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THE EFFECT OF THE ADDITION OF ALLOPURINOL ON BLOOD PRESSURE CONTROL IN AFRICAN AMERICANS TREATED WITH A THIAZIDE-LIKE DIURETIC

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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 I hypertension without clinically significant renal disease. 150 African-Americans men or women between the ages of 18 and 65 years of age who met the exclusion/inclusion criteria with untreated or treated hypertension were started on chlorthalidone (25 mg/day) and potassium chloride. After a 5 week run-in on chlorthalidone baseline testing was performed and they were randomized to allopurinol (300mg/dl) or placebo with doses adjusted based on uric acid levels and followed for 4 weeks. 110 subjects completed the study. Baseline systolic blood pressures after the 5 week chlorthalidone run-in was 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 weeks post-randomization, the difference in mean change in systolic blood pressure in allopurinol less placebo from visit 5 to 3 was 4.3 mm Hg (95% CI -0.2 to 8.7, $p=0.059$). The difference in mean change in uric acid levels over the same period was 2.1 mg/dl (95% CI 1.7 to 2.6 $p<0.001$). The use of chlorthalidone with or without allopurinol resulted in excellent blood pressure control. The addition of allopurinol tended to improve clinic blood

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Conflict of Interest/Disclosure Statement

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.

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pressure, but the difference from the group receiving chlorthalidone alone was not statistically significant.

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 to the majority of mammals who have uric acid levels of <1 to 2 mg/dL. While 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 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 as well as 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 sub analysis 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 (SHEP), the use of chlorthalidone was associated with significant reduction in stroke, heart failure and cardiovascular events as compared to 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 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 Blacks¹⁵ and the JNC 7¹⁶ to use low dose thiazide monotherapy for African-Americans with uncomplicated (Urine protein < 1.0 g/day) stage I 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 prior to 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 four 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 NHLBI 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, etc.) men or women between the ages of 18 and 65 years of age gave informed consent to be screened for the trial. Screening evaluation occurred in the morning at the Clinical Research Center at UF Health Shands at Gainesville and consisted of a complete history, physical, initial laboratory testing (CBC, basic metabolic panel, a random spot urine protein and urine creatinine, along with a urine pregnancy test in women capable of childbearing), and an electrocardiogram. We excluded any patient with: 1) A history of malignant or accelerated hypertension; 2) A confirmed total white cell count of less than 2,500/mm³, anemia or thrombocytopenia; 3) A known history of liver disease; 4) A known secondary cause of hypertension; known presence of diabetes or fasting blood glucose 126

mg/dL. In the event that a fasting blood sugar exceeded 126 mg/dL, it was reconfirmed on a blood glucose measurement obtained on a subsequent day per American Diabetes Association criteria¹⁷. If a subject had not fasted, we excluded those subjects with casual blood glucose levels of ≥ 200 mg/dL; 5) A history of heart failure, myocardial infarction, cardiovascular disease, or stroke or on a β -blocker or calcium channel blocker for cardiovascular indications, by history, other than for lowering blood pressure; 6) Abnormal EKG requiring acute medical intervention; 7) History of clinical or renal biopsy evidence of renal parenchymal disease; 8) Acute gout attack within two weeks prior to enrollment in study; 9) History of drug abuse in the last 2 years, including narcotics, cocaine, or alcohol (>21 drinks/week); 10) An arm circumference > 52 cm, which precludes measurement with a 'thigh' blood pressure cuff; 11) History of a reaction to allopurinol or chlorthalidone; 12) Pregnancy, lactation, or subjects who are planning to become pregnant during the study period; and 13) History of noncompliance, or unable to comply with the study requirements, or who were participating in another study. All study procedures followed the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects.

