Bumetanide for the Autism Spectrum Clinical Effectiveness Trial

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Ethical review	Approved WMO
Status	Completed
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON45411

Source
ToetsingOnline

Brief title
BASCET

Condition

- Mental impairment disorders
- Developmental disorders NEC

Synonym
ADHD, Autism, Autism Spectrum Disorders, epilepsy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Hersenstichting subsidie ("Snel Beter Behandelen")

Intervention

Keyword: Autism, Bumetanide, Epilepsy, Treatment

Outcome measures

Primary outcome

The primary study parameters is the Aberrant Behavior Checklist-Irritability

subscale.

Secondary outcome

Secondary study parameters are behavioral and quality of life parameters and

seizure frequency

Study description

Background summary

Sensory processing difficulties are extremely prevalent within the pediatric psychiatric population and transcend classifications of developmental disorders (such as Autism Spectrum disorder (ASD) and ADHD). They constitute a group of devastating neurodevelopmental disorders that have no cure at present. It is estimated that approximately 1 in 100 children display signs and symptoms that lead to a diagnosis of ASD , making it more common than childhood cancer and juvenile diabetes together. Individual differences in ASD and ADHD manifestation are characterized by substantial variability in symptomatology, severity and comorbidities. Despite this heterogeneity, common treatment targets are beginning to be elucidated on a biological level, which may finally bring the urgently needed etiology driven treatments. A promising example in this respect is the selective chloride transporter NKCC1 antagonist bumetanide. Bumetanide has been used for decades as a diuretic drug and its safety has been confirmed. Bumetanide has recently been proposed as a rational treatment for sensory processing difficulties based on its capacity to reinstall the inhibitory action of the principal neurotransmitter gamma-aminobutyric acid (GABA). A first trial has tested bumetanide in a modest sample (n = 56) of children with ASD showing an decrease in symptom severity after three months of treatment with bumetanide. In a recent pilot study, we have confirmed the potential of bumetanide to treat autism core symptomatology. In addition, we have established a positive effect on brain activity using EEG. Building on these previous experiences, we now aim to conduct a larger trial to

confirm the efficacy of bumetanide in ASD, ADHD and/or epilepsy and analyze which types of neurodevelopmental disorders are most responsive to bumetanide in terms of severity, intellectual functioning and comorbidity. Here, we propose to conduct a large, multicenter, placebo-controlled randomized trial testing bumetanide plus usual care treatment versus placebo plus usual care in 172 children with ASD, ADHD and/or epilepsy. With this design, we expect to confirm effectiveness of bumetanide as cheap, safe and rational treatment option for an important subset of developmental disorders.

Study objective

The primary objective of the study is to test the effectiveness of bumetanide across the whole spectrum of sensory processing disorders within ASD, ADHD and/or epilepsy. We also want to determine which subgroups (high/low IQ, comorbidities or not) are associated with a favorable treatment response .

Study design

A multicenter (2 centers: UMC Utrecht and Jonx Groningen) double-blind, randomized, placebo-controlled trial with 91 days bumetanide treatment, followed by a 28-day washout period. Children with ASD, ADHD and/or epilepsy are randomly assigned to either bumetanide or placebo, according to a computer-generated randomization schedule.

Intervention

Patients will be treated (randomly) with bumetanide or placebo, for 91 days, followed by 28 days of wash-out. Bumetanide or placebo can be used as add-on treatment in addition to the regular use of permitted concomitant medications. Patients will be given twice daily a dose between 0.25 and 1.0 mg bumetanide/placebo (before breakfast and at the end of the afternoon, at least 2.5 hours before bedtime). Bumetanide/placebo is provided in the form of a 0.5 mg tablet and taken orally. The starting dose for children with body weight * 17 kg and < 33 kg is 0.5 mg/day divided over 2 dosages (i.e., 2 x 0.25 mg/day), and increased to 1.0 mg/day divided over 2 dosages (i.e., 2 x 0.5 mg/day) when blood electrolytes are normal and no signs of dehydration are present during the blood and urine control on day 7 of the study. The starting dose of children with a bodyweight of * 33 kg is 1.0 mg/day divided over 2 dosages (i.e., 2 x 0.5 mg/day), which is increased to 2.0 mg/day divided over 2 dosages (i.e., 2 x 1.0 mg/day) when blood electrolytes are normal and no signs of dehydration are present during the blood and urine control on day 7 of the study. The treatment period will be followed by a wash-out period of 28 days to evaluate return of symptomatology and the reversibility of the treatment effect.

Study burden and risks

The burden and risks associated with participation in this study are acceptable, while the intervention can greatly improve the quality of life for patients and caregivers. Bumetanide has been used as a diuretic for decades. Since the 1970s, the safety and tolerabilityof 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 which leads to a decrease in electrolytes; notably mild hypokalemia are frequently reported. To monitor the diuretic effects, physical examination (8 times in total), 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 administered during the 91 treatment days. The effect of the treatment will be measured at 3 times by means of (parent)-questionnaires.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Males or females aged *5 years to *15 years;
2. Above clinical cut-off scores on the Sensory Profile and either a clinical ASD or ADHD diagnosis based on DSM-5 (or DSM-IV) or an epilepsy diagnosis;
3. Written informed consent.

Exclusion criteria

1. Total IQ < 55 (WISC) and/or inability to comply with the protocol-specified procedures for the duration of the study, including treatment, blood sampling to control diuretic effects;
2. Presence of a severe medical or genetic disorder other than related to ASD 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 behavioural treatmen during studyt;
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 <17 kg.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-06-2017
Enrollment:	172
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:	16-08-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	19-10-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	22-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Approved WMO

Date:	04-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-11-2017
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: 20585
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-002875-81-NL
CCMO	NL58621.041.16

Study results

Date completed:	01-12-2020
Results posted:	09-02-2021

First publication
09-02-2021

URL result
URL
Type
int
Naam

M2.2 Samenvatting voor de leek
URL

Internal documents
File