IND 116,208 Amendment 2, new protocol
September 15, 2021
Title of Project: Value of Potassium Magnesium Citrate in Preventing and Treating Hypertension in African Americans

Investigators

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Specific Aims

In the DASH (Dietary Approaches to Stop Hypertension) trials, a diet rich in fruits, vegetables, nuts and dairy products, and limited in fat content, was shown to be useful in controlling hypertension, particularly in African Americans (AA)(Svetkey, 1999). Key components of such a diet are potassium, magnesium, and alkali, each of which has been implicated in lowering blood pressure. In the original IND 116,208 (STU072012-001), we explored whether potassium-magnesium citrate (KMgCit) as a powder pharmaceutical formulation (dissolved in water before ingestion) could serve as a surrogate for the DASH diet and would lower blood pressure among patients with pre- or Stage I hypertension. Unfortunately, the completed study in 30 patients with pre- and Stage I hypertension revealed no overall effect of KMgCit on blood pressure (Vongpatanasin, 2016).

However, a recent subgroup analysis based on ethnicity of the completed study showed that KMgCit significantly reduced 24-h blood pressure compared to placebo among African Americans (AA) (n=12), but not in non-AA (n=18). Vascular studies in 12 AA revealed that KMgCit produced a marginal reduction in central systolic blood pressure. Accordingly, we propose an amendment to IND study 116,208 to address the following:

Aim 1. To conduct a double-blinded 2-phase crossover trial, comparing the effect on blood pressure of KMgCit vs. Placebo given over 4 weeks each in 36 new AA patients with pre- or untreated Stage I hypertension. The study will seek to confirm the finding of subgroup analysis of an earlier study (STU072012-001) in 12 AA patients by showing that KMgCit produces a significant reduction in blood pressure in a larger number of AA patients.

Aim 2. As a secondary goal, to determine the effect of KMgCit on arterial stiffness in the same groups of individuals. It is hoped that vascular studies in a larger number of AA (n = 36) would reveal a more robust change in central systolic blood pressure and indices of arterial stiffness.

Background

DASH Diet

Hypertension is a major cause of morbidity and mortality. Various drugs are available to manage hypertension, such as beta blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARB), and diuretics. To avoid potential complications of such drugs, lifestyle changes – including dietary modifications – have been sought to manage hypertension in early stages.

Accordingly, the National Institutes of Health sponsored the DASH trial, assessing the value of a diet rich in fruits, vegetables, nuts, and dairy products, and limited in fat. At an intermediate sodium intake, this diet produced a significant decline in systolic blood pressure of 5 mm and diastolic of 2.5 mm (Sacks, 2001).

The DASH diet is rich in potassium and magnesium. It is also high in alkali content since the anions are provided mostly by citrate rather than chloride. Considerable data are already available in the literature invoking a protective role on hypertension of potassium, magnesium, and alkali (extensively reviewed in the original IND 116,208 (STU072012-001)).

Despite many publications citing efficacy in the control of hypertension, the DASH diet never gained wide-spread popularity because of cost and demands of long-term dietary adherence.

KMgCit as a Surrogate for the DASH Diet

Our group has conducted extensive studies with potassium magnesium citrate in a tablet form for the prevention of kidney stones (Koenig, 1991, Ruml, 1999). This preparation was shown to confer equivalent potassium bioavailability as potassium chloride, similar magnesium bioavailability as magnesium citrate, and slightly greater alkali load than potassium citrate. The mineral composition of KMgCit at the recommended daily dose approximated the amounts of extra potassium, magnesium and alkali conferred by the DASH diet.

Thus, our original IND 116,208 (STU072012-001) submitted on August 15, 2012, was designed to explore whether KMgCit might serve as a surrogate of the DASH diet and would be useful in the control of hypertension. The tablet

form previously used in renal stone prevention was impractical due to need for daily ingestion of many tablets and difficulty in manufacturing. Accordingly, a powder formulation was developed in a sachet form to be dissolved in water before ingestion. Designed to be taken twice daily, each sachet contained 20 meq K, 10 meq Mg and 37 meq citrate.

