Oxytocin treatment in neonates and infants aged from 0 to 3 months with prader-willi syndrome: a study of the safety and efficacy on oral and social skills and, feeding behavior of intranasal administrations of oxytocin vs. placebo (phase iii clinical trial)

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The primary objective is to demonstrate the superiority versus placebo of a 4 weeks intranasal OT administration on oral skills assessed by the Neonatal Oral-Motor Assessment Scale (NOMAS) in infants with PWS aged less than or equal to 3 months at...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55101

Source
ToetsingOnline

Brief title
OTBB3

Condition

- Neurological disorders congenital
- Inborn errors of metabolism
- Neonatal and perinatal conditions

Synonym
Prader-Willi-syndrome, rare gentic disease

Research involving
Human

Sponsors and support

Primary sponsor: CHU de TOULOUSE
Source(s) of monetary or material Support: French Ministry of Health (PHRC-N 2015);Paediatric Clinical Research Infrastructure Network - PedCRIN (2017);OT4B;Prader-Willi france

Intervention

Keyword: Infants, Oxytocin, Prader-Willi syndrome

Outcome measures

Primary outcome

The primary endpoint is the proportion of neonates/infants who achieve a score

*10 i.e a normal or sub-normal score (defined as responders) on

sucking/swallowing as assessed by the Neonatal Oral-Motor Assessment Scale

(NOMAS) centrally scored on videos, after 4 weeks (V4) OT/ Placebo intranasal

treatment.

Supportive data:

- Changes of NOMAS score from baseline (V1) at 1 week (V3) and 4 weeks (V4)

- % of responders to NOMAS at 1 week (V3)

- % of infants with abnormal score and who reached a null score (normalisation)

on the item *incoordination of suck/swallow and respiration* after treatment at

1 (V3) and 4 (V4) weeks.

Secondary outcome

The secondary endpoints are: *

- Proportion of infants with abnormal score of videofluoroscopy at baseline (on at least one of the two items) who reached a normal score after 4 weeks treatment for all of the 2 items, namely i) pharyngeal propulsion ii) airway protection at 4 weeks (V4).
- The change from baseline of the Alarm Distress Baby Scale (ADBB) score at 4 weeks (V4).
- The change from baseline of the Coding Interacting Behaviour (CIB) subscores at 4 weeks (V4).
- The change from baseline of proficiency score which is the volume of milk taken in the first five minutes of feeding at 1 week (V3) and at 4 weeks (V4).
- The change from baseline of ghrelin (unacylated/UAG and acylated/AG) concentration at 1 week (V3) and at 4 weeks (V4).
- The change from baseline (V1) of the parent assessment of feeding (Severity) at 4 weeks (V4)
- The Parent assessment of feeding (Improvement) at 4 weeks (V4)
- The change from baseline of plasma OT concentration at 4 weeks (V4).
- Biological safety parameters (natremia, plasmatic osmolality, capillary blood glucose, total bilirubin level, urinary density, kalemia), vital signs, ECG and emergent adverse events in all groups of patients.

Study description

Background summary

Prader-Willi syndrome (PWS) is a genetic neurodevelopmental orphan disease caused by the lack of expression of paternally derived alleles of imprinted genes in the 15q11-q13 chromosomal region. It is the main cause of syndromic obesity, with an incidence of around 1/20 000 at birth. From birth to 9 months, all infants with PWS display severe hypotonia combined with poor appetite similar to anorexic behavior, poor suck and swallowing troubles that lead to nasogastric tube feeding in 80% of cases to ensure normal weight gain. Genetic diagnosis made in the first months of life based on the neonatal phenotype initiates multidisciplinary care and offers a unique window of opportunity for early treatment. Both PWS mouse models and patients display a significant decrease in the number and volume of hypothalamic Oxytocin (OT)-producing neurons. OT is a neuropeptide which, besides its known actions on uterus and lactation, is involved in social interactions and mother-infant bonding. Interestingly, OT has opposite effects throughout life i.e. stimulating food intake in the neonatal period and then controlling satiety later on. Our hypothesis is that a deficit of OT may explain the neonatal phenotype with poor feeding and social cues and may be involved in the lack of satiety later in life in PWS. We already performed a tolerance study (OTBB1, phase I) and a proof-of-concept study (OTBB2, phase I/II multiple-ascending dose safety/efficacy). We showed that OT is well tolerated in neonates/infants with PWS and improves feeding and social skills when administered early in life. These results offer promising perspectives for early treatment in neurodevelopment diseases with feeding problems and prompt us to perform a phase III study to demonstrate the effect of OT on oral and social skills in neonates/infants with PWS. This phase III is a multicentric, prospective, randomized trial which comprises two parts: a part 1 which is an efficacy study (OT versus Placebo) and a part 2 which is an exploratory study to provide further information on the use of intranasal OT.

Study objective

The primary objective is to demonstrate the superiority versus placebo of a 4 weeks intranasal OT administration on oral skills assessed by the Neonatal Oral-Motor Assessment Scale (NOMAS) in infants with PWS aged less than or equal to 3 months at inclusion.

