Journal of the American Society of Hypertension 9(8) (2015) 610–619

Research Article

The effect of the addition of allopurinol on blood pressure control in African Americans treated with a thiazide-like diuretic

Mark S. Segal, MD, PhD[a,b,*,1], Titte R. Srinivas, MD[c,1], Rajesh Mohandas, MD[a,b], Jonathan J. Shuster, PhD[d], Xuerong Wen, PhD[b], Elaine Whidden, ARNP[b], JogiRaju Tantravahi, MD, PhD[a,b], and Richard J. Johnson, MD[e]

[a]*Nephrology and Hypertension Section, Medical Service, North Florida/South Georgia Veterans Health System, Gainesville, FL, USA;*
[b]*Division of Nephrology, University of Florida, Gainesville, FL, USA;*
[c]*Division of Nephrology, Medical University of South Carolina Charleston, SC, USA;*
[d]*Department of Health Outcomes and Policy, University of Florida, Gainesville, FL, USA; and*
[e]*Division of Nephrology, University of Colorado, Denver, CO, USA*

Manuscript received January 16, 2015 and accepted May 9, 2015

Abstract

We tested the hypothesis that xanthine oxidase inhibition among African Americans receiving the thiazide-type diuretic chlorthalidone may improve blood pressure control with fewer hyperuricemia-related side effects. We performed a randomized, double-blind, placebo-controlled study of African Americans with Stage 1 hypertension without clinically significant renal disease. One hundred fifty African American men or women between the ages of 18 and 65 years who met the exclusion/inclusion criteria with untreated or treated hypertension were started on chlorthalidone (25 mg/d) and potassium chloride. After a 5-week run-in on chlorthalidone, baseline testing was performed and they were randomized to allopurinol (300 mg/dL) or placebo with doses adjusted based on uric acid levels and followed for 8 weeks. One hundred ten subjects completed the study. Baseline systolic blood pressures after the 5-week chlorthalidone run-in were 119.9 ± 13.6 in the allopurinol group and 117 ± 11.2 in the placebo group indicating excellent blood pressure control with the single agent. After at least 4 week postrandomization, the difference in mean change in systolic blood pressure in allopurinol less placebo from visits 5 to 3 was 4.3 mm Hg (95% confidence interval, −0.2 to 8.7; $P = .059$). The difference in mean change in uric acid levels over the same period was 2.1 mg/dL (95% confidence interval, 1.7–2.6; $P < .001$). The use of chlorthalidone with or without allopurinol resulted in excellent blood pressure control. The addition of allopurinol tended to improve clinic blood pressure, but the difference from the group receiving chlorthalidone alone was not statistically significant. J Am Soc Hypertens 2015;9(8):610–619. Published by Elsevier Inc. on behalf of American Society of Hypertension.

Keywords: Chlorthalidone; hypertension; uric acid.

Funding: This study was funded by NHLBI grant R01HL079352 to MS, TS, and RJ. This work was supported in part by the NIH/NCATS Clinical and Translational Science Award to the University of Florida UL1 TR000064 and Division of Nephrology Gatorade Research Funds.

Conflict of interest: Dr Johnson has patent applications related to the lowering of uric acid and/or blocking fructose metabolism as a means for slowing diabetic nephropathy or improving insulin resistance and has shares with XORT Therapeutics related to these patents. No other authors report any other disclosures.

*Corresponding author: Mark S. Segal, MD, PhD, CG-98, 1600 Archer Road, Gainesville, FL 32608. Tel: 352-273-8820; Fax: 352-392-5465.

E-mail: segalms@medicine.ufl.edu

[1] These authors contributed equally.

Introduction

During the course of hominoid evolution 24–13 million years ago, a series of mutations occurred in the gene for uricase[1] causing man and other higher primates to have higher uric acid levels of 3 to 6.0 mg/dL as compared with most of mammals who have uric acid levels of <1 to 2 mg/dL. Although higher levels of uric acid have been proposed to provide an advantage due to its antioxidant properties and to its potential ability to support blood pressure especially under low-salt dietary conditions, the downside of hyperuricemia is an increased incidence of gout.[2] Uric acid has also been identified as a marker for a number of metabolic abnormalities and may be a unique

1933-1711/$ - see front matter Published by Elsevier Inc. on behalf of American Society of Hypertension.
http://dx.doi.org/10.1016/j.jash.2015.05.009

cardiovascular risk factor.[3] Evidence for this association includes inhibition of uricase in rat models resulting in a rise in serum uric acid and development of systemic hypertension, which is prevented by lowering uric acid with either xanthine oxidase inhibitors or uricosuric agents.[4–6] More recently in a randomized, placebo-controlled trial, allopurinol was shown to lower blood pressure in hyperuricemic pediatric patients with newly diagnosed hypertension.[7]