In the original IND study, KMgCit was compared with placebo, KCl, and KCitrate in 30 patients with pre- or Stage I hypertension treated for 4 weeks each in a crossover design (Vongpatanasin, 2016). No significant reduction in 24-h blood pressure was disclosed between KMgCit and placebo (Fig. 1).

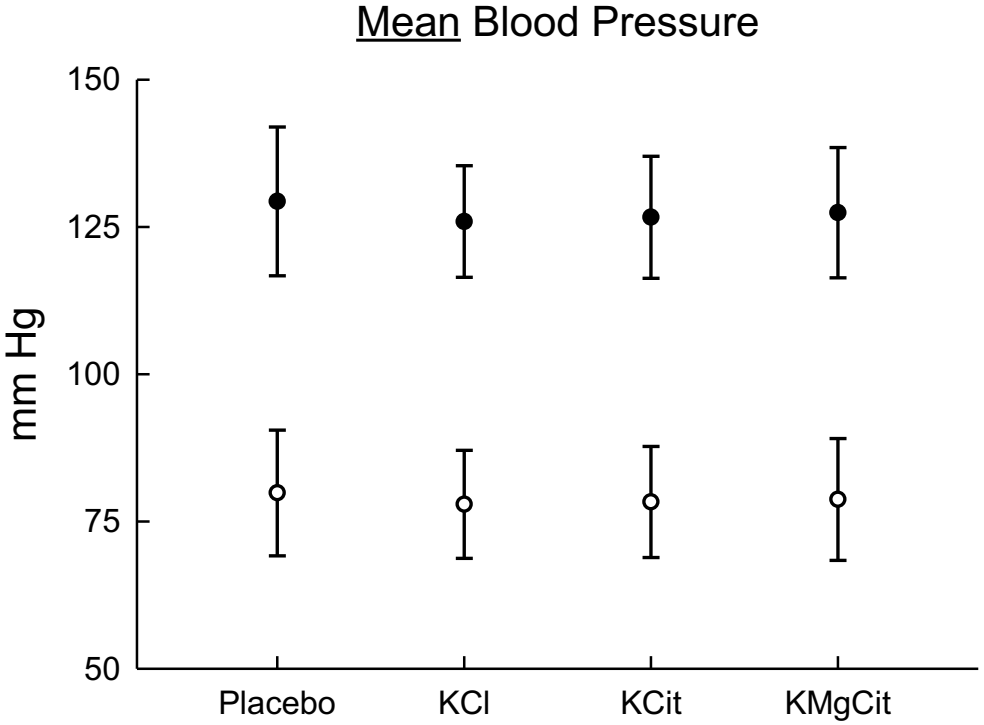

Fig. 1. 24-h systolic (top) and diastolic (bottom) blood pressure among 30 patients taking placebo, KCl, KCit or KMgCit for 4 weeks each. Bars indicate mean ± SD. The potassium preparations delivered 20 meq K bid.

Subgroup Analysis of Data from the Completed Study

Recently, there has been increased interest regarding the health of underserved populations, including AA. Hypertension and related cardiovascular-renal complications are more common in African Americans than in other ethnicities (Muntner, 2017; Aviv, 2004). In the DASH trial, the reduction in blood pressure from the DASH diet was more pronounced among AA than in white Americans (Svetkey, 1999).

The above circumstance prompted us to conduct a subgroup analysis based on ethnicity of blood pressure data from the completed trial (Vongpatanasin, 2016) conducted under the original IND 116,208 (STU072012-001). The subgroup analysis showed that KMgCit induced a significant reduction in 24-h systolic blood pressure only in African American subjects. Moreover, central systolic blood pressure (SBP) derived from vascular studies was reduced marginally by KMgCit in AA but not by other preparations or in non-AA.

