A phase I study investigating local tolerability and pharmacokinetics of Isoniazid (INH) inhalation by wet nebulization in patients with tuberculosis

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This study has been transitioned to CTIS with ID 2024-517793-25-00 check the CTIS register for the current data. The primary objective of this study is to investigate the local tolerability of isoniazid inhalation by wet nebulization at ascending...

Ethical review	Approved WMO
Status	Pending
Health condition type	Mycobacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON56472

Source
ToetsingOnline

Brief title
INHalation-01

Condition

- Mycobacterial infectious disorders

Synonym
Tuberculosis

Research involving
Human

Sponsors and support

Primary sponsor: Rijksuniversiteit Groningen

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

Intervention

Keyword: inhalation, isoniazid, pharmacokinetics, tuberculosis

Outcome measures

Primary outcome

For the local tolerability, spirometry will be performed and adverse events

will be recorded.

Secondary outcome

The following serum pharmacokinetic parameters will be calculated: AUC0-24

(area under the concentration-time curve 0-24 h post-administration), Cmax

(maximum serum concentration), Tmax (time to maximum serum concentration).

Study description

Background summary

To halt the global tuberculosis (TB) crisis, and particular the ongoing threat of drug-resistant TB (DR-TB), it is essential to reduce transmission. This could be done by shortening the period that patients with pulmonary TB secrete viable bacilli, and are therefore contagious to others, by prompt initiation of effective treatment. Pulmonary administration of anti-TB drugs might play an important role since it yields higher local concentrations and lower systemic concentrations compared to systemic (oral or parenteral) administration. Isoniazid (INH) has very high bactericidal activity and is one of the most effective drugs in the treatment of TB. Although the occurrence of mutations leading to resistance to INH at systemic concentrations has hindered the use of this drug, INH can still be effective when administered in a high concentration at the site of infection even in case of drug resistance. This cannot easily be achieved by oral dosing because of the associated risk of systemic toxicity. However, pulmonary administration of INH may be a solution. The concept of inhalable antimicrobials is not new; for example it is a well-established therapy for the treatment of Pseudomonas aeruginosa infection in cystic fibrosis patients. INH has been used by inhalation before in patients with TB but only up to a dose of 200 mg/day. In this protocol, we will perform a local

tolerability and pharmacokinetic study of higher doses of INH inhalations by wet nebulization in patients with TB. We hypothesize that single doses up to 1200 mg INH are safe.
In future studies we want to demonstrate that high intrapulmonary concentrations enhance the initial reduction of the bacterial load in both drug-susceptible TB (DS-TB) as well as TB with reduced susceptibility to INH. If proven, this novel inhalation-based approach may lead to a massive decline in further spread of (drug resistant) TB.

Study objective

This study has been transitioned to CTIS with ID 2024-517793-25-00 check the CTIS register for the current data.

The primary objective of this study is to investigate the local tolerability of isoniazid inhalation by wet nebulization at ascending dosages. Secondary objective is systemic pharmacokinetics of inhaled isoniazid compared to intravenous dose administration.

Study design

multicenter, ascending dose tolerability study Participants will receive one intravenous dose of 300 mg INH and three inhaled doses of INH by using an e-Flow nebulizer in ascending order (200 mg, 600 mg and 1200 mg) with at least 48 hours and maximal 7 days in between doses. Before each INH administration, an indwelling venous cannula will be inserted and before and after each administration, serum samples will be collected for pharmacokinetic analysis (6 after IV administration and 12 to 13 after every inhalation administration). To investigate local tolerability, lung function tests will be performed once before and twice after inhalation of INH and the occurrence of adverse events will be scored. After every inhalation dose the study team will decide on escalation to the next dose step whereby a drop of forced expiratory volume in the first second (FEV1) of >15 % is considered critical and any reported adverse events will be evaluated.

Intervention

All participants receive in sequence one intravenous dose of isoniazide 300 mg and three inhaled dosies isoniazide inhaled via e-Flow nebulizer in increasing dosing (200 mg, 600 mg and 1200 mg)

Study burden and risks

Patients with DS-TB receive INH as part of usual care and this will temporarily be replaced by levofloxacin during the study period in order not to interfere with the intervention (this is not applicable for other forms of TB). From INH

resistant TB (Hr-TB) it is known that this replacement does not impact on the efficacy of the treatment or its duration. An electrocardiogram will be performed before and after initiation of levofloxacin, because of the potential risk of Qtc prolongation.
There is no benefit with participation in the study. Taking part in the study takes extra time and the measurements such as spirometry and drawing of bloodsamples may give slight inconvenience. Participants may also experience adverse effects of isoniazid inhalations or levofloxacin tablets. Common adverse effects reported with administration of aerosolized antibiotics include wheezing, haemoptysis, and dyspnoea.

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 and older
- Diagnosis of TB with known drug susceptibility, either by culture or molecular testing
- Clinically stable or improving after at least 2 weeks of effective TB treatment
- Obtained written informed consent

Exclusion criteria

- Patients that are pregnant, or breast feeding - History of adverse events on previous or current INH use - FEV1 < 30% predicted - Concurrent use of corticosteroids in varying dose (a stable dose one week before participating and during the study is allowed). - Concurrent use of aluminum containing medicines (i.e. antacids) - Concurrent use of carbamazepine, phenytoin or theophylline Additionally, a potential subject with DS-TB (eliciting switch to levofloxacin) who meets any of the following criteria will be excluded from participation in this study: • History of epilepsy • History of adverse events on previous levofloxacin or other fluorquinolone use • Risk of QTc prolongation (prolonged QTc-interval (>450 msec), long-QT syndrome (LQTS) or concurrent use of high risk QTc prolongating drugs (amiodarone, erythromycin (daily dose > 1000 mg) or sotalol)

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2023
Enrollment:	8

Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	24-01-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2024-517793-25-00
EudraCT	EUCTR2022-004144-10-NL
CCMO	NL83502.056.22