Initially, subjects with untreated stage I hypertension were started on chlorthalidone (25 mg/day) and potassium chloride (20–40 mEq/day). After four weeks on chlorthalidone, the subjects were brought back to the CRC to determine serum potassium levels. If the serum potassium level was below 3.5 mEq/L, an oral bolus of 40 mEq potassium was given 2 to 3 times daily for 2 to 3 days, as clinically indicated, and a maintenance dose of 40–50 mEq per day was initiated. After at least 7 days of increased potassium and continued chlorthalidone, the participants were admitted overnight to the CRC for their baseline study visit prior to randomization to allopurinol versus placebo. On admission to the CRC, an initial blood draw was performed along with a history and physical examination, during the overnight stay the patient was placed on a nitrate/nitrite free diet. The patient completed a questionnaire related to baseline prevalence of conditions that would be considered side-effects of the study medications and underwent comprehensive testing including clinic blood pressure (Primary endpoint). At the completion of this visit the subject was randomized to add-on allopurinol (300 mg/day) or an identical, looking placebo. Two weeks after initiation of allopurinol/placebo the subject was brought in to the CRC for a clinic blood pressure reading and drawing of a uric acid level. If the subject had a uric acid above 5.5 mg/dl, the dose of allopurinol or placebo was increased to two pills a day, 600 mg of allopurinol or two placebo pills. Of those that completed the study and were assigned to allopurinol, 6 had their dosage increased to 600 mg a day and of those assigned to placebo, 38 were increased to two placebo pills a day. After a total of at least 8 weeks on allopurinol/placebo we repeated the baseline testing (Figure 1). At each study visit, a pill count was performed to monitor adherence.

Randomization

Due to the expected higher recruitment of women and since males have higher uric acid levels, randomization was stratified by the subject's gender.

Measurements

Blood pressure Measurements and Quality Control: Seated blood pressure was taken with a Tycos aneroid sphygmomanometer with a two-piece cuff and bladder utilizing specific manufacturer-provided cuffs after 15 minutes of rest and after measurement for proper cuff size; 3 such measurements were recorded, and the last two values averaged. Blood pressure was performed on two separate days at recruitment and at all clinic visits. All personnel involved in blood pressure measurements were trained by a nurse specialist (Blood Pressure trainer in the CRC). The average of the last two of three consecutive readings on a sphygmomanometer at each visit was the blood pressure used for adjudication of the primary endpoint

Study End Points

The *primary end-point* was change in *clinic systolic blood pressure* at 4 weeks after start of allopurinol or placebo. The question tested was whether the addition of allopurinol to chlorthalidone would improve blood pressure control.

Statistical Analysis

Sample Size and Power Analysis—The study was powered for the primary end point, clinic systolic blood pressure. Given a conservative presumed entry range of 20 mm Hg in systolic blood pressure, the standard deviation in adults for systolic blood pressure would be of the order of at most 5 mm Hg (Range/4) for single readings¹⁸. As a conservative estimate, we assumed that the standard deviation of the 4 week changes in systolic blood pressure is governed by the correlation coefficient of the order $\rho=0.75$ (or higher: early blood pressure explains about half the variation in follow-up blood pressure in the same person), leading to a paired standard deviation of at most 0.566 standard deviations. Based on this correlation, with a sample size of 100 patients, the study would have 80% power to detect a difference of 0.4 standard deviations (2.0 mm hg if the true correlation between baseline and eight weeks is 0.75, and even better if this correlation is higher), in the dependent variable systolic blood pressure just before randomized treatment start less systolic blood pressure at six weeks later.

Continuous variables, changes from visit 5 to visit 3, were compared using the two-sided student t test, corrected by the Satterthwaite method to account for unequal variance. All of the statistical analyses were conducted using SAS 9.3 (Cary, NC). P value <0.05 was considered significant level for all tests.

Results

Study Subjects

Utilizing a screening protocol that was a companion to the study protocol, study staff performed blood pressure screening in the community at 114 sites and assessed blood pressures for 4,503 individuals, including 2,538 African Americans. From these screenings, 127 individuals were referred to their primary care providers for evaluation of hypertension, including several who were referred for same-day appointments or to the emergency room for those without health providers. Of these 2,538 patients, 500 had a community blood

pressure in the Stage 1 hypertension range and whose answers to a screening questionnaire (Supplemental Figure 1) suggested that they would be appropriate candidates for participation in the study. These candidates were referred for a baseline visit at the CRC to be formally consented for the study. Of these 500, 150 subjects met full inclusion/exclusion criteria, agreed to be in the study, and signed the consent. The first subject was consented for this study on January 25, 2006. The last subject completed the study on February 22, 2011.