Objective of the Current Proposal

In this IND amendment 2, we wish to confirm the findings from retrospective subgroup analysis of the completed study, by enrolling additional 36 AA untreated patients with pre- or Stage I hypertension to participate in a new randomized crossover trial. (This amendment 2, STU2021-0912, differs from another amendment to IND to be referred to as amendment 1, STU092015-058, that examined the effect of KMgCit in averting complications of chlorthalidone therapy in patients with hypertension. This trial is ongoing and is expected to be completed by Spring 2022.)

Table 1 compares key features of studies under IND 116,208 (STU072012-001) – original and the current amendment (STU2021-0912) 2. The current amendment proposes to evaluate 36 AA, while the original examined 12 AA. Amendment 2 proposes to evaluate only 2 phases (KMgCit vs. Placebo) out of 4 from the original. Other features are the same between the original and proposed IND.

Table 1. Comparison of Trials under IND 116,208

	Original	Amendment 2
Ethnicity	AA and non-AA	AA
No. subjects	AA n=12, 30 total	36
Phases	KMgCit, KCl, KCit, Placebo	KMgCit, Placebo
Diagnosis	pre- and Stage I	pre- and Stage I
KMgCit dose, meq/d	40 K, 20 Mg, 74 citrate	same
Placebo	microcrystalline cellulose	same
Design	crossover	crossover
Treatment duration	4 weeks	4 weeks
24-h bp monitoring	yes	yes
Vascular studies	yes	yes
Other tests	same	same

Significance

In this protocol (IND 116,208 amendment 2), we want to explore whether KMgCit taken during a customary dietary setting, might serve as a "surrogate" for the DASH diet to lower blood pressure in African Americans, a group who are at increased risk of developing hypertension. Although the original IND revealed that KMgCit was ineffective in lowering blood pressure in a combined group of hypertensive patients of diverse ethnicities, a retrospective subgroup analysis indicated that this drug was effective in AA patients (n=12) though not in non-AA (n=18). If KMgCit were to prove effective in a larger number of AA patients, it would potentially promise a safe and convenient alternative to the DASH diet in population at risk.

Methods of Procedure

Patients to be Studied

Forty-five African American patients with pre- or Stage I hypertension, with systolic blood pressure of 120-139 mm or diastolic of < 90 mmHg according the 2017 ACC/AHA high BP guideline (Welton, 2018), will be recruited into the trial, with the expectation that 36 patients would complete both phases of the trial (assuming 20% dropout). They may be AA adult men or women (≥ 18 years of age). They may be on ACE inhibitor or ARB, but not on spironolactone or diuretic.

Excluded will be patients with

1. Diabetes mellitus,
2. Renal impairment (serum creatinine > 1.4 mg/dL),
3. Any heart diseases such as congestive heart failure or sustained arrhythmia,
4. Chronic NSAID use,
5. Treatment with diuretics,
6. Gastroesophageal reflux disease (GERD) requiring treatment with acid reducing agent or antacid more than once a week,
7. Esophageal-gastric ulcer,
8. Chronic diarrhea,
9. Hyperkalemia (serum K > 5.0 mmol/L,
10. Abnormal liver function test (AST or ALT above upper limit of normal range),
11. Subjects who require any potassium supplement on a regular basis for any reason,
12. Pregnancy,
13. History of major depression, bipolar disorder, or schizophrenia, and
14. History of substance abuse.

With these exclusions, severe hyperkalemia is unlikely to develop even among patients taking ACE inhibitors or ARB. A careful history will be taken for symptoms of hyperkalemia at each clinic visit. Patients will be asked to contact the principal or associate investigator should they experience these symptoms. Serum potassium will be measured at 0, 2 and 4 weeks of each phase. If serum potassium is > 5.7 meq/L is disclosed and found to be clinically relevant by the principal investigator, the patient will be withdrawn from the study.

