase of 12 mm Hg to a decrease of 76 mm Hg. The average systolic decrease from prerandomization blood pressure was 43 mm Hg. There was a tighter distribution curve for diastolic pressure. The response to placebo ranged from an increase of 28 mm Hg to a decrease of 44 mm Hg; active treatment response was from an increase of 12 to a decrease of 60 mm Hg. Average diastolic decrease from baseline was 29.7 mm Hg. Average change from baseline for placebo was nonsignificant: a reduction of 1.3 mm Hg for diastolic blood pressure. No systolic blood pressure value was given. The graphic display of systolic and diastolic blood pressure responses to treatment in African American and white populations (Figures 1 and 2) in the Mokwe article is much more demonstrative of the variability, but the pattern is similar to the figure in the 1967 article. Mokwe et al had far more patients than the Veterans Administration (VA) study, used

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Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000127916.65346.5c

2004 American Heart Association, Inc.
more sophisticated statistical analyses, and enrolled patients with baseline levels of blood pressure that were far lower and less variable. The point is still the same: there is substantial variation in blood pressure response to antihypertensive therapy.

The VA Cooperative Study Group on Antihypertensive Agents is one of many that have demonstrated differences in response of groups of African Americans and whites to various classes of antihypertensive drugs. Drugs that affect the renin-angiotensin-aldosterone system seem to typify this effect. The data presented by Mokwe et al appear to add to this observation. The overlap of response caused by variation is quite obvious, but the group mean and median blood pressure differences between the racial groups is substantially clinically.

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As I noted previously, we do not yet have an accurate means of identifying the individuals who comprise these group response distribution curves who respond quite well to drugs that interfere with the renin-angiotensin-aldosterone system. Pharmacogenomics offers that promise, but if and when that will be realized is unknown. In the meantime, the age by race construct was demonstrated to be at least as accurate in predicting response as was plasma renin profiling.

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In summary, Mokwe et al have provided a clear demonstration of the variability of blood pressure response to single-drug therapy, have confirmed the previously known group differences in response, and have reiterated that race alone is not sufficient to predict response to monotherapy. That is the idealistic position. The pragmatic point is that the clinical practitioner still must be aware of that in contrast to the uncertainty of random initial drug selection, the age by race construct is a simple, cost-free, and relatively accurate way of guiding the choice of single-drug therapy for patients with stage 1 hypertension.

References
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Hypertension. published online April 26, 2004;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/early/2004/04/26/01.HYP.0000127916.65346.5c.citation

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