7 December 2004 | Annals of Internal Medicine | Volume 141 Number 11

Annals of Internal Medicine

www.annals.org | Established in 1927 by the American College of Physicians

01175214 0423 ANNALS
KENJI WATANABE, MD FACP
DEPT OF ORIENTAL MED
KEIO UNIV SCH OF MED
35 SHINANOMACHI, SHINJUKU
TOKYO 160-8582
JAPAN

Angiotensin-Converting Enzyme Inhibitors and Diuretics: Optimal Combination Therapy

TO THE EDITOR: Davis and colleagues' insightful review of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (1) concludes by raising 2 important questions: If thiazide diuretics are the first choice for antihypertensive therapy, then what class of drugs should be used next in a stepped-care treatment program? Should treatment begin with 2 drugs? I propose that angiotensin-converting enzyme (ACE) inhibitors should be selected next and initiated simultaneously with diuretics. In support of this strategy, a secondary stroke prevention trial demonstrated no clinical benefits with ACE inhibitor monotherapy but found that ACE inhibitors used in combination with a diuretic dramatically reduced major vascular events (relative risk reduction, 40%; number needed to treat for benefit, 14) while providing synergistic blood pressure reduction (2). The mean systolic blood pressure at baseline among study participants was only 147 mm Hg, suggesting that the recommendation from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure to start 2 agents only when the systolic blood pressure is more than 20 mm Hg above target (2) may be far too stringent in high-risk patients. Moreover, Davis and colleagues argued that diuretic-associated diabetes might be prevented through maintenance of serum potassium concentration. Angiotensin-converting enzyme inhibitors uniformly increase potassium concentration, and multiple trials, including ALLHAT, have demonstrated a reduction in the development of new diabetes with ACE inhibitor therapy (4, 5). This paradigm is now being tested prospectively (6). Thus, in terms of improving clinical outcomes and ameliorating the adverse effects of diuretics (hypokalemia, hyperglycemia), ACE inhibitors are an attractive choice for concurrent therapy with diuretics.

Mori J. Krantz, MD
Philip S. Mehler, MD
Colorado Prevention Center
Denver, CO 80204

References

1. Davis BR, Furberg CD, Wright JT Jr, Cutler JA, Whelton P. ALLHAT: setting the record straight. Ann Intern Med. 2004;141:39-46. [PMID: 15238369]

2. Combined therapy with indapamide and perindopril but not perindopril alone reduced the risk for recurrent stroke [Abstract]. ACP J Club. 2002 Mar-Apr;136:2. Abstract of: PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033-41. [PMID: 11589932]

3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560-72. [PMID: 12748199]

4. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003;290:2805-16. [PMID: 14657064]

5. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000;342:145-53. [PMID: 10639539]

6. Prisant LM. Preventing type II diabetes mellitus. J Clin Pharmacol. 2004;44:406-13. [PMID: 15051749]

IN RESPONSE: We thank Dr. Krantz for his thoughtful letter. The proposed strategy of using a diuretic and an ACE inhibitor simultaneously is supported by the effects of combined treatment in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) (1). However, that study could also be (and was) interpreted as showing that it's the blood pressure that matters, especially for stroke, and blood pressure reduction is much more effective with a diuretic in the regimen. Although the use of ACE inhibitors could in theory offset the metabolic effects (higher glucose and lower potassium levels) of thiazides, other potassium-sparing regimens may be just as or more effective, and a randomized trial to compare such regimens would be valuable. In addition, minimizing the metabolic effects would not necessarily translate into lower rates of important clinical outcomes, including coronary heart disease, stroke, and heart failure. Therefore, an events trial is also needed to test initiating treatment with different 2-drug combinations where 1 of the drugs is a thiazide diuretic.