Study Design

The patients will participate in a randomized crossover trial comprising two phases:

Placebo Phase (microcrystalline cellulose in water)

KMgCit Phase (KMgCit powder in water)

Eligible patients will be block randomized by our research coordinators to two equal groups using a computer-generated random number list prior to the start of the study. One group will undergo Placebo phase first, followed by KMgCit phase. The other group will start with KMgCit phase first followed by Placebo.

During each phase, subjects will receive one of the test drugs for 4 weeks, following by at least 1 week of withdrawal; the other drugs will then be given for 4 weeks. Both drugs will be prepared in a similar powder sachet form, to make the study double blinded.

Test Drugs

Placebo will comprise microcrystalline cellulose, equivalent in volume in each sachet as other test products (made by Sterling Pharmaceutical Services, Dupo, IL, formerly Meta Pharma). During the Placebo Phase, subjects will suspend/dissolve the entire content of a sachet in 250 ml water and drink it with breakfast and again with dinner.

Potassium magnesium citrate will be prepared by Sterling Pharmaceutical Services. The content of each sachet will be dissolved in 250 ml water and will be drunk with breakfast and again with dinner during the KMgCit Phase, to deliver 40 meq K, 20 meq Mg and 74 meq citrate per day.

A taste enhancer will be added to improve tolerance of the test medications. Each sachet will be marked by a code, the identity of which will be known only to an independent study monitor. Each sachet will be labeled: Study drug # --; Diet Study in Hypertension; Investigator: W. Vongpatanasin, M.D.

Outline of the Study

During each phase, subjects will take one of the test medications for the first four weeks (Table 2). The test drugs will then be stopped for at least 1 week. Subjects will then take the other test medication for 4 weeks.

Table 2. Study Outline

Week	0	1	2	3	4	5
Treatment		----------	----------	----------	----------	off
24-h blood pressure monitoring*					√	
Vascular studies					√	
Urinary chemistry					√	
Office blood pressure	√		√		√	
Serum electrolytes, chemistry	√		√		√	
Side effect questionnaire	√		√		√	
Diet history, body weight	√		√		√	
"Sachet" count			√		√	

*To be also performed at baseline of the first phase, but not in the other phase. Subject will pick up 24-hour ambulatory monitor prior to visit 4 visit.

Diet and Other Drugs

Subjects will be maintained on their customary diet throughout the study.

Tests

24-hour blood pressure monitoring. At baseline of the first phase and on week 4 of both phases, 24-hour blood pressures will be recorded in an ambulatory setting by using the Spacelab 90217 ambulatory oscillometric blood pressure monitor (ABPM) (Spacelabs Medical, Issaquah, WA). Thus, each patient will undergo three 24-hour blood pressure monitoring. Recordings will be made every 20 minutes during the day and every 30 minutes at night; the data during the first hour will be discarded.

Noninvasive measurement of central aortic pressure and arterial stiffness (vascular studies). During the fourth week of treatment in each phase, arterial tonometry and simultaneous ECG will be obtained from the brachial, radial, femoral and carotid arteries using a custom pulse transducer device manufactured by Cardiovascular Engineering, Inc. The body surface distances from the suprasternal notch to the brachial (SSN-B), radial (SSN-R), femoral (SSN-F) and carotid (SSN-C) recording sites will be obtained with a tape

measure. All data will be digitized during the primary acquisition (ECG and tonometry pressures at 1000 Hz, audio at 12 kHz) and analyzed in a blinded fashion. This technique has been implemented with a high degree of reproducibility in several large multicenter clinical trials. The principal investigator of this proposal (W. Vongpatanasin) has an extensive experience in this procedure (Inrig, 2011).

