Wishing to decrease Aquaresis in ADPKD patients Treated with a V2Ra; the Effect of Regulating protein and salt

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To demonstrate the effect of salt and/or protein intake on aquaresis in patients with ADPKD who are treated with a vasopressin V2 receptor antagonist as measured by 24-hour urine volume.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract disorders congenital
Study type	Interventional

Summary

ID

NL-OMON50000

Source
ToetsingOnline

Brief title
WATER

Condition

- Renal and urinary tract disorders congenital
- Nephropathies

Synonym
Autosomal dominant polycystic kidney disease, polycystic kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Dutch Kidney Foundation;eigen fondsen

Intervention

Keyword: ADPKD, aquaresis, Diet, Vasopressine V2 receptor antagonist

Outcome measures

Primary outcome

The primary outcome variable will be change in 24-hour urine volume as a percentage, comparing with the mean of the two 24-hour urine volumes collected at baseline versus the mean of the two volumes collected at the end of the two-week treatment periods with low salt, low protein and placebo.

Secondary outcome

Secondary outcomes of this study will be changes in serum copeptin levels (the stable precursor of vasopressin), changes in mGFR (iohexol clearance), changes in blood pressure and quality of life using a questionnaire. Adverse events will be monitored, serum electrolytes will be checked.

Study description

Background summary

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by the formation of numerous cysts in both kidneys and progressive renal function decline leading to renal replacement therapy (RRT) at a median age of 58 years. The first (and at the moment only) drug to slow down renal function decline, is a vasopressin V2 receptor antagonist (V2RA). This medicament slows renal function decline by 26 to 34%. V2RA also causes aquaresis associated side-effects such as polyuria of >6 liter per day in the majority of patients. These side-effects limit wide spread use among ADPKD-patients. Therefore, there is a need to improve its tolerability. Currently, an METc-approved study is performed in which the influence of hydrochlorothiazide and metformin on urine volume while treated with a V2RA is investigated (METc 2017.662). While using a V2RA, urine concentrating ability is strongly diminished. Therefore, urine volume is largely determined by total osmolar excretion. This is a well-known fact in nephrogenic diabetes insipidus, a disease with clear pathophysiological

similarities to treatment with a vasopressin V2 receptor antagonist (a defect receptor versus pharmacological blockade). In a recent study we found osmolar excretion to be associated with urinary volume during V2RA treatment. Whether a change in osmolar load changes polyuria during V2RA has not yet been investigated. Furthermore, it is not known whether change in sodium or protein influence the aquaresis to the same amount.

Study objective

To demonstrate the effect of salt and/or protein intake on aquaresis in patients with ADPKD who are treated with a vasopressin V2 receptor antagonist as measured by 24-hour urine volume.

Study design

After screening, subjects enter a first run-in period in which compliance to the recommended diet is assessed. When subjects comply to the salt- and protein recommendations, they enter a second run-in period with addition of 6 grams of salt and 40 grams of protein. After run-in, four treatment periods start.
During the four treatment periods, subjects will receive:
1. Sodium chloride capsules of 750 mg 2dd4 (= 6 gram extra) or matching placebo.
2. Protein beverage with 40 grams of protein per day or matching placebo.

Intervention

After screening, subjects enter a first run-in period in which compliance to the recommended diet is assessed. When subjects comply to the salt- and protein recommendations, they enter a second run-in period with addition of 6 grams of salt and 40 grams of protein. After run-in, four treatment periods start.
During the four treatment periods, subjects will receive:
• Salt continuation - protein continuation
• Salt continuation - protein restriction (placebo)
• Salt restriction (placebo) - protein continuation
• Salt and protein restriction (placebo, placebo)

Study burden and risks

Patients who are using tolvaptan as part of regular clinical care will be included. These patients have frequent visits and there is a need to control laboratory values every month during the first 18 months of treatment. Participating in this study entails a minimum of 2-4 extra visits within 8 weeks of treatment plus the run-in period (6 study visits versus 2-4 in regular care). Run-in period can be extended unlimited times until the subject complies to the recommended diet. Extending the run-in period will be discussed with the subject and will be scheduled after the subject gives oral approval.

Patients have to comply to a diet which is low in salt (6 g/day) and protein intake (0,8 g/kg ideal body weight), which is in accordance with the advices for healthy food in the national guidelines for treatment of chronic kidney disease.

Other study procedures are:
- Minimum of 6 times 2x24-hours urine collections;
- 6 times venous blood samples;
- 6 times collecting spot urine;
- 5 times GFR measurement (iohexol method)
- 6 times 3-day diet diary

Possible discomfort/risks associated with intervention
- Increased aquaretic side-effects during high-salt and high-protein intervention such as polyuria, thirst, polydipsia and nocturia;
- The high salt diet may lead to a modest increase in mean arterial pressure, however these effects are only temporarily (maximal 6 weeks) and reversible after returning to the reduced salt intake and pose no danger. Moreover, for most patients, this is normal salt intake.

Potential benefit of participation
There are no expected direct benefits to participation. However, participants will receive dietary advice from a dietician and have to comply to a diet which is low in salt and protein intake for at least 12 weeks. This diet is in accordance with the guideline chronic kidney disease, so participating in this study gives subjects the opportunity to implement this diet to their regular life style. Furthermore, the study will gain insight in dietary factors influencing urine volume and lead to advices the patient can use during the rest of the V2RA treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of ADPKD, based upon modified Ravine criteria, or documented by their nephrologist or internist.
2. Prescribed tolvaptan as part of routine clinical care in the highest dose tolerable (preferably 120 mg daily)
3. Age >= 18 years.
4. eGFR >30 ml/min/1.73m2.
5. Providing informed consent.
6. Compliance to the recommended diet (<9 grams of salt per day, < 1,2 grams of protein per kg ideal bodyweight per day) at two consecutive times.

Exclusion criteria

1. Patients who, in the opinion of the investigator may present a safety risk.
2. Patients who are unlikely to adequately comply to the trial*s procedures (due for instance to medical conditions likely to require interruption or discontinuation, history of substance abuse or non-compliance).
3. a. Patients taking medication likely to confound endpoint assessments (lithium, systemic corticosteroids, diuretics).
3. b. Patients having concomitant illnesses likely to confound endpoint assessments (e.g. diabetes mellitus for which medication is needed or diabetes insipidus).
4. Women who are pregnant or breastfeeding.
5. Patients with limited access to water.
6. Patients with an abnormal sense of thirst.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-09-2020
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	20-02-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL71622.042.19
Other	Volgt, protocol is onder beoordeling van www.clinicaltrials.gov