Efficacy of Diuretics in Kidney Disease

NCT04542304

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1. PURPOSE OF THE STUDY

a. Brief Summary

This research will study how well a diuretic, a medication which enhances the kidneys' removal of sodium and fluid, works in people with kidney disease. We will measure urine production and levels of waste chemicals in these samples to figure out how the diuretic and the kidneys remove waste chemicals from the body. Overall, we hope to learn more about how diuretics and the kidneys work so that we can improve the health of people with kidney disease.

b. Objectives

Kidney disease is common and more than 100,000 people with kidney disease start dialysis every year. There is limited data regarding the optimal dose or type of diuretic for patients with kidney disease. In addition, a majority of patients have their diuretic stopped once they start dialysis. Many however have enough residual kidney function so that diuretics may still be beneficial in controlling volume status, blood pressure, and serum potassium levels. We in addition would like to learn more about how the efficacy of diuretics is affected by the plasma accumulation of waste solutes that are cleared by the same secretory mechanisms of the kidneys as the diuretics.

c. Rationale for Research in Humans

This study will assess the effect of diuretics on urine production in patients with kidney disease and the effect of plasma accumulation of waste solutes on the efficacy of diuretics. We therefore need to include human subjects.

2. STUDY PROCEDURES

a. Procedures

We will conduct two types of studies to investigate diuretics in kidney disease. Patients with kidney disease will be asked to participate in one or both of the studies.

One study is a cross-over study comparing a one-time dose of a diuretic and then a one-time dose of a placebo at least one week later.

Screening:
- nephrologists at Stanford, VA Palo Alto, and SCVMC will be contacted to identify patients with kidney disease and patients on dialysis who report still producing urine.
- informed consent will be obtained from eligible patients.

- patients who consent will then undergo randomization to determine the order of diuretic and placebo in the cross-over study.

The patients will complete two 1-week study periods:
- One period of taking a one-time dose of a diuretic.
- One period of taking a one-time dose of a placebo.

During the study periods which will be performed at least 1 week apart:
- patients will be asked to take a one-time dose of a diuretic or a placebo. If patients are already on a diuretic, we may ask them to briefly stop taking the diuretic and to take a different diuretic or a placebo.
- the patient's blood pressure will be checked prior to taking the diuretic or placebo.
- the patient will be asked to weigh him/herself daily.
- the patient will collect urine for at least 24 hours.
- a blood sample will be collected, up to 20 ml (5 teaspoons). If the patient is on hemodialysis, a pre- and post-treatment blood sample will be collected. Blood will be collected through the dialysis tubing in the same fashion as the patients' routine lab monitoring.
- the patient will complete symptom questionnaires.

We may ask the patients to repeat the diuretic and/or placebo study periods.

The other study is a study investigating how kidney disease and/or dialysis affects the plasma levels of diuretics over time.

Screening:
- nephrologists at Stanford, VA Palo Alto, and SCVMC will be contacted to identify patients with kidney disease and patients on dialysis.
- informed consent will be obtained from eligible patients.

Patients who consent will then perform the following:
- take a one-time dose of a diuretic. If patients are already on a diuretic, we may ask them to briefly stop taking the diuretic and to take a different diuretic.
- a blood sample will be collected after the patients take the diuretic, up to 20 ml (5 teaspoons). If the patient is on hemodialysis, a pre- and post-treatment blood sample will be collected. Blood will be collected through the dialysis tubing in the same fashion as the patients' routine lab monitoring.
- up to 5 repeat blood samples may be collected, each at least 24 hours apart.
- if the patient is on dialysis, waste dialysate fluid (which normally goes down the drain) will be collected during a dialysis treatment.
- if the patient makes urine, we may ask the patient to collect timed urine samples.

b. Procedure Risks

Blood would be collected in the same sterile fashion as the patients' routine lab checks. If the patients are on hemodialysis, blood will be collected in the same fashion as their routine monthly labs through the hemodialysis tubing.