Office blood pressure. During clinic visits at baseline, 2 weeks and 4 weeks of treatment, the research nurse will obtain blood pressure by using the clinic's oscillometric device (Welch Allyn, Vital Signs, WA). At each visit, three blood pressure measurements will be made after subjects sit quietly for at least 10 minutes. The first reading will be discarded. The 2nd and 3rd measurements will be averaged.

Urinary chemistry. A 24-hour urine sample will be collected during the last week of treatment for "stone risk factors" by the Mineral Metabolism Laboratory (Pak, 1985). The tests will include: potassium, ammonium, pH, citrate, magnesium, sodium, potassium, calcium, phosphorus, sulfate, creatinine, and total volume.

On week 4 of each phase, a fresh spot urine sample will be collected for calciprotein particles (CPP, to be measured by A. Pasch) and Klotho 3 (to be measured in the laboratory of Moe), and for FGF23 and WNK1 protein and mRNA (in Moe's laboratory) and creatinine. Klotho and FGF23 are emerging as major calciophosphoregulatory hormones and are implicated in vascular diseases. Urinary CPP might be involved in renal-cardiac injury. Increased renal excretion of citrate and magnesium (from potassium magnesium citrate treatment) might alter formation of CPP in urine. WNK1 might be a mediator of changes in renal (sodium handling) and vascular (resistance) determinants of blood pressure that might ensue from potassium and magnesium.

On week 4, a sample from spot urine will be frozen for urinary exosomes and aldosterone. Exosomes are shed membranes enclosing cytoplasm from the kidney. The measurement will allow us to assess levels of proteins and signaling molecules involved in the renal mineral transport. The analysis will be performed later in the laboratory of co-investigator (O. Moe), when warranted by the results.

Serum electrolytes and chemistry. At baseline, 2 weeks and 4 weeks of treatment, a venous blood sample will be obtained for electrolytes (potassium, sodium, chloride and carbon dioxide), magnesium, creatinine, calcium, phosphorus, and albumin. Serum electrolytes will be sent to Quest Diagnostic

Laboratories for analysis. Serum PTH, 1,25-dihydroxyvitamin D, C-terminal-telopeptide (CTX) will be measured by the Mineral Metabolism Laboratory. On week 4, a sample will be frozen for renin and aldosterone (to be determined later when warranted by the results).

On week 4 of each phase, a serum sample will be obtained for Klotho, FGF23, and CPP (to be measured by A. Pasch).. Serum CPP might be a marker and/or pathogenetic factor for cardiovascular injury. It might also affect vascular function.

Side effect questionnaire. At baseline, 2 weeks and 4 weeks of treatment, the research nurse will complete the side effect questionnaire by interviewing the patients (Table 3). This history permits computation of "gastrointestinal symptom score", a quantitative estimate of frequency and severity of gastrointestinal side effects (Ruml, 1999).

Table 3. Side Effect Assessment

Gastrointestinal Symptoms: (Indicate frequencies of none, < 2/wk, 2-7/wk or > 7/wk. Indicate severities of none, mild, moderate or severe.)

	Frequency				Severity				Notes
	None	<2/wk	2-7/wk	>7/wk	None	Mild	Moderate	Severe	
Vomiting									
Nausea									
Belching									
Diarrhea									
Loose BM									
Pain/Cramps									
Melena									
Dyspepsia									
Anorexia									
Dysphagia									
Other									

Other tests. At 2 weeks and 4 weeks of treatment, the research nurse (D. Pittman) will collect the test medications and count the number of unused packets, to estimate compliance of patients in taking medications. At each visit,

the research nurse will obtain history of unusual dietary intakes and complete side effect questionnaire. Body weight will be measured.

Subject Payment for Participation

At study completion, subject will be paid $500. If subjects stop taking part in the study or is withdrawn by the research team, the subject will be paid $55 per week of participation. Payment will be issued with UT Southwestern Greenphire ClinCard.

Recruitment Methods

Recruitment methods will include database searches (UTSW research registry and i2b2), referrals, study flyers, and advertisements in UTSW campus newsletter.