One hundred and fifty participants enrolled in the study, 11 subjects withdrew from the study after signing the informed consent, but prior to being randomized to allopurinol or placebo. Twenty-nine subjects withdrew after randomization to allopurinol or placebo and 110 subjects completed the entire study.

At screening, the mean systolic blood pressure was 123.6 ± 17.5 mm Hg with the mean diastolic blood pressure of 78.9 ± 10.5 . The baseline characteristics of the subjects, at the time they received allopurinol or placebo, were similar in the two groups (Table 1). The mean age of both groups was 51 and there was a preponderance of women with nearly 70% women in both groups. The baseline blood pressures after run-in were 119.9 ± 13.6 over 75.9 ± 7.9 and 117 ± 11.2 over 73.7 ± 8.1 in the allopurinol and placebo groups, respectively. The baseline uric acid was 6.6 ± 1.4 and 6.8 ± 1.7 in the allopurinol and placebo groups, respectively.

Adverse Events

After treatment with chlorthalidone, but prior to randomization to allopurinol or placebo, there were 5 serious adverse events, 3 not study related (1 participant had nausea, vomiting and stomach cramps, 1 participant had a panic attack, 1 participant was a passenger in a motor vehicle accident) and 2 possibly study related (1 participant had chest pain, 1 participant had syncope after exercising). After randomization to allopurinol or placebo there were 3 serious adverse events, 2 in the allopurinol group and 1 in the placebo group. Of these, only 1 was considered study related; a study participant in the allopurinol arm developed a rash, which was thought secondary to chlorthalidone or allopurinol, and both medications were discontinued and the patient was withdrawn from the study. The other 2 non-study related serious adverse events were 1 participant had fibroid induced abdominal pain, and another was admitted with fatigue and shortness of breath and was diagnosed with recurrence of breast cancer.

With regard to adverse events, while on chlorthalidone, before randomization to allopurinol or placebo, we had a total of 107 adverse events with the most frequent categories being headache/dizziness, musculoskeletal and pulmonary/upper respiratory tract symptoms (Table 2). After randomization to allopurinol or placebo there were 32 and 52 reported adverse events, respectively (Table 2). There was no statistical difference in the number of reported events in each group. With regard to erectile dysfunction there were 2 complaints on chlorthalidone alone and 1 complaint each in those subjects randomized to allopurinol and placebo. Erectile dysfunction was not a cause for early withdrawal from the study.

Blood Pressure Control on Chlorthalidone

Of the 150 subjects who enrolled in the study, 109 were on blood pressure medications at time of study entry. Of these 109 subjects, 67 were on a single agent, 38 were on two medications, and 4 were on 3 blood pressure medications. Sixty-four subjects were on a thiazide, 35 were on an ACEI, and 24 were on a calcium channel blocker (Table 3). Considering only those individuals on a single agent, 39% were on a thiazide, 34% were on an ACEI or ARB, 16% on a calcium channel blocker, 9% were on a beta-blocker, and 1.5% were on minoxidil. Those patients who were on a single agent when they were switched to chlorthalidone saw a significant reduction in their systolic blood pressure from 121.0 ± 14.6 to 113.8 ± 10.8 mm Hg ($p=0.001$; Figure 2A). Even those patients who were on a two antihypertensive agents prior to being switched to chlorthalidone saw a significant reduction in their systolic blood pressure from 122.8 ± 16.4 to 115.4 ± 11.8 ($p=0.0043$; Figure 2B). The degree of change in mean systolic blood pressure was not different between those who were on 1 or two antihypertensive medications ($p=0.9547$). Although there were only 4 subjects on three blood pressure medications, even in these subjects, single agent chlorthalidone still controlled their blood pressure with a mean systolic blood pressure at visit 3 of 115.0 ± 9.3 mm Hg.

