Bumetanide to Ameliorate Tuberous Sclerosis Complex Hyperexcitable Behaviors

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Primary aim: to confirm that treatment with bumetanide improves daily life functioning and reduces behavioral symptoms related to hyperexcitability in children and adolescents with TSC.Secondary aim: to identify neurophysiological and cognitive...

Ethical review	Approved WMO
Status	Completed
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON45855

Source
ToetsingOnline

Brief title
BATSCH

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Mental impairment disorders
- Developmental disorders NEC

Synonym
Bourneville disease, Tuberous Sclerosis, Tuberous Sclerosis Complex

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Michelle subsidie

Intervention

Keyword: Bumetanide, Chloride, Treatment, Tuberous Sclerosis Complex

Outcome measures

Primary outcome

The primary endpoint will be the change in score on the Aberrant Behaviour

Checklist-Irritability subscale.

Secondary outcome

Secondary endpoints involve neurocognitive, behavioural and quality of life

parameters; markers from neurophysiological investigations: brain evoked P50

suppression, prepulse inhibition, mismatch negativity and resting-state EEG.

Study description

Background summary

Neurological and behavioural problems are central features of children with tuberous sclerosis complex (TSC). Much attention in the treatment of TSC patients is given to seizure management, while cognitive and behavioural problems are often under evaluated. At present, treatments to reduce the tremendous behavioural burden associated with TSC are lacking. There is an urgent need to develop novel targeted treatment options.

It has been shown that the structural brain abnormalities in TSC, notable the tubers, constitute a source of excessive and dysfunctional brain activity. Different studies have shown that the balance between excitatory (via the neurotransmitter glutamate), and inhibitory (via the neurotransmitter GABA) brain activity is disturbed in tubers, a phenomenon also referred to as the balance between excitation-inhibition (E / I). The inhibitory quality of GABA depends on chloride concentration in neuronal cells, when chloride is high then GABA is excitatory instead of inhibitory. Disturbances in chloride maintenance have been linked to epilepsy and autism spectrum disorders, both highly prevalent in TSC. Landmark studies have shown that the diuretic agent

bumetanide can lower chloride levels and may reinstate GABAergic inhibition in these conditions. This may be extremely relevant to TSC as disturbances in chloride maintenance were shown in surgically resected tuber specimens of TSC patients.

Before a randomized controlled trial in TSC cohorts can become feasible, positive effects of bumetanide need to be confirmed in children with TSC and appropriate endpoints need to be established. We propose to conduct a pilot study to establish the efficacy of bumetanide as add-on treatment to reduce irritability and other behavioural symptoms typical in children and adolescents with TSC, with and without mental retardation. In addition, we will perform EEG measurements to assess the effect of treatment on measures of hyperexcitability and to identify neurophysiological characteristics that may improve and specify future application of bumetanide treatment.

In sum, this mono-centre pilot study will prepare the repositioning of a common diuretic drug with limited side effects to treat the severe lifelong cognitive and behavioural problems associated with TSC that have no medical therapy at present.

Study objective

Primary aim: to confirm that treatment with bumetanide improves daily life functioning and reduces behavioral symptoms related to hyperexcitability in children and adolescents with TSC.
Secondary aim: to identify neurophysiological and cognitive characteristics that relate to efficacy of bumetanide treatment.

Study design

We will conduct a 91 day monocenter pilot study with bumetanide, followed by a 28 day wash-out period.

Intervention

Patients will be treated with bumetanide, which will be provided as an add-on treatment, supplementary to the regular use of AEDs or other (allowed) co-medications. Patients will be given a dose between 0.5 mg and 1.0 mg twice a day (before breakfast and at the end of the afternoon, at least 2.5 hours before bedtime) for 91 days. Bumetanide will be administered in the formulation of half a 1.0 mg Bumetanide tablet, containing 0.5 mg bumetanide, and taken orally. Starting dosage will be 0.5 mg twice a day, then the dose will be increased to 1.0 mg twice a day, if blood electrolytes are normal and no signs of dehydration are present in the clinic visit at day 7. The treatment period will be followed by a 28 day wash-out period to evaluate return of

symptomatology and reversibility of treatment effect.

Study burden and risks

The burden and risks associated with participation are acceptable while the intervention may greatly improve quality of life for patients and caregivers. Bumetanide has been used as a diuretic drug for decades. Since the 1970s, the safety and tolerability of bumetanide after short and prolonged treatment has been established in both children and adults. The main adverse events are related to the diuretic activity of the molecule leading to a decrease in electrolytes, notably mild hypokalaemia are frequently reported. To monitor the diuretic effects, physical examination (8 times in total) and blood testing (6 times in total) and urine test (1 time) will be performed with negligable and known risks. To prevent hypokaliemia, potassium suppletion will be adminstered in during the 91 treatment days. To monitor treatment effect, questionnaires, cognitive tasks and EEG measurements will be performed three times. These tests are generally well tolerated and are all non-invasive.

Importantly, neurobehavioral problems pose one of the greatest burdens in daily life of patients with TSC and their caregivers and until now, targeted treatments are lacking. The study proposed here is therefore relevant for several reasons. Our application builds on existing pre-clinical and clinical research on the application of bumetanide in neurodevelopmental disorders, including ASD, epilepsy and TSC. Bumetanide has shown a long known safety and has proven effective to reinstate GABA inhibitory properties, which may restore important developmental capacities. Treatment with bumetanide may constitute a rational treatment for cognitive and behavioural disruptions. If bumetanide treatment is confirmed to be effective this intervention will ultimately improve quality of life for patients and caregivers.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Males or females aged *8 years;
2. Definite diagnosis of TSC: either meeting criteria for clinical definite TSC, or a mutation identified in the TSC1 or TSC2 gene;
3. History of behavioural problems;
4. Written informed consent.

Exclusion criteria

1. Inability to comply with the protocol-specified procedures for the duration of the study, including treatment and blood sampling to control diuretic effects;
2. Presence of a severe medical or genetic disorder other than related to TSC or epilepsy;
3. Serious, unstable illnesses including, gastroenterological, respiratory, cardiovascular (arrhythmias, QT interval lengthening), endocrinologic, immunologic, hematologic disease, dehydration or hypotension, electrolyte disturbances (Na <133 mmol/L, K <3.5 mmol/L or Ca <2.17 mmol/L [<13y] or <2.2 mmol/L [>13y]);
4. Renal insufficiency (CKD st2-5; estimated glomerular filtration rate < 90 ml/min/1.73m2), congenital or acquired renal disease with decreased concentration capacity (tubulopathy, diabetes insipidus) and liver insufficiency interfering with excretion or metabolism of bumetanide;
5. Start of behavioral treatment during study;
6. Treatment with psychoactive medications, including antipsychotics and AEDs, except methylphenidate is allowed albeit on a stable regime in terms of types and dosage from 2 months prior to the study to the end of the study;
7. Treatment with NSAIDS, aminoglycosides, digitals, antihypertensive agents, indomethacin,

probenecid, acetazolamide, Lithium, other diuretics (e.g., furosemide, hydrochlorothiazide), drugs known to have a nephrotoxic potential;
8. Documented history of hypersensitivity reaction to sulfonamide derivatives;
9. Body weight < 30 kg.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-03-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	25-07-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	07-02-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26926
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-002408-13-NL
CCMO	NL58183.041.16

Study results

Date completed:	10-09-2018
Results posted:	04-09-2019
Actual enrolment:	17

First publication

04-09-2019