Barry R. Davis, MD, PhD
The University of Texas School of Public Health at Houston
Houston, TX 77030

Curt D. Furberg, MD, PhD
Wake Forest University School of Medicine
Winston-Salem, NC 27157

Jackson T. Wright Jr., MD, PhD
Case Western Reserve University
Cleveland, OH 44106

Jeffrey A. Cutler, MD, MPH
National Heart, Lung, and Blood Institute
Bethesda, MD 20892

Paul Whelton, MD, MSc
Tulane University Health Sciences Center
New Orleans, LA 70112

Reference

1. Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. Stroke. 2004;35:116-21. [PMID: 14671247]

Ginseng and Warfarin Interactions

TO THE EDITOR: Yuan and colleagues' Brief Communication (1) provides an important opportunity to recognize 2 caveats when interpreting the significance of botanical medicine research.

First, terms such as *ginseng* may actually represent many species. For example, North American ginseng (*Panax quinquefolius* L.) is just one type of commercially available ginseng. From a scientific point of view, data from a study of *P. quinquefolius* are not applicable to other commercially available *Panax* species that may also go by the general name *ginseng*. These include *P. ginseng* CA Meyer (Asian

ginseng,) *P. japonicus* CA Meyer (Japanese ginseng), *P. pseudoginseng* Wallich (Himalayan ginseng), and *P. notoginseng* (Burk) FH Chen (Sanqui ginseng, China). In addition, data from a study of any *Panax* species cannot be applied to Siberian ginseng, or *Eleutherococcus senticosus* (Rupr. & Maxim.) Maximowicz, which is a different genus in the same family as ginseng (Araliaceae) but does not share any marker compounds with plants in the *Panax* genus.

Second, high-performance liquid chromatography identification, quantification, and comparison of marker compounds by validated methods are essential to understanding the significance of the results. Marker compounds vary substantially on the basis of plant age, part, source, and processing (2, 3). For the genus *Panax*, the pharmacologically active marker compounds are saponic triterpene glycosides termed *ginsenosides*. Among the *Panax* species, significant variation exists in both the type and ratio of ginsenosides. For example, *P. quinquefolius* does not contain the ginsenoside Rf, which is found in the more commercially popular *P. ginseng*. Likewise, 24(R)-pseudoginsenoside F11 is specific to American ginseng (4). The most abundant ginsenosides in *P. ginseng* are Rb_1 and Rg_1, which generally occur in a ratio from 1 to 3 (4). For the *P. quinqefolius* used in this study, the Rb_1/Rg_1 ratio was approximately 6 to 1. For *P. quinquefolius*, Rb_1 and Rb_2 ginsenosides have been well documented to be higher and lower in concentration than those in *P. ginseng* (5). Such variations in constituents may explain why physicians who routinely prescribe *Panax ginseng* in Japan have not reported warfarin interference.

Unfortunately, in the absence of comparative data from other *P. quinquefolius* species and other species in the genus *Panax*, the clinical implications of this pioneering study cannot be generalized.

Gregory A. Plotnikoff, MD, MTS
Dennis McKenna, PhD
University of Minnesota Medical School
Minneapolis, MN 55455

Kenji Watanabe, MD, PhD
Keio University Medical School
Tokyo 160-8582, Japan

Mark Blumenthal, BA
American Botanical Council
Austin, TX 78723

References

1. Yuan CS, Wei G, Dey L, Karrison T, Nahlik L, Maleckar S, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. Ann Intern Med. 2004;141:23-7. [PMID: 15238367]

2. Assinewe VA, Baum BR, Gagnon D, Arnason JT. Phytochemistry of Wild Populations of *Panax quinquefolius* L. (North American Ginseng). J Agric Food Chem. 2003;51:4549-53. [PMID: 14705875]

3. Shibata S, Tanaka O, Shoji I, Saito H. Chemistry and Pharmacology of Panax. In: Wagner H, Hikino H, Farnsworth NR, eds. Economic and Medicinal Plant Research. vol 1. New York: Academic Pr; 1985:217-84.

4. Awang DVC. The neglected ginsenosides of North American Ginseng. Journal of Herbs, Spices, and Medicinal Plants. 2000;7:103-9.

5. Asafu-Adjaye EB, Wong SK. Determination of ginsenosides (ginseng saponins) in dry root powder from *Panax ginseng, Panax quinquefolius*, and selected commercial products by liquid chromatography: interlaboratory study. J AOAC Int. 2003;86: 1112-23. [PMID: 14979691]

IN RESPONSE: We appreciate the comments of Dr. Plotnikoff and his colleagues. Their letter addresses important issues that warrant clarification and further discussion.

