Targeting Antibiotics to Pseudomonas Aeruginosa in Small airways (TAPAS) study in patients with cystic fibrosis: pharmacokinetics (PK)

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Primary objective: To determine the safety of once daily inhalation of the recommended daily dose of tobramycin with the Akita® and the PARI-LC® Plus nebulizer in patients with CF. Systemic absorption can be used as surrogate parameter for safety....

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

Summary

ID

NL-OMON40371

Source
ToetsingOnline

Brief title
TAPAS-PK study in patients with CF

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Bacterial infectious disorders
- Respiratory tract infections

Synonym
Cystic fibrosis en CF

Research involving
Human

Sponsors and support

Primary sponsor: HagaZiekenhuis
Source(s) of monetary or material Support: Fondsen van dr. H.M. Janssens (co-investigator) verkregen uit consultancies en adviserende rollen

Intervention

Keyword: Cystic fibrosis, Inhalation, Pharmacokinetics, Tobramycin

Outcome measures

Primary outcome

Primary endpoint: systemic bioavailability of inhaled tobramycin, defined as

serum tobramycin AUC0-24hr.

Secondary outcome

Secondary endpoints include: serum tobramycin peak and trough levels, time to

maximum serum level, adverse events.

Study description

Background summary

Small Airways Disease (SAD) plays an important role in the pathophysiology of cystic fibrosis (CF) lung disease. Chronic infection and airway inflammation lead to progressive structural tissue damage. Chronic infection with Pseudomonas aeruginosa (Pa) causes faster progression of CF lung disease. Inhaled tobramycin has proven to be effective in delaying lung function decline in chronic Pa infections. However, SAD is not improving with current inhaled therapy, either with standard jet-nebulizer or with dry powder inhaler. The newly introduced smart nebuliser Akita® is substantially more efficient to reach the small airways. Recently, the Akita® has been shown to improve SAD when delivering dornase alpha. Hence, the use of smart nebulisers like the Akita® for tobramycin inhalation therapy in CF patients chronically infected with Pa disease might significantly reduce SAD.
The bactericide efficacy of tobramycin is better with high peak levels. For intravenous use, tobramycin once daily is as effective as thrice daily and results in less toxicity. Inhaled tobramycin is dosed twice daily. Whether dosing once daily is as effective has never been studied. This would

significantly reduce treatment burden.
Before we can investigate whether tobramycine inhalation once daily with the Akita is as effective or more effective than once or twice daily inhalation with the standard nebulizer, it is important to investigate tobramycin pharmacokinetics. No information about tobramycin pharmacokinetics following once daily inhalation exists. Systemic absorption can be used as surrogate for safety.

Study objective

Primary objective: To determine the safety of once daily inhalation of the recommended daily dose of tobramycin with the Akita® and the PARI-LC® Plus nebulizer in patients with CF. Systemic absorption can be used as surrogate parameter for safety.

Secondary objectives:
- To assess tolerability of inhalation of a double dose of tobramycin by registering adverse effects (coughing, bronchospasm).
- To compare pharmacokinetics of the recommended dose of inhaled tobramycin once daily with either the Akita® or PARI-LC® Plus to pharmacokinetic data from the literature about standard twice daily tobramycin inhalation with the PARI-LC® Plus.

Study design

Open label, randomised controlled cross-over trial.

Intervention

Intervention: Ten patients will be inhaling tobramycin twice at the outpatient clinic department in a cross-over setting: once with the Akita® nebulizer and the other time with the PARI-LC® Plus nebulizer.

Study burden and risks

The target population in this study are adults. The risks associated with participation are small. Tobramycin (BRAMITOB®) is a registered drug since 2007 for treatment of chronic PA lung infection in CF-patients 6 years and older. Inhalation of tobramycin in children with CF is proven to be effective and safe in multiple studies. The Akita® nebulizer is already in use off label for inhalation of tobramycin. However, information on the efficacy in improving SAD is lacking. Serious and life threatening side effects have not been described. The Akita® set to small airways design may lead to a higher systemic exposure of tobramycin in patients. Due to the dose reduction, proven to be safe in a previous study (9), all potential toxic effects are expected to be small and

presumably reversible.

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

* Age * 18 years;
* FEV1 predicted * 30%;
* Clinical diagnosis of CF and a positive sweat test or two CF-related mutations;
* Chronic PA colonization requiring;
* Ability to breathe through a mouthpiece and to use the inhaler;
* Ability to perform lung function tests;
* Written informed consent.

Exclusion criteria

* Severe acute exacerbation of pulmonary infection (needing intravenous treatment);
* Patients receiving intravenous tobramycin treatment;
* Patients who are pregnant, planning to become pregnant or breastfeeding;
* Known impaired kidney function (estimated creatinine clearance < 60 ml/min);
* Known aminoglycoside hypersensitivity;
* Therapy (e.g. furosemide) or disease which may complicate evaluation of the study protocol, as judged by the investigator;
* Participation in another drug-investigating clinical study at the start or within 1 month prior to the start;
* Inability to follow instructions of the investigator.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-03-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Akita nebulizer
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Bramitob

Generic name:	Tobramycin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-12-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-01-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2013-004488-30-NL
CCMO	NL46747.098.13