Pharmacokinetic evaluation and tolerability of dry powder tobramycin via the Cyclops® in children with cystic fibrosis

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The main objectives are to investigate the pharmacokinetic properties of DP tobramycin via the Cyclops® at different dosages in children with CF, together with the local tolerability.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50074

Source
ToetsingOnline

Brief title
DPI-tobra-child

Condition

- Bacterial infectious disorders
- Congenital respiratory tract disorders

Synonym
Cystic Fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cystic Fibrosis, Dry powder inhalation, Tobramycin

Outcome measures

Primary outcome

The following pharmacokinetic parameters will be calculated: AUC0 till 8-12

(area under the curve from 0 till 8-12 h)

Secondary outcome

The following pharmacokinetic parameters will be calculated: actual dose (dose

minus remainder in inhaler after inhalation), Cmax (maximum plasma

concentration), Tmax (time to maximum plasma concentration), Ka (absorption

rate constant), T1/2 el (terminal elimination half-life), CL/F (clearance

following pulmonary administration (F= bioavailability)). Local tolerability of

DP Tobramycin is determined by scoring adverse events, specifically coughing,

and lung function measurement.

Study description

Background summary

Cystic fibrosis is the most common life-shortening autosomal recessive disease among Caucasian populations. It is a chronic progressive disease causing deterioration of pulmonary function, and of general condition as well. Although it is a multisystem disease, the primary cause of death is respiratory failure, resulting from chronic pulmonary infection. Pseudomonas aeruginosa is the predominant pathogen. The presence of P. aeruginosa in patients with CF is an unfavourable prognostic indicator and is associated with accelerated lung tissue destruction and loss of lung function, subsequently leading tot increased morbidity and mortality. Preventing, limiting and treating chronic infection with P. aeruginosa is therefore crucial in the management of CF, to

improve survival and quality of life.
Currently most children with CF who are colonized with P. aeruginosa receive inhaled tobramycin every other month, mostly by use of a nebulizer. This delivery system however has several disadvantages. For example, the nebulisation itself and the cleaning of the nebulizer is time consuming. This places a high burden on a CF patient, especially for children, which will negatively influence compliance and quality of inhalation, thereby jeopardizing effective treatment. Therapy with a (disposable) dry powder inhaler (DPI) is less time consuming. Besides this, nebulisation brings the risk of auto-re-infection of the patient (contamination of nebulisation fluid and/or device). Other more technical disadvantages of nebulisation are a low lung deposition and pollution with tobramycin in the surrounding environment. With an efficient DPI, a three to six fold higher lung deposition compared to a nebulizer can be obtained. Nebulised tobramycin is used most in routine care, but sometimes a DPI is used, for example the Podhaler®. Although the dispersion behaviour of these dry powder systems is often good, the engineering processes make the products expensive, and the high excipient fractions make the inhaled powder doses high. Furthermore because these devices are not disposable, there is a risk of bacterial resistance development in the device. Next to this is the hygroscopic nature of tobramycin a risk for good dispersion when a used DPI is stored inappropriately and powder residues in the inhaler become sticky or even liquefied when they absorb moisture from the air. There is one disposable DPI for tobramycin available, called the Cyclops®, though this DPI is not registered for children with CF. We will investigate dry powder tobramycin (DP tobramycin) in the Cyclops® in children with CF.

Study objective

The main objectives are to investigate the pharmacokinetic properties of DP tobramycin via the Cyclops® at different dosages in children with CF, together with the local tolerability.

Study design

Single center, single ascending, single dose study.

Intervention

All patients have to inhale dry powder tobramycin via the Cyclops in three different dosages, and once tobramycin via wet nebulization.

Study burden and risks

Target population of this study consists of children aged 6-18 years, because no information is available for inhalation of tobramycin using the Cyclops® in this population. Moreover, especially for children with CF a more easy to use

and less time consuming treatment may improve quality of life.
Children participating in this study will receive instructions before using the DPI and their inspiratory flow will be tested. Before each test dose an infusion catheter will be inserted and after each test dose blood will be collected. To investigate safety, lung function tests will be performed before and 15, 30 and 90 minutes after inhalation and the occurrence of adverse events will be scored.
Tobramycin is a registered drug for the treatment of chronic P. aeruginosa infection in CF-patients of 6 years and older. Inhalation of tobramycin is proven to be effective and safe in multiple studies. Dry powder tobramycin inhalation via the Cyclops® has been evaluated in adults with non-CF bronchiectasis. In this study a good drug dose * serum concentration correlation was obtained in adults, and the dry powder tobramycin inhalation via the Cyclops has been found save with only mild tobramycin-related cough was reported once.

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

- Clinical diagnosis of CF and a positive sweat test or two CF-related mutations
- Age 6 - 18 years
- Ability to breathe through a mouthpiece and to use the Cyclops
- Ability to perform pulmonary function tests
- Written informed consent (child and parents)

Exclusion criteria

- Acute exacerbation
- FEV1 < 60%
- Subjects with known or suspected renal, auditory, vestibular of neuromuscular dysfunction, or with severe, active haemoptysis
- History of adverse events on previous tobramycin or other amino glycoside use
- History of adverse events on previous dry powder inhalation
- Concurrent use of cyclosporine, amphotericin B, cephalosporins, polymyxins, vancomycin and NSAID*s

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-08-2018
Enrollment:	10

Type:	Actual

Medical products/devices used

Generic name:	Cyclops
Registration:	No
Product type:	Medicine
Brand name:	Tobramycin
Generic name:	Tobramycin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-04-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-01-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-02-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2016-005014-21-NL
CCMO	NL60250.000.17