The effect of glycopyrroniumbromide on nocturnal clozapine induced sialorrhea in psychiatric patients: a randomized, cross-over, double blind, placebo controlled trial with an extended open label phase (QUITSPIT study)

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Main objective: to determine the effect, defined as the percentage of patients that show a clinical relevant improvement on the severity of complaints of nocturnal sialorrhea, of oral glycopyrroniumbromide in comparison with placebo in psychiatric...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39699

Source
ToetsingOnline

Brief title
QUITSPIT-study

Condition

- Other condition
- Salivary gland conditions
- Therapeutic and nontherapeutic effects (excl toxicity)

Synonym
drooling, hypersalivation

Health condition

behandeling van een bijwerking (speekselverlies) van een geneesmiddel (iatrogeen effect)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Foreest Medical School;onderdeel van het Medisch Centrum Alkmaar (1e geldstroom is onderzoeksgeld ziekenhuisapotheek UMC Utrecht)

Intervention

Keyword: clozapine-induced-sialorrhea, glycopyrroniumbromide, hypersalivation

Outcome measures

Primary outcome

The percentage of patients showing a clinically significant improvement on the

severity of complaints of nocturnal sialorrhea, defined as a score

of 1 ("very much improved") or 2 ("much improved") on the PGI-I (Patient Global

Impression of improvement questionnaire).

Secondary outcome

The mean score on the PGI-I, PGI-S, NHRS (Nocturnal Hypersalivation Rating

Scale) and MSQ (Medication Satisfaction Questionnaire), the

occurence of side effects and patients satisfaction with oral

glycopyrroniumbromide.

Study description

Background summary

Hypersalivation or sialorrhea is one of the most frequently occuring side effects of clozapine use with an incidence ranging from 30 to 90%. In most cases it occurs at the start of clozapine treatment, mostly at night and persists during further treatment.
Several symptomatic (farmacologic) therapies exists that reduce sialorrhea by reducing saliva excretion. There is no drug therapy registered for clozapine induced sialorrhea and most of the medications that are used often have central side effects.
Glycopyrroniumbromide is a quaternairy ammonium compound and an effective and potent anticholinergic agent with poor penetration across the blood-brain-barrier, causing less central side effects than other anticholinergics.
In a number of relatively small studies oral glycopyrroniumbromide was found to be effective in reducing sialorrhea in children with cerebral palsy, patients suffering from Parkinson*s disease and schizophrenic patients using clozapine. The effect on nocturnal sialorrhea in patients using clozapine compared to placebo has not been studied yet.

Study objective

Main objective: to determine the effect, defined as the percentage of patients that show a clinical relevant improvement on the severity of complaints of nocturnal sialorrhea, of oral glycopyrroniumbromide in comparison with placebo in psychiatric patients treated with clozapine.

Secondary objectives:
1) to determine patient's satisfaction with oral glycopyrroniumbromide compared to placebo regarding nocturnal sialorrhea
2) to determine the effect of oral glycopyrroniumbromide compared to placebo on patient's opinion to clozapine
3) to determine the effect of oral glycopyrroniumbromide compared to placebo on the occurence of side effects
4) previously mentioned primary and secundary objectives in a subset of patients receiving a double dose of oral glycopyrroniumbromide in an open label extension compared to single dose oral glycopyrroniumbromide treatment in the randomized, double-blind phase

Study design

Double blind, randomized, cross-over trial with an extended open label phase. The length of the study will be, from randomisation visit, 3 or 5 weeks in total. To this comes a period of screening and baseline measurements before (period 1), it takes about 7 days, with a range of up to 28 days. The first phase (period/week 2 up to and including period/week 4) of the study will be a randomised, double blind, placebo controlled and cross-over design, where an equal amount of glycopyrroniumbromide oral solution 0,2 mg/ml (1 mg = 5 ml) and

placebo oral solution are compared.
The second phase (period/week 5 and 6) is an extended open-label phase, with patients receiving a double dose of glycopyrroniumbromide oral solution 0,2 mg/ml (2 mg = 10 ml) if they well tolerated the oral solution in the first phase of the study.
In period/week 2 and period/week 4 the patients will take during 6 days oral glycopyrroniumbromide 1 mg or placebo before the night. In period/week 3 and period/week 5 no studymedication is taken (wash-out period). In a weekly consult in period/week 2 up to and including period/week 6 the patient scores the severity and possible improvement of the sialorrhea. Also the occurence of side effects will be questioned.
In period/week 6 the patients who well tolerated the glycopyrroniumbromide oral solution in the first phase of the study receive a double dose glycopyrroniumbromide oral solution 2 mg during 6 days before the night. At the end of period/week 4 or 6 a concluding visit will take place.

Intervention

Alternating treatment with 1 mg oral glycopyrroniumbromide or placebo for 1 week interrupted by 1 week wash-out. Patients that have no problems enduring the 1 mg glycopyrroniumbromide will be treated with 2 mg glycopyrroniumbromide in the extended open label phase.

Study burden and risks

The risk will be mainly possible side effects of anticholinergic origin. In clinical studies with oral glycopyrroniumbromide the following side effects are most reported: dry mouth, miction problems, nausea, obstipation, flushing, nasal congestion and inner unrest. Furthermore, there is a small risk (< 2%) of cardial effects with oral usage, like tachycardia and palpitations.

The strain of the study includes five or seven visits at the researcher. In four to six of these visits (depending on the participation in the extended phase) five short questions will be asked, a set of side effects questioned and the occurence of obstipation will be asked.
Physical exam: two times blood pressure and body weight measurements, also four or six times (depends on the participation in the extended phase) measurement of pulse frequency.

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

-patients using clozapine who are diagnosed with schizophrenia, a schizoaffective disorder or other psychiatric condition meeting DSM-IV criteria;
-a clozapine dosage that remained unchanged for one months prior to inclusion;
-age between 18 and 65 years;
-nocturnal sialorrhea defined as a score > 2 on the PGI-S (Patient Global Impression of Severity Questionnaire)
-no change in dosages of specific comedication (clonidine, sulpride, moclobemide) that potentially reduces salivary flow for 16 days prior to inclusion
-the patients is able to answer questionnaires during a weekly consultation (by telephone) with the researcher
- the patient is willing to give informed consent for participating in the study
-the patient is, according to the treating psychiatrist, competent and able to give informed consent for participating in the study.

Exclusion criteria

-known hypersensitivity to glycopyroniumbromide, sorbic acid or saccharine sodium;

-a comorbidity associated with sialorrhea (Parkinsons disease, cerebral palsy);
-one of the following comorbidities: inadequately treated constipation, urine retention, bladder obstruction
-concurrent use of anticholinergic agents: tricyclic antidepressants or anticholinergics (atropine, ipratropiumbromide, trihexyfenidyl,
biperiden, scopolamine, oxybutinine);
-concurrent use of medications that potentially interact with glycopyrroniumbromide (potassium chloride retard tablets, digoxine, corticosteroids)
-pregnancy or lactation
-a history of myasthenia gravis, cardiac arrhythmia, symptomatic coronary insufficiency, glaucoma, pyloris stenosis, paralytic ileus, prostate hypertrophy, renal failure
-unable to autonomic medication intake

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-04-2013
Enrollment:	33
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing, er is geen specialiténaam
Generic name:	glycopyrroniumbromide

Ethics review

Approved WMO Date:	04-07-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-10-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-08-2014
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-002299-15-NL
CCMO	NL40810.041.12