Effects on Blood Pressure of Addition Of Allopurinol Versus Placebo

Allopurinol treatment resulted in a drop in the uric acid of 2.3 ± 1.3 mg/dl at visit 5 compared to visit 3 ($P<0.0001$). In the group who received placebo there was an increase of uric acid of 0.14 mg/dl at visit 5 compared to visit 3 ($p=.27$; Table 4). Since studies in humans suggest that low dietary intake of potassium contributes to poor blood pressure control¹⁹, we looked at potassium levels. Importantly the difference in serum potassium concentrations between visit 3 and 5 was not statistically different in either group (Table 4).

The baseline blood pressure was performed after 5 weeks of being on chlorthalidone and was 119.9 ± 13.6 in the allopurinol group and 117 ± 11.2 in the placebo group. Thus we achieved excellent control with a single agent. Four weeks after being randomized to placebo versus allopurinol, there was no significant change in the clinic blood pressure between the placebo and allopurinol group ($p=0.059$; Table 4). However, those randomized to allopurinol tended to show a greater fall in blood pressure, with a 3.4 mm Hg decrease in systolic blood pressure at visit 5 compared to visit 3 whereas the group randomized to placebo saw a 0.8 mm Hg increase in systolic blood pressure at visit 5 compared to visit 3 (Table 4). The same trend was seen in the clinic diastolic blood pressure. When we consider baseline blood pressure, blood pressure at visit 3, only for those that completed visit 5, systolic blood pressure in those subjects randomized to receive allopurinol was 120.9 ± 13.7 and in those that were randomized to receive placebo was 117.9 ± 11.3 . An ANCOVA adjusting for the blood pressure at baseline demonstrated an average difference between the two groups for systolic blood pressure of 2.4 ± 4.0 ($P=0.23$), and for diastolic blood pressure of 0.0 ± 2.7 ($P=0.99$).

Discussion

Our study was designed to test the hypothesis that the addition of allopurinol would result in a greater decrease in blood pressure compared to placebo in subjects receiving chlorthalidone. However, the striking finding was that in this study chlorthalidone alone was extremely effective in controlling the hypertension, resulting in optimal blood pressure control regardless of whether subjects received allopurinol or placebo. As such, no statistically significant difference in blood pressure could be shown in the allopurinol versus placebo groups, although there was a tendency for a greater fall in blood pressure in the allopurinol group. While our findings did not reach statistical significance, they are nevertheless important because: 1) the effect size was substantial given the subjects low blood pressure at the time of administration of placebo versus allopurinol; and 2) the treatment was well tolerated.

Whether our subjects were on 1, 2, or 3 agents prior to substitution for chlorthalidone, excellent blood pressure control was achieved. One explanation for the excellent blood pressure control on the study drug chlorthalidone, could be secondary to enhanced compliance with blood pressure medications by being part of a study. However the finding of excellent blood pressure control with chlorthalidone is consistent with the prespecified subgroup analysis from ALLHAT, that demonstrated that a thiazide-type diuretic was more effective in improving cerebrovascular, heart failure, and combined cardiovascular outcomes compared to an ACEI in the African American patient subgroup¹⁴. While sixty-four of the subjects were on a thiazide diuretic at the time of enrollment, given that our population was not diabetic and had no cardiovascular history, it was surprising to find fully 34% were on an ACEI or ARB and 9% were on a beta-blocker as a single agent prior to study entry. Of course, we do not know whether the ACEI/ARB or beta-blocker was initiated after intolerance of the more appropriate, for this population, calcium channel blocker or thiazide-type diuretic. However we do know that all of the subjects in the study tolerated chlorthalidone except for one that had an allergic reaction to either chlorthalidone or allopurinol.

The mechanism by which allopurinol may result in a decrease in blood pressure is not clear, since allopurinol has two measurable effects, lowering uric acid and lowering oxidative stress by blocking oxidants generated during the reaction of hypoxanthine and xanthine with xanthine oxidase. The relationship between uric acid and oxidant stress is complex as uric acid can function as a reducing agent but can generate urate-based radicals in the process.²⁰ In addition, uric acid can generate oxidative stress in both endothelial and vascular smooth muscle cells, likely by stimulating NADPH oxidase^{21,22}. In the absence of an intervention that lowers uric acid independent of xanthine oxidase inhibition, such as with a uricosuric agent, we are unable to determine the exact mechanism by which allopurinol tended to lower blood pressure.