Our data showed that American ginseng (*Panax quinquefolius* L.), a commonly used herb in the United States, reduces the anticoagulant effect of warfarin. Limitations on the length of our article prevented us from providing information about other types of ginseng, which were discussed in our previous publications (1, 2). We did not extrapolate our data on American ginseng to other species of ginseng. Our study, however, provides an example of drug–herbal interaction. Herbal medicines, such as American ginseng, have beneficial effects (1). But herbs contain pharmacologically active constituents that may also interact with drugs. This interaction is particularly important if the drug has a narrow therapeutic index, such as warfarin. A slight alteration to warfarin's effect may have clinical consequences. To prevent the possible clinical consequences of herbal therapies, more controlled trials of drug–herbal interaction are needed.

The major active constituents of ginseng are ginsenosides. Dr. Plotnikoff and his colleagues point out that the American ginseng in our study has an Rb_1/Rg_1 ratio of approximately 6 to 1, a ratio higher than usual. We believe, however, that this ratio falls within the range of 5.5 to 9.6, a range found in previous reports (3, 4). Nonetheless, we acknowledge the variability of the chemical composition of botanicals. The composition of herbal products can vary from manufacturer to manufacturer and from lot to lot from the same manufacturer (4). Data from our laboratory found significant variation in ginsenoside content between measured samples (5). Cultivation conditions such as soil, temperature, moisture, period of cultivation, and harvest season can change total ginsenoside concentration, as well as the percentage of individual ginsenosides. Asian ginseng (*Panax ginseng*) has a different ginsenoside profile than American ginseng. Whether Asian ginseng interacts with warfarin remains to be tested.

Since animal studies and clinical trials performed in the past to test the effects of ginseng often used preparations with variable phytochemical content, results of these studies are difficult to compare. Lack of standardized processing methods contributes to the variations in a ginseng product. Some herbal manufacturers have tried to standardize products to fixed concentrations of selected chemical constituents. The benefit of this effort is uncertain, however, because herbs may achieve their effects through the combined or synergistic actions of different constituents. Thus, future investigation toward standardization of preparations is clearly needed.

Chun-Su Yuan, MD, PhD
Tang Center for Herbal Medicine Research, University of Chicago
Chicago, IL 60635

References

1. Attele AS, Wu JA, Yuan CS. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol. 1999;58:1685-93. [PMID: 10571242]

2. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. JAMA. 2001;286:208-16. [PMID: 11448284]

3. Assinewe VA, Baum BR, Gagnon D, Arnason JT. Phytochemistry of wild populations of *Panax quinquefolius* L. (North American Ginseng). J Agric Food Chem. 2003; 51:4549-53. [PMID: 14705875]

4. Harkey MR, Henderson GL, Gershwin ME, Stern JS, Hackman RM. Variability in

commercial ginseng products: an analysis of 25 preparations. Am J Clin Nutr. 2001; 73:1101-6. [PMID: 11382666]

5. Yuan CS, Wu JA, Osinski J. Ginsenoside variability in American ginseng samples [Letter]. Am J Clin Nutr. 2002;75:600-1. [PMID: 11864869]

CLINICAL OBSERVATIONS

Editor's Note: The lead author of the following Clinical Observation was one of a dozen Associates of the American College of Physicians selected to present a clinical vignette at the 2004 Annual Session in Philadelphia. We are proud to present this case report through a special arrangement with the Council of Associates of the College.

B-Type Natriuretic Peptide Is Effective Therapy before Care

TO THE EDITOR: *Background:* B-type natriuretic peptide (BNP) is an endogenous hormone secreted by the ventricular myocardium in response to increased wall stretch. Actions of BNP include diuresis, natriuresis, and vasodilatation of both the systemic and pulmonary vascular systems. Recombinant BNP (nesiritide) is given as a continuous intravenous infusion and is approved for treating heart failure exacerbations. Studies have shown the efficacy of short-term BNP infusions for acutely decompensated heart failure (1–3). Data on prolonged BNP infusions before cardiac transplantation are limited.