Statistical Analysis

Expectations

a. 24-hour blood pressure at 4 weeks would reveal a lower BP with KMgCit than Placebo. The trend toward a decline would be greater for systolic blood pressure than diastolic blood pressure.

b. Blood pressure at office visits would be lower on KMgCit compared with Placebo.

c. From vascular studies at 4 weeks, carotid to femoral pulse wave velocity (PWV) and central aortic blood pressure would be lower on KMgCit than on Placebo, while carotid to radial PWV would not be different between the phases, indicating specific improvement in aortic elastic function.

d. On treatment, gastrointestinal symptom score of KMgCit would be equivalent to Placebo.

g. At 4 weeks, 24-hour urinary potassium, pH, citrate and Mg would be higher during KMgCit than on Placebo.

Subject Safety and Data Monitoring

Serum potassium will be monitored every 2 weeks during the study. Subjects who develop serum K > 5.7 during treatment will have a repeated measurement to confirm the value immediately. If repeated potassium level remains above 5.7, subject will be excluded from the study.

If serum K is above 6.0 mmol/L, EKG will be obtained immediately and the study procedures will be discontinued in these subjects. Subjects will be transferred to the emergency department for further evaluation and management. Questionnaire will be used to monitor gastrointestinal side effects.

If subject is withdrawn early, it may be reasonable to conduct a final study visit to complete the study if determined appropriate by the study team. This visit will include data points as the 4-week close out visit including 24-hour blood pressure monitoring, 24-hour urine collection, fresh urine collection, blood draw, vascular studies, symptom questionnaire, and returning study drugs.

Conditions under which an Individual Subject will be Withdrawn from the Study

- Development of hyperkalemia with serum K > 5.7 during treatment.
- Severe gastrointestinal side effects of more than 2 times per week or moderate symptoms of more than 7 times per weeks.
- Withholding of study medication for > 4 weeks for whatever reason.
- Any reason including serious adverse events that results in participant's inability to continue with study protocol and procedures.
- Severe hypertension defined as persistent elevation of systolic BP > 180 mmHg or diastolic BP > 110 mmHg on 3 consecutive measurements after randomization
- Refractory hypotension defined as persistent systolic BP < 90 mmHg
- Pregnancy
- Development of diabetes mellitus or a new medical condition necessitating initiation of any diuretics or spironolactone after enrollment in the study.

Sample Size Calculations

The sample size was calculated based on the primary outcome of 24h SBP. In our previous crossover study, the SD of mean difference in 24h SBP within the same patient among our AA group was 7.2. With this SD, the sample size of 36 will allow us to detect mean difference in 24h SBP of 4.9 mmHg between placebo and KMgCit at the α of 0.05 and power of 0.8. Assuming a 20% dropout rate, we plan on recruiting 45 patients to enroll 36 patients completing both phases to drive a robust clinically meaningful finding.

Statistical Methods

Descriptive statistics will be used to summarize patient demographic and clinical characteristics, as well as the primary and secondary outcomes. All analysis will be performed on the principle of intention-to-treat basis, including all randomized patients in the allocated sequences for two treatment groups. Per protocol analysis will be also conducted on those patients with no major protocol deviations. The primary hypothesis of evaluating treatment effect on 24h BP will be analyzed using a linear mixed-effect model with both fixed and

random effects. The treatment (KMgCit and Placebo), period and treatment by period interaction are included as fixed effects, whereas participant is included as a random effect. The sequence effect of the supplement will be tested in this model. Similar mixed regression model analysis will be also carried out to evaluate secondary outcomes. Data transformation will be made if normality assumption is violated. Interim analysis may be performed at 50% completion of the trial. All analyses will be performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P < 0.05$ will be considered statistically significant.

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Investigator Data

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Authorized representative of the sponsor: Charles Y.C. Pak, M.D.

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