A large body of evidence (reviewed in²³) supports that potassium intake is associated with a lower blood pressure and there is an inverse relationship between serum potassium levels and blood pressure²⁴. Importantly the serum levels of potassium was similar between the

two study arms indicating that serum potassium levels alone does not account for the differential blood pressure effects.

We were very concerned about serum potassium levels affecting blood pressure since the AASK study suggests that serum potassium appears to be a significant predictor of time to blood pressure response, independent of drug class.²⁵ In addition, a single center study also suggests that there is an inverse relationship between serum potassium and blood pressure.²⁴ However, in the Framingham Heart Study serum potassium was not associated with current BP, longitudinal BP tracking, or progression to hypertension²⁶ and from this study, little variation in the serum potassium levels is felt to be the result in differences in dietary potassium intake, since dietary intake of potassium varied very little across the population.²⁷ While some subjects were on greater serum potassium supplementation than others, their potassium dose was fixed prior to visit 3. This is critical since some studies suggest that potassium chloride supplementation will decrease blood pressure. In one study subjects on an isocaloric diet were randomized to either potassium chloride (120 mmol/day) or placebo. Systolic blood pressure decreased 8.6 mm Hg (95% confidence interval -14.6, -2.6) and diastolic blood pressure decreased 4.0 mm Hg (-6.9, -1.0) during potassium chloride supplementation²⁸. Potassium supplementation has been shown to decrease systolic blood pressure in other studies as well.^{29,30} While other studies did not find an effect of potassium supplementation on blood pressure.³¹

Some may be concerned about possible imbalances between the treatment groups on the baseline covariates. Covariate imbalance is always true for randomized trials. Such imbalances do not, however, invalidate any inferences, since randomization assures that the underlying target populations (not samples) are identical for the competing treatments. Our study, however, actually adjusts for potential imbalances, since its dependent variables are changes from baseline values, just before randomization is implemented, to their final values, making each person have an internal control.

We believe the study was complicated by the excellent blood pressure control achieved with chlorthalidone. Since the magnitude of decrease seen with the addition of an antihypertensive is dependent on the initial blood pressure, larger differences would be expected with higher initial blood pressures³². Thus, with a baseline blood pressure of between 116–120 mm Hg recorded among our subjects, it is not surprising that we were not able to see a significant effect on blood pressure of allopurinol intervention with our sample size. Given these considerations, a decrease of 3.3 mm Hg, if shown to be reproducible is significant. It should also be acknowledged that our results are prone to type 2 error and may reflect inadequate power. We cautiously submit that a larger study may be justified that could allow recruitment of suitable subjects outside the confines of a single institution.

Perspectives

The addition of allopurinol to chlorthalidone did not lead to improved blood pressure control in comparison to chlorthalidone alone in African Americans with stage 1 hypertension. These findings may reflect excellent and maximal control of blood pressure with

chlorthalidone alone or could reflect an inadequate sample size with consequent lack of power. These findings need to be confirmed and investigated in a larger study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What Is New?

This the first randomized, placebo controlled study investigating the effect of allopurinol on blood pressure when added to chlorthalidone in African Americans.

What Is Relevant?

In these patients with Stage 1 hypertension, no matter what blood pressure regimen they were on, their blood pressure was very well controlled with chlorthalidone. The difference in mean change in systolic blood pressure in allopurinol less placebo from week 5 to 3: 4.3 mm Hg (95% CI -0.2 to 8.7, $p=0.059$).

Summary

These findings may reflect excellent and maximal control of blood pressure with chlorthalidone alone or could reflect an inadequate sample size with consequent lack of power. These findings need to be confirmed and investigated in a larger study.

Highlights

Chlorthalidone, as a single agent, provided excellent blood pressure control in the African Americans with stage 1 hypertension studied.

The addition of allopurinol to chlorthalidone did not lead to improved blood pressure control in comparison to chlorthalidone alone in African Americans with stage 1 hypertension.