Objective: To evaluate the clinical outcomes and hemodynamic effects of BNP infusions before cardiac transplantation.

Methods: Clinical outcomes, duration of infusions, and hemodynamic measures were reviewed for all patients who had received BNP as cardiac transplantation candidates at our institution through December 2002.

Findings: Twelve patients received BNP infusions (0.01 to 0.03 μg/kg of body weight per minute) while on the active cardiac transplantation list or during transplantation evaluation. Mean duration of BNP infusion was 12.3 days. Six patients (50%) continued to receive prolonged BNP infusions until their transplantation, 2 patients (17%) continued to receive BNP until the placement of left ventricular assist devices, and 2 patients (17%) were discharged on the active transplantation list after stabilization of their heart failure. Two patients (17%) died before transplantation. Mean pulmonary artery pressures decreased from 50.4 to 35.8 mm Hg, and mean cardiac index increased from 1.88 to 2.54 L/min per m^2 within 72 hours of initiation of BNP infusions. Four patients (33%) became transplantation candidates only after pulmonary vascular resistance (PVR) reversibility was demonstrated with BNP infusions; mean PVR decreased from 486 to 236 dynes/sec per cm^5 in this population. None of these patients had previously shown PVR reversibility with sodium nitroprusside, dobutamine, nitroglycerin, or milrinone infusions.

Discussion: More than 2000 cardiac transplantations are done each year in the United States, most often for end-stage heart failure. A major challenge in the pretransplant patient is maintaining a viable cardiac output while minimizing tissue edema. This goal often requires prolonged infusions of inotropes (for example, dobutamine and milrinone), which have side effects that result in substantial morbidity and mortality (4–6). In our review, 10 of 12 patients who received prolonged BNP infusions had favorable outcomes, and hemodynamic measures improved in all patients who had invasive monitoring.

Another major challenge in the pretransplant population is elevated PVR. Irreversibly elevated PVR (from intimal or medial hyperplasia of the pulmonary vasculature) is considered an absolute contraindication to cardiac transplantation because of the risk for post-transplant right ventricular failure. Reversibility of PVR is often shown with infusion of intravenous vasodilators (such as nitroprusside). Although preliminary investigators showed that natriuretic peptides lower pulmonary artery pressures and PVR, routine use for this purpose has not been validated (7–9). In our study, 4 patients had PVR reversibility demonstrated with BNP infusions only.

Conclusion: B-type natriuretic peptide is a promising therapeutic option for in-hospital maintenance therapy for severe heart failure in the pre–cardiac transplant population. In addition, BNP infusions can be used to demonstrate reversibility of elevated PVR.

Ronald Witteles, MD
Kelly Matsuda, PharmD
Michael B. Fowler, MB, FRCP
Stanford University School of Medicine
Stanford, CA 94305-5406

References

1. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized, controlled trial. JAMA. 2002;287:1531-40. [PMID: 11911755]

2. Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. J Am Coll Cardiol. 1999;34:155-62. [PMID: 10400005]

3. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med. 2000;343:246-53. [PMID: 10911006]

4. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med. 1991;325:1468-75. [PMID: 1944425]

5. Burger AJ, Horton DP, LeJemtel T, Ghali JK, Torre G, Dennish G, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. Am Heart J. 2002;144:1102-8. [PMID: 12486437]

6. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol. 2002;39:798-803. [PMID: 11869844]

7. Hill JA, Hsu K, Pauly DF, Schofield R, Aranda JM Jr. Sustained use of nesiritide to aid in bridging to heart transplant. Clin Cardiol. 2003;26:211-4. [PMID: 12769247]

8. Cargill RI, Lipworth BJ. Atrial natriuretic peptide and brain natriuretic peptide in cor pulmonale. Hemodynamic and endocrine effects. Chest. 1996;110:1220-5. [PMID: 8915224]

9. Bhat G, Costea A. Reversibility of medically unresponsive pulmonary hypertension with nesiritide in a cardiac transplant recipient. ASAIO J. 2003;49:608-10. [PMID: 14524574]