The secondary objectives are to document the effects of 1 week and 4 weeks intranasal OT administration versus Placebo on:
- Sucking/swallowing troubles assessed by videofluoroscopy
- Social withdrawal assessed by Alarm Distress Baby Scale (ADBB)
- Child state, social engagement and mother-infant interactions assessed by Coding Interactive Behaviour (CIB) subscores *
- Food intake assessed by proficiency score
- Levels of circulating forms of ghrelin
- Parent assessment of feeding
- OT levels
- To document the safety of repeated OT administration for 4 weeks or 8 weeks

with total follow-up over 26 weeks.

The exploratory objectives are to further evaluate the effects of intranasal OT vs. placebo on:
- Videofluoroscopy total score
- CIB subscores (parental sensitivity, parental intrusiveness, child withdrawal, dyadic joint negative state)
- Duration of nasogastric tube (NGT) feeding
- Modifications of brain connectivity during resting state (MRI)
- Growth, weight and Head Circumference
- Nutritional phase
- Parental skills
Blood and gut microbiota
- OT circulating levels after OT/placebo administration
- Urinary OT levels Parent observation of feeding (diary-report)
And to
- Compare 4 vs. 8 weeks of intranasal OT administration in terms of NOMAS score and other criteria.
- Compare delayed vs. non-delayed administration of intranasal OT administration in terms of NOMAS score and other criteria.
- Evaluate the maintenance of effect in terms of other criteria.

For all these parameters: NOMAS score, ADBB score, CIB subscores, circulating forms of ghrelin, OT levels, growth and body weight, HC, nutritional phase, parental skills, blood and gut microbiota:
- Perform correlations on biological and MRI biomarkers, and clinical endpoints.

Study design

Phase III: prospective, randomized, Placebo controlled double blind study for 4 weeks, two-arm superiority trial with parallel groups.

Patients will be allocated in four groups at the time of randomization according to a randomization scheme per centre that will randomize patients in a 1:1:1:1 ratio in Group 1, 2, 3 or 4 as described below;
Group 1 will receive OT for 8 weeks then Placebo for 4 weeks
Group 2 will receive OT for 4 weeks then Placebo for 8 weeks
Group 3 will receive Placebo for 4 weeks then OT for 8 weeks
Group 4 will receive Placebo for 4 weeks then OT for 4 weeks then Placebo for 4 weeks
After Week 12, neither OT nor Placebo will be administered.

Intervention

The investigational medicinal product in this study is intranasal oxytocin. A

matching intranasal placebo solution will also be provided as this is a double-blind study.

Study burden and risks

There is no specific treatment for sucking-swallowing problems observed in neonates/infants with PWS. Based on preliminary results obtained in OTBB2 study regarding the efficacy of OT not only on sucking-swallowing problems but also on social behavior and mother-infant interactions without any safety concern, it is justified to study the safety and the efficacy of OT in a double-blind Placebo controlled study. As exposure to OT will be extended either to 30 or 60 days depending upon the group of patients allocated at the randomization, we cannot exclude the onset of adverse event that would not occur during a short 7-day exposure. However, the study design comprises 8 visits from the first OT administration and safety will be closely monitored. Furthermore, extended patient follow-up during the 26 weeks study period will be scheduled. Long term safety will be also monitored during a study for all the children up to 4 years. The risks of participation in the study are thus minimized and the information to be gained from 30 to 60 days OT exposure in this cohort of neonates/infants with PWS is of critical importance. Indeed, should the results confirm our previous results, the benefit for children with PWS and for their family will be highly significant. In any case, all patients included will benefit from an optimal follow-up.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

- Male or female neonate or infant, with PWS genetically confirmed
- Age <92 days (plus a tolerance of up to 8 days maximum) (for preterm infants, born before 37 weeks, corrected age will be applied)
- Signed informed consent obtained from the parents/holders of parental authority
- Parents willing and able to comply with all study procedures.

Exclusion criteria

- Neonate or infant admitted to the emergency care unit for ongoing life-threatening comorbidities like severe respiratory, cardiovascular or neurological abnormalities
- Neonate or infant with prolongation of the QT interval
- Neonate or infant without medical insurance
- Neonates or infants whose parents* situations may jeopardize the interpretation of the results
- Neonate or infant with known hypersensitivity to oxytocin or the excipients of the product
-Neonate or infant with concomitant treatment prolonging QT interval (cf. annex 16).
-. Neonate or infant with family history of genetic pathology causing QT interval prolongation.
-. Neonate or infant with hypokalemia (clinically relevant at the discretion of the doctor).
-. Neonate or infant participating simultaneously in another interventional study.
-. Neonates or infants whose parents* situations may jeopardize the interpretation of the results.
-. Neonates or infants whose parents* refuse video recording, required to respond to the primary objective of the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	08-09-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

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	EUCTR2019-002385-12-NL
ClinicalTrials.gov	NCT04283578
CCMO	NL72188.078.20