Figure 1.
Outline of the timing of the study visits and the major events that occur in each visit.

Figure 2.

Shown are systolic blood pressure (mm Hg) at visit 1 and visit 3 for subjects who at the time of recruitment were on 1 medication prior to being switched to chlorthalidone (A) or who were on 2 medications prior to being switched to chlorthalidone (B). The mean systolic blood pressure at Visit 1 is on their baseline medications and visit 3 indicates the mean systolic blood pressure after being switched to only chlorthalidone.

Table 1

Baseline Demographics of Study Participants.

Characteristic	Allopurinol N=69	Placebo N=70
Age, Mean $\pm$ SD	50.8 $\pm$ 10.1	51.1 $\pm$ 7.7
Number of Women, N (%)	50 (69%)	50 (68%)
Uric Acid, mg/dl, Mean $\pm$ SD	6.6 $\pm$ 1.4	6.8 $\pm$ 1.7
Mean Blood Pressure, Mean $\pm$ SD	92.3 $\pm$ 10.7	90.2 $\pm$ 8.5
BMI, Mean $\pm$ SD	34.5 $\pm$ 7.3	34.5 $\pm$ 6.8
Clinic Systolic Blood Pressure, Mean $\pm$ SD	119.9 $\pm$ 13.6	117 $\pm$ 11.2
Clinic Diastolic Blood Pressure, Mean $\pm$ SD	75.9 $\pm$ 7.9	73.7 $\pm$ 8.1
Serum Potassium, Mean $\pm$ SD	3.9 $\pm$ 0.4	3.7 $\pm$ 0.4

Table 2

Adverse Event Table

Adverse Events	On Chlorthalidone Alone	On Chlorthalidone & Allopurinol	On Chlorthalidone & Placebo
Cardiac	4	0	1
Dental/Oral	7	0	3
Dermatologic	3	1	2
GI	14	4	4
Gynecologic	2	0	2
Headache/Dizziness	27	5	7
Metabolic	2	0	3
Musculoskeletal	17	7	11
Nephrologic	1	0	0
Other	7	6	9
Pulmonary/Upper Respiratory	18	7	6
Urologic Total	3	1	3
Urologic: Erectile Dysfunction	2	1	1
Serious Adverse Events			
Cardiac	1	0	0
Dermatologic	0	1	0
GI	1	1	0
Headache/Dizziness	1	0	0
Other	2	0	1

Table 3

Blood Pressure Medications at the Time of Recruitment and Assigned Treatment Group

Baseline Blood Pressure Medications	Allopurinol N=69	Placebo N=70	P Value
Thiazide	29 (41)	34 (49)	0.36
ACEI	21 (30)	14 (20)	0.19
Calcium Channel Blocker	14 (20)	9 (13)	0.27
ARB	5 (7)	11 (16)	0.10
Beta Blocker	5 (7)	6 (9)	0.74
Potassium Sparing Diuretic	2 (3)	2 (3)	0.99
Minoxidil	0 (0)	1 (1)	0.50

Baseline Blood Pressure Regimens	Allopurinol N=69	Placebo N=70	P Value
Single Medication	30 (56.6)	35 (63.6)	0.83
Two Medications	20 (37.7)	18 (32.7)	
Three Medications	2 (3.8)	2 (3.6)	

Table 4

Change in systolic and diastolic blood pressure and uric acid: Visit 5 minus Visit 3

Variable	Allopurinol N=56 Mean (SD)	Placebo N=54 Mean(SD)	Difference in Means Estimate (P-Value)	95% CI
Systolic blood pressure (mm Hg)	−3.4 (12.25)	0.8 (10.63)	4.3 (0.059)	−0.2 to 8.7
Diastolic blood pressure (mm Hg)	−0.2 (7.37)	1.0 (8.90)	1.2 (0.47)	−2.0 to 4.3
Uric Acid (mg/dl)	−2.3 (1.3)	−0.1 (0.88)	2.1 (<0.001)	1.7 to 2.6
Serum Potassium (mg/dl)	−0.051 (0.38)	−0.19 (0.35)	0.14 (0.054)	−0.002 to 0.28