Taking a diuretic medication once has minimal risk unless taking other medications which tend to reduce blood pressure; we would check the patients' blood pressure and review their medications before asking them to take a diuretic.

Stopping a diuretic medication and taking a placebo instead has minimal risk of higher blood pressure and fluid accumulation in carefully followed patients. We will check the patients' blood pressure and weight before and after stopping their diuretic.

c. Will it be possible to continue the more (most) appropriate therapy for the participant(s) after the conclusion of the study?

Yes

d. Study Endpoint(s)

The primary endpoint is urine production as assessed by a timed urine collection. Other endpoints are symptom questionnaires (KDQOL-36 and the Dialysis Symptom Index).

Laboratory and clinical endpoints will be plasma levels of urea and secreted uremic solutes, blood pressure, and weight changes.

Because the patients will take only a one-time dose of a diuretic and a one-time dose of a placebo, we do not anticipate a difference which would force study termination.

If no important differences are detected, the study will end once the projected total patient population has completed the study.

3. BACKGROUND

a. Past Experimental and/or Clinical Findings

We have previously found that the residual native kidney can control plasma levels of secreted solutes better than those of the index solute urea. We would like to assess whether diuretics can enhance the residual kidneys' ability to control organic solutes and fluid gain.

b. Findings from Past Animal Experiments

N/A

4. DRUGS, BIOLOGICS, REAGENTS, OR CHEMICALS USED IN THE STUDY

a. Commercial Drugs, Biologics, Reagents, or Chemicals

Commercial Product 1	
Name:	Metolazone
Dosage:	range of 2.5 to 20 mg in a single daily dose
Commercial Product 2	
Name:	Furosemide
Dosage:	range of 40 to 600 mg/day in two doses per day
Commercial Product 3	
Name:	Bumetanide
Dosage:	range of 0.5 to 10 mg/day in two doses per day
Commercial Product 4	
Name:	Placebo
Commercial Product 5	
Name:	Chlorthalidone
Dosage:	range of 25 to 100 mg in a single daily dose
Commercial Product 6	
Name:	Torsemide
Dosage:	range of 10 to 200 mg/day in single daily dose or in two doses per day

5. PARTICIPANT POPULATION

a. Planned Enrollment

i) 20 subjects expected to be enrolled from Stanford-affiliated sites and 35 subjects expected to be enrolled from the VA.
ii) an anticipated 75 subjects expected to be enrolled from all sites, including VA Palo Alto and SCVMC. We will obtain approval from the SCVMC IRB; we will not recruit patients from SCVMC until we obtain approval.
iii) patients with kidney disease and dialysis patients

b. Age, Gender, and Ethnic Background

The age range will be 18 to 85 years old. The gender and ethnic background will be representative of the diverse Bay Area population.

c. Recruitment Details

We will notify the primary nephrologists to help identify patients with kidney disease and patients on dialysis who still have residual kidney function. We will also accept direct referrals from nephrologists.

We are requesting a waiver of HIPAA for recruitment to review medical charts to identify eligible patients. When we identify a possible participant by chart review, we will contact the patient's primary nephrologist to obtain their approval for the patient's potential participation and arrange for the primary nephrologist to personally ask the patient or have clinic or dialysis unit personnel ask the patient if s/he would be willing to talk to us about involvement in a study.

d. Eligibility Criteria

i. Inclusion Criteria

- patients with chronic kidney disease
- patients on hemodialysis or peritoneal dialysis with or without residual kidney function. Such patients must be on dialysis for at least 2 months with regular adherence to treatments.

ii. Exclusion Criteria

- hospitalized within the past 2 months.

e. Screening Procedures

We will notify the primary nephrologists who will help identify patients with kidney disease, patients who are on dialysis with residual kidney function (suggested by report of urine production of at least 250 ml/day or about 1 cup/day), and patients who are on dialysis without residual kidney function.

6. PRIVACY AND CONFIDENTIALITY

All participant information and specimens are handled in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and privacy policies of Stanford University, Stanford Health Care, and Stanford Children's Health.