The glutamate/GABA balance as novel therapeutic target for psychotic and cognitive symptoms in 22q11.2 deletion syndrome

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

Summary

ID

NL-OMON52172

Source
ToetsingOnline

Brief title
Riluzole in 22q11.2 DS

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Structural brain disorders
- Schizophrenia and other psychotic disorders

Synonym
Velocardiofacial syndrome (VCFS); DiGeorge syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Stanford University

Intervention

Keyword: 22q11.2DS, cognitie, psychose, riluzole

Outcome measures

Primary outcome

The primary study endpoint will be the change in glutamate and GABA

concentrations in the anterior cingulate cortex.

Secondary outcome

The secondary endpoint will be the change in psychotic and cognitive symptom

severity.

Study description

Background summary

22q11.2 deletion syndrome is a genetic disorder caused by a microdeletion on the long arm of chromosome 22 and is associated with an increased risk of developing a variety of psychiatric disorders, including psychotic disorders, and cognitive dysfunction. Both idiopathic psychosis and 22q11DS are associated with cognitive decline, which has been found to be steeper in those 22q11.2DS patients developing psychosis. Patients with 22q11DS and comorbid psychosis have been found to be less responsive to several dopamine-targeting antipsychotics and more susceptible to their potential adverse effects. Therefore, there is a strong need for novel therapeutics targeting other neurotransmitters to reduce psychotic and cognitive symptoms, and disease burden in these patients. Candidate neurotransmitters are glutamate and γ-aminobutyric acid (GABA). The role of both neurotransmitters in psychosis is increasingly acknowledged and studied. Altered glutamate and GABA transmission in 22q11DS may be caused by reduced proline dehydrogenase (PRODH) (also known as proline oxidase) enzyme activity resulting from haploinsufficiency of the PRODH gene. PRODH is important for breaking down proline. Proline is converted to glutamate and acts as a co-agonist at the glutamatergic NMDA receptor.

Decreased PRODH enzyme activity can thus lead to increased proline levels and subsequently, increased activation of the NMDA receptor and excessive glutamate release. Indeed, increased proline levels have been reported in 22q11DS. Moreover, a previous study by our research group reported hyperprolinemia in 31.3% of 22q11DS patients. Although hyperprolinemia has been found to be a risk factor for psychotic disorders, the association between hyperprolinemia and proline levels and brain glutamate levels has not been directly studied in-vivo. However, preclinical studies demonstrated altered glutamate and GABA levels in PRODH knock-out mice. Therefore, it can be hypothesized that modulating the glutamate/GABA balance will alleviate cognitive and psychotic symptoms in 22q11DS, which is supported by our recent pilot data.

Study objective

The objective of this study is to examine the effect of riluzole on the glutamate/GABA balance in the brain in patients with 22q11.2DS. The secondary objective is to examine the effects of riluzole on psychotic symptoms and cognitive functioning. In this manner we can increase our insight in the neurobiological underpinnings of these symptoms.

Study design

Partially blind, fixed-order cross-over trial in 22q11.2DS patients.

Intervention

All subjects will undergo two 8-week intervention periods, once with placebo and once with 100 mg. riluzole daily (50 mg. twice daily).

Study burden and risks

The burden and risks associated with this study are moderate. Patients will undergo two 8-week intervention periods, once with placebo and once with riluzole. Riluzole is an approved drug registered in the Netherlands for amyotrophic lateral sclerosis (ALS). Potential side effects include a.o. tiredness, nausea, headache and are mild and transient when they occur. In some cases, riluzole can cause more serious side effects including neutropenia, shortness of breath, symptoms of hepatitis and pancreatis. Patients are instructed to contact the research team in case the experience acute fever, acute and heavy stomach ache, shortness of breath or dark urine or jaundice. In these case, clinical protocol will be followed and treatment with riluzole terminated if necessary. Patients will be screened for contra-indications (abnormal liver function tests and pregnancy). Subjects will have to come to Scannexus in Maastricht twice and undergo MRI scanning. In addition, at the end of both intervention periods a blood sample will be taken to determine liver function and riluzole plasma levels. Potential disadvantages of the MRI

scanner for the participant are I) loud noise, II) dizziness and III) metallic taste in the mouth. These potential effects of the MRI scan are considered mild and transient. Furthermore, abnormalities in psychiatric questionnaires and cognitive functioning can potentially be found. If an abnormality is found, we will notify the participants* general practitioner. The study is group related; it is only possible to examine the efficacy of riluzole on psychotic and cognitive symptoms in 22q11.2DS in this particular population.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

• Confirmed diagnosis of 22q11.2 deletion syndrome established by FISH, microarray or MLPA
analysis.

• 16 year or older of age and mentally competent (determined by an experienced physician) to
decide about participation and give informed consent.
• 16 years, incompetent to provide written informed consent. In these cases consent will be
obtained from the legal representative of the subject.
• Presence of psychotic and/or cognitive symptoms (defined as a score of >=4, moderately ill, on the
Clinical Global Impression-Schizophrenia Scale (CGI-SCH)).

Exclusion criteria

• Other chromosomal abnormalities.
• Current substance abuse / dependence.
• Use of psychotropic medication and / or first-generation antipsychotics or clozapine, with the
exception of second-generation antipsychotics.
• Contraindications for MRI.
• Pre-existing liver function disorders and / or ALAT/ASAT > 3x ULN.
• Contraindications for riluzole.
• Pregnancy, or trying to get pregnant and breastfeeding.
• In case of mentally incompetent patients, resistance to participation will be an additional exclusion
criterion.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-03-2022

Enrollment:	46
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	21-06-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-08-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-11-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-12-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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: 28681
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-002011-61-NL
CCMO	NL77267.068.21
Other	Nummer nog niet toegekend