Riluzole in 22q11DS

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON28681

Source
Nationaal Trial Register

Brief title
Riluzole 22q11DS

Health condition

22q11.2 deletion syndrome / psychotic disorder

Sponsors and support

Primary sponsor: MUMC
Source(s) of monetary or material Support: Stanford University

Intervention

Outcome measures

Primary outcome

The main endpoint will be the change in psychotic and cognitive symptom severity.

Secondary outcome

The secondary study endpoint will be the change in glutamate and GABA concentrations in the anterior cingulate cortex (ACC)

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. The objective of this study is to examine the efficacy of riluzole, a modulator of the glutamate /GABA balance, for treatment of psychotic symptoms and cognitive impairment in 22q11.2DS patients. The secondary objective is to examine effects of riluzole on the glutamate/GABA-balance in order to increase insight in the neurobiological underpinnings of these symptoms.

Study objective

Riluzole treatment will reduce psychotic and cognitive symptoms

Study design

Three

Baseline: primary outcome measures: psychotic symptom severity determined by the Positive and Negative Syndrome Scale (PANSS) and cognitive functioning assessed with the Computerized Neurocognitive Battery (CNB)

Intervention period 1: primary outcome measures: psychotic symptom severity determined by the Positive and Negative Syndrome Scale (PANSS) and cognitive functioning assessed with the Computerized Neurocognitive Battery (CNB) and secondary outcome measures: ACC glutamate and GABA concentrations (1H-MRS)

Intervention period 2: primary outcome measures: psychotic symptom severity determined by the Positive and Negative Syndrome Scale (PANSS) and cognitive functioning assessed with the Computerized Neurocognitive Battery (CNB) and secondary outcome measures: ACC glutamate and GABA concentrations (1H-MRS)

Intervention

8 - week riluzole treatment

Contacts

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Eligibility criteria

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.
• 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.
• Contraindications for MRI.
• Contraindications for riluzole.
• Pre-existing liver function disorders and / or ALAT/ASAT > 3x ULN.
• Pregnancy or trying to get pregnant and breastfeeding.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Non-randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2021
Enrollment:	45
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	15-07-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 52172
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9611
CCMO	NL77267.068.21
OMON	NL-OMON52172

Study results