pharmacokinetics and toxicity of linezolid in MDR-TB patients

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To study the pharmacokinetics of linezolid in MDR-TB patients, specifically in the relationship to dose, treatment duration and toxicity.

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

Summary

ID

NL-OMON29905

Source
ToetsingOnline

Brief title
Linezolid in MDR-TB

Condition

- Mycobacterial infectious disorders

Synonym
tuberculosis MDR-TB

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: UMCG zelf/stichting Beatrixoord

Intervention

Keyword: linezolid, MDR-TB, pharmacokinetics, toxicity

Outcome measures

Primary outcome

-Primary: PK of linezolid in MDR-TB patients

Secondary outcome

-Secondary: toxicity related to linezolid; i.e. anemia, and neurotoxicity

Study description

Background summary

MDR-TB is a potentially lethal form of tuberculosis, associated with prolonged suffering, prolonged treatment, and drug toxicity. In MDR-TB, sub-therapeutic drug plasma levels should be avoided as otherwise additional drug resistance due to inappropriate dosing and subsequent selection of less susceptible strains may ensue. In the limited number of potentially helpful agents, linezolid has emerged as a potentially helpful component, but toxicity is an important concern.

In Beatrixoord (UMCG, Haren, the Nertherlands), a specialised centre for treatment of MDR-TB in the Netherlands linezolid has been evaluated in the initial treatment of some MDR-TB patients. From a preliminary evaluation, it appeared that 3/12 patients developed severe toxicity which led to discontinuation of therapy(1). Recently a case series of 3 patients being treated with linezolid was reported. The authors showed that a 50% dose reduction of linezolid led to reduced toxicity. Although the authors suggested that efficacy was maintained they failed to produce evidence for this claim (2). As patients with MDR-TB are typically treated with combinations of drugs, and as response to treatment is a multifactorially determined event, only PK/PD data help to decide whether single agents in a drug combination contribute to total effectiveness. Efficacy of linezolid is correlated with AUC0-24h/MIC (2). To perform a dose reduction without losing efficacy it might be necessary to measure the AUC0-24h/MICratio after the dose reduction. Particularly in case of MDR-TB sub-therapeutic and toxic plasma levels should be avoided.

Study objective

To study the pharmacokinetics of linezolid in MDR-TB patients, specifically in the relationship to dose, treatment duration and toxicity.

Study design

This study is designed as pharmacokinetic study: on day 2 and day 4, on each day 6 blood draws will be taken to evaluate whether target blood concentrations can be achieved with the two dosing regimens studied - i.e., the standard-recommended dosing of 600 mg bid, and 300 mg bid. Plasma samples are analysed using a liquid chromatography-tandem mass spectrometry(3;4). The target-blood concentrations of linezolid assumed to be effective are based on resistance break-off data obtained from the RIVM. The attending physician can decide based on individual results to continue treatment with 600mg or 300mg b.i.d. Monitoring for side effects (affecting blood, nervous- and GI system) is continued during treatment with linezolid.

Intervention

n/a

Study burden and risks

There is a potential benefit for the subjects in this study. As pharmacokinetics of linezolid are evaluated in each individual the decision to reduce dosage of linezolid or stop treatment can be performed based on individual pharmacokinetic findings. As the AUC0-24h /MIC of linezolid is correlated with a favourable outcome therapy is optimised in every individual patient. An potential benefit is monitoring of nervous system side effects with EMG and VEP monitoring. Side effects are now detected before becoming clinical relevant. The burden for participation is sequential venous blood sampling; six samples (each 2 mL) for the two dosing regimens are required; i.e., 24 mLs of blood to be drawn in total. For the purpose of this study, an indwelling intravenous cannula will need to be inserted. Patients may experience some discomfort of the procedure of sampling. The benefit probably outweighs the burden and risk.

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

MDR-TB
attending physician initiates treatment with linezolid

Exclusion criteria

allergy for linezolid

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2006
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Zyvoxid
Generic name:	Linezolid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-09-2006
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2006-004220-36-NL
CCMO	NL13912.042.06