3-1-2006

Individualized therapy for hypertension

J. David Spence
Stroke Prevention and Atherosclerosis Research Centre, jdspence@uwo.ca

Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed, double-spaced) in length and may be subject to editing or abridgment.

Individualized Therapy for Hypertension

To the Editor:

The recent publication of the Blood Pressure Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) has again occasioned a flurry of media pronouncements and editorials contending that now the truth is known and that "newer" therapies are more effective than "old" therapies for hypertension—β-blockers and diuretics. A similar flurry of media pronouncements, but in the opposite direction, was trumpeted after the publication of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), which showed that diuretics were "the best" therapy for hypertension. Largely unnoticed amid all this fuss was the second Australian National Blood Pressure study (ANBP2), which followed closely on the heels of the ALLHAT trial, and, like ASCOT-BPLA, also showed that angiotensin-converting enzyme inhibitors were better than diuretics. So what are these trials trying to tell us?

The fundamental fallacy underlying all this nonsense is the assumption that all patients are the same and therefore that there exists a single "best therapy" for all hypertensive patients. We should know better.

It has been clear for many years that patients with African ancestors, on average, had lower levels of plasma renin than did patients without African ancestors and that patients with African ancestors responded better to diuretics.[1] It has also been clear for many years that measuring plasma renin is very helpful in the management of resistant hypertension. As pointed out by the authors of ANBP2, "In ALLHAT, 32% of the patients were non-Hispanic blacks, 16% were Hispanics, and 47% were non-Hispanic whites, whereas in ANBP2, almost the entire study population was white (95%)" (and less than 2% had African ancestors [personal communication, Dr Lindon Wing, 2003]). In ASCOT-BPLA, only 5% of the subjects were "ethnic minorities: mainly South Asian or Afro-Caribbean"; only 2.4% had African ancestors (personal communication, Dr Neil Poulter, 2005). Thus, it seems that there is no mystery.

Although patients with African ancestors made up only 1% of our hypertension clinic population, they accounted for 40% of our patients who needed adrenalectomy for primary hyperaldosteronism.[2] Low-renin hypertension accounts for an important proportion of resistant hypertension in hypertension clinics around the world.[3,4]

What ASCOT-BPLA, ALLHAT, and ANBP2 have been trying to tell us is that there is no single "best therapy" for all patients with hypertension: what physicians need to do is to define the underlying cause of the hypertension in each patient, and individualize the therapy for that patient.

It is very simple to use plasma renin and aldosterone to individualize therapy in resistant hypertension. After excluding rare causes such as pheochromocytoma and licorice, there are essentially 3 kinds of hypertension, each with a different primary therapy. If the renin is low and the aldosterone high, the problem is primary hyperaldosteronism, and the primary therapy is aldosterone antagonists (or amiloride where eplerenone is not available for men, who commonly get gynecomastia with spironolactone). Primary hyperaldosteronism is usually caused by bilateral hyperplasia, so it is rarely surgical.[5] If the renin is low and the aldosterone is low, the problem is Liddle's syndrome or a variant, which account for 5% of hypertension in patients with African ancestors, and the primary treatment is amiloride.[6] If the renin is high and the aldosterone is high, the primary treatment is angiotensin receptor blockers (and sometimes revascularization is required for true renovascular hypertension).

Individualized therapy has tremendous potential for reducing the burden of cardiovascular disease, particularly of stroke, especially among African-Americans in the US Stroke Belt, and perhaps among Africans. It is long past time that clinical trials of this strategy be carried out. A straightforward approach would be to randomize hypertension clinics to usual care versus individualized therapy for hypertension based on aldosterone:renin ratios, using a cluster randomization design. Data needed to calculate cost-utility should be collected.

J. David Spence
Stroke Prevention & Atherosclerosis Research Centre
London, Ontario, Canada

1. Frazier L, Turner ST, Schwartz GL, Chapman AB, Boerwinkle E. Multilocus effects of the renin-angiotensin-aldosterone system genes on blood pressure response to a thiazide diuretic. *Pharmacogenomics J.* 2004;4:17–23.
2. Spence JD. Physiologic tailoring of therapy for resistant hypertension: 20 years' experience with stimulated renin profiling. *Am J Hypertens.* 1999; 12:1077–1083.
3. Eide IK, Torjesen PA, Drolsum A, Bobovic A, Lilledahl NP. Low renin status in therapy-resistant hypertension: a clue to efficient treatment. *J Hypertens.* 2004;22:2217–2226.
4. Grim CE, Cowley AW Jr, Hamet P, Gaudet D, Kaldunski ML, Kotchen JM, Krishnaswami S, Pausova Z, Roman R, Tremblay J, Kotchen TA. Hyperaldosteronism and hypertension. ethnic differences. *Hypertension.* 2005;45:766–772.
5. Spence JD. The current epidemic of primary aldosteronism: causes and consequences. *J Hypertens.* 2004;22:2038–2039.
6. Baker EH, Duggal A, Dong Y, Ireson NJ, Wood M, Markandu ND, MacGregor GA. Amiloride, a specific drug for hypertension in black people with T594M variant? *Hypertension.* 2002;40:13–17.