Hydrochlorothiazide and metformin cross-over study for attenuating aquaretic side-effects in ADPKD patients treated with tolvaptan

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To demonstrate whether hydrochlorothiazide or metformin can diminish aquaresis in patients with ADPKD who are treated with tolvaptan 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-OMON46358

Source
ToetsingOnline

Brief title
Medication for excessive urine production in tolvaptan

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: Nefrologie

Source(s) of monetary or material Support: Eigen fondsen

Intervention

Keyword: ADPKD, biguanide, thiazide, Vasopressin V2 receptor antagonist

Outcome measures

Primary outcome

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

Secondary outcome

-Change in glomerular filtration rate (as measured with the iohexol plasma clearance technique)

-Change in plasma copeptin

-Tolerability of the study medication

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) in 70% of the patients at a median age of 58. Despite a relatively low prevalence of 3-4:10.000, ADPKD is the most common hereditary renal disease and accounts for 10% of all dialysis patients. Recently, the first drug to slow down renal function decline, vasopressin 2 receptor antagonist tolvaptan was approved to be prescribed to ADPKD patients. Tolvaptan slows renal function decline by 26%, thereby postponing RRT by one year every four years it is being used. Tolvaptan slows down cyst growth by 49%.

As a vasopressin (antidiuretic hormone) receptor antagonist, aquaresis

associated side effects such as polyuria, thirst, nycturia and polydipsia occur in the majority of patients. Aquaresis-related side effects are the most common reason for discontinuing tolvaptan, and in our personal experience patients regard the prospect of polyuria, which can amount to over 8 litres per day, as the most important threshold for starting treatment. Currently, there are no adjuvant treatment options to reduce these side effects. If the side effects prove to be intolerable to a patient the only possibilities are to either cease tolvaptan treatment, or to reduce the dose. In the TEMPO trial the average dose of tolvaptan was 95mg, the majority of patients completed the study on the maximum dose of 120mg per day. Therefore, there is little evidence for the efficacy of reduced doses of 90mg or even 60mg per day.

Tolvaptan causes aquaresis by competitive antagonism of the vasopressin V2 receptor, thereby inhibiting migration of aquaporin 2 (AQP2) to the apical cell membrane in the principal cells of the distal collecting duct. As a result the distal collecting duct remains impermeable to water, which consequently cannot be reabsorbed and is thus urinated. The mechanism by which tolvaptan causes aquaresis is similar to the pathophysiology of nephrogenic diabetes insipidus (NDI). In NDI The collecting duct is (relatively) impermeable to water due to insensitivity to vasopressin, caused either by defects in the V2 receptor or defects downstream, inhibiting migration of AQP2 to the apical cell membrane of principal cells. Because of these similarities it is likely that the same treatments that are effective to reduce polyuria in NDI may also be effective to reduce polyuria in patients who use tolvaptan.

Hydrochlorothiazide has been an established treatment for polyuria in NDI for over 50 years and is known to lower urine output by up to 30-50%. We hypothesize that additional treatment with hydrochlorothiazide will lead to reduction of polyuria in ADPKD-patients using tolvaptan by similar margins as treatment with hydrochlorothiazide in NDI.

Recently, metformin has been shown to be a vasopressin-independent activator of water transport in the inner kidney medulla through stimulation of AMP-activated protein kinase (AMPK) in rats. This made metformin a viable candidate as treatment for polyuria in NDI. in a study by Efe et al. rats were treated with tolvaptan as a model for NDI, increasing 24-hour urine volume from 10mL to 22mL. Addition of metformin normalized urine volume within five days. We hypothesize that metformin will attenuate polyuria and increase urine osmolality in humans through nonvasopressor activation of AMPK.

Study objective

To demonstrate whether hydrochlorothiazide or metformin can diminish aquaresis in patients with ADPKD who are treated with tolvaptan as measured by 24-hour urine volume.

Study design

A placebo-controlled, double-blind, double dummy, cross-over trial in subjects with ADPKD that are using tolvaptan at the maximum dose of 120mg per day. Treatment consists of metformin, hydrochlorothiazide and placebo in random order. The study will consist of three treatment periods, each treatment period contains two treatment weeks and one wash-out week, save for the last treatment period, which does not have a wash-out week. Total study duration will be 8 weeks.

Intervention

Subjects will be treated with hydrochlorothiazide, metformin and placebo for two weeks each, followed by one wash-out week, in random order. Hydrochlorothiazide will be initiated at 12,5mg QD, after one week the dose will be increased to 25mg QD if well tolerated. Metformin will be initiated at 500mg BID, after one week the dose will be increased to 1000mg BID, if well tolerated.

Study burden and risks

Burden and risk associated with participation are:
-Patients who are using tolvaptan as part of regular clinical care usually have to come to the out-patient clinic every month during the first 18 months of treatment. Participating in this study entails a minimum of 1 and a maximum of 4 extra study visits within 8 weeks of treatment plus the variable screening period (5 study visits versus 1- 4 in regular care). A maximum of 5 additional times venous blood has to be drawn (8 times versus 3 or 4 in regular care).
-4 times GFR measurement using the iohexol plasma clearance technique
-8 times 24-hour urine collection
-Patients will be exposed to metformin and hydrochlorothiazide (not combined), while already using tolvaptan

Potential benefit of participation:
The potential benefit of this study is to reduce aquaretic side-effects of tolvaptan. Potentially leading to less polyuria, nycturia, thirst and polydipsia. Due to reduced polyuria, patients may be able to tolerate higher, more effective doses of tolvaptan, which could ultimately lead to postponement of or preventment of renal replacement therapy.

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
2. Using tolvaptan 120mg daily
3. Age between 18 and 50 years
4. *45 eGFR (CKD-EPI)
5. Providing informed consent

Exclusion criteria

1. 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)
2. a. Patients taking medication likely to confound endpoint assessments (e.g. NSAID or diuretics such as furosemide or spironolactone)
2. b. Patients having concomitant illnesses likely to confound endpoint assessments such (e.g. diabetes mellitus for which medication is needed or diabetes insipidus)
3. Women who are pregnant or breastfeeding
5. Patients with known contra indications to the study medication such as

5. a. Hydrochlorothiazide: gout, hepatic impairment, illnesses that cause potassium loss, history of hypokalaemia, known allergy to hydrochlorothiazide
5. b. Metformin: Illnesses that can cause tissue hypoxia (e.g. recent myocardial infarction, heart failure, respiratory failure), known allergy to metformin

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-10-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrochlorothiazide
Generic name:	Hydrochlorothiazide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Metformin
Generic name:	Metformin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-03-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-05-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-05-2019
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
Other	6734
EudraCT	EUCTR2017-003864-10-NL
CCMO	NL62608.042.17