Among those in whom serum uric acid may be more strongly associated with an increased frequency of hypertension and cardiovascular disease are African Americans. Several studies suggest a relationship between hyperuricemia and hypertension in African Americans. First, both uric acid levels[8] and the frequency of gout[9] are increased in African Americans. Second, as in Caucasians, uric acid levels correlate stepwise with both the frequency of hypertension[10] and with the risk for cardiovascular events[8]; similar observations have been reported in blacks from Africa.[11] Uric acid is an independent predictor of cardiovascular disease for African Americans both in the general population[8] and in subjects with established, treated hypertension.[12] Interestingly, the onset of hypertension has been found to correlate with the initial gout attack in African Americans.[9]

The need to study the effect of hyperuricemia on blood pressure has become even greater with the knowledge that thiazide-type diuretics such as chlorthalidone lower blood pressure effectively but are associated with significant degrees of hyperuricemia.[13] In the Hypertension Detection and Follow-up Program, in which chlorthalidone (50 mg/d) was used as step 1 therapy for hypertension, both the baseline uric acid level and increase in uric acid level during therapy independently predicted renal progression in men and women (including a subanalysis in African Americans) and baseline uric acid was also an independent risk factor for mortality in women.[14] Similarly, in the Systolic Hypertension in the Elderly Program, the use of chlorthalidone was associated with significant reduction in stroke, heart failure, and cardiovascular events as compared with placebo. However, approximately half of the subjects receiving chlorthalidone had a rise of uric acid of 1 mg/dL or more, and in this subset, the benefit of chlorthalidone on cardiovascular events was not observed.[13] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, chlorthalidone was more effective than lisinopril in lowering blood pressure in African Americans and resulted in a 4-mm Hg lower systolic blood pressure.[14] The finding that thiazide-type diuretics are effective in this population has led to the recommendation by the International Society on Hypertension in Blacks[15] and the JNC 7[16] to use low-dose thiazide monotherapy for African Americans with uncomplicated (urine protein <1.0 g/d) Stage 1 hypertension.

Given that in African Americans, there may be a strong association between uric acid and hypertension and that current guidelines suggest treating hypertensive African Americans with a thiazide diuretic (which would worsen uric acid levels), we decided to test the hypothesis that xanthine oxidase inhibition in African Americans receiving diuretics can result in improved blood pressure control with fewer side effects. This hypothesis was tested in a randomized, double-blind, placebo-controlled study of African Americans with Stage I hypertension in the absence of clinically significant renal or other end-organ damage. All participants were treated with chlorthalidone with the addition of either placebo or allopurinol to determine effects on blood pressure control.

Methods

Study Design

The initial protocol consisted of a randomized 2×2 factorial double-blind, controlled trial in which participants were randomized to chlorthalidone or placebo and allopurinol or placebo. Recruitment initially focused on individuals with Stage 1 hypertension who were drug naïve. This protocol was met with a significant recruitment challenge in that drug-naïve Stage 1 hypertensive African Americans had limited prevalence in our catchment area. We then decided to enroll hypertensive subjects on treatment who would be subjected to washout before enrollment. However, this modification was met with concerns about: (1) safety of washouts and the risk of adverse events with uncontrolled hypertension, (2) ethical concerns about using placebo to treat hypertension, and (3) medico-legal concerns regarding the consequences related to items 1 and 2. In November 2006, after consultation with the DSMB and the NIH project office, the protocol was modified to a two-arm study wherein subjects with Stage 1 hypertension were placed initially on chlorthalidone and potassium chloride for a minimum of 4 weeks and then randomized to the addition of either allopurinol or placebo. The protocol modification also allowed for the inclusion of subjects with hypertension controlled on a single agent or a single fixed–dose combination antihypertensive formulation. All subjects also received the National Heart, Lung, and Blood Institute guide on a low sodium diet.

After obtaining IRB approval and registering the trial at clinicaltrials.gov (identifier: NCT00241839), 150 African American (including black individuals born in the Caribbean, Africa, Canada, and so forth) men or women between the ages of 18 and 65 years gave informed consent to be screened for the trial. Screening evaluation occurred in the morning at the Clinical Research Center (CRC) at UF Health Shands at Gainesville and consisted of a complete history, physical, initial laboratory testing