Pharmacokinetics and safety of moxifloxacin; a dose escalation in patients with tuberculosis

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Primary Objective: The main objective of this prospective clinical trial is to compare pharmacokinetics and safety and tolerability of a standard dose (400 mg) with an escalated dose of 600 and 800 mg MFX. Secondary Objectives: * To evaluate limited...

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

Summary

ID

NL-OMON36271

Source
ToetsingOnline

Brief title
Pharmacokinetics and safety of moxifloxacin

Condition

- Mycobacterial infectious disorders

Synonym
tuberculosis

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Stichting Beatrixoord

Intervention

Keyword: Moxifloxacin, pharmacokinetics, safety, tuberculosis

Outcome measures

Primary outcome

Main study parameter/endpoint

Pharmacokinetics

Bound AUC0-24h/MIC ratio

o The percentage of patients who will reach an AUC0-24h/MIC ratio of at least

100 after administration of different dosages (400; 600; 800 mg)

Unbound AUC0-24h/MIC ratio as predictive parameter for efficacy

of unbound MFX dose escalated treatment of tuberculosis

o The percentage of patients who will reach an unbound AUC0-24h/MIC ratio of at

least 60 after administration of different dosages (400; 600; 800 mg)

Bound AUC0-24h/MPC ratio

o Percentage of patients who will reach an adequate AUC0-24h/MPC ratio of at

least 93 after administration of different dosages (400; 600; 800 mg)

Unbound AUC0-24h/MPC ratio as predictive parameter for efficacy

of unbound MFX dose escalated treatment of tuberculosis and suppression of MFX

resistance

o Percentage of patients who will reach an unbound AUC0-24h/MPC ratio of at

least 53 after administration of different dosages (400; 600; 800 mg)

Safety

Percentage of patients having adverse effects, including QT interval prolongation, hypersensitive reactions, diarrhoea, vomiting and hepatic or renal injury

o QT interval in msec

o Percentage of patients developing hepatic toxicity grade >= 2 or 3 CTC

o Percentage of patients developing renal toxicity grade >= 2 CTC

Secondary outcome

Evaluation of the predictive performance of the limited sampling strategies based on a pharmacokinetic population model to calculate AUC0-24h. Several limited sampling points will be evaluated.

Correlation between MFX concentration (mg/L) and QT interval (msec).

Correlation of drug exposure (AUC) and adverse effects

o vomiting and diarrhoea

o QT interval (msec)

Correlation between the genetic risk score and MFX induced QT prolongation.

Evaluation of medical chart including age, sex, weight, length, ethnicity, co-morbidity, diagnosis, localization of TB, resistance pattern, medical history, dose and duration of (TB) co medication as potential explanatory

factors for pharmacokinetic parameters

Study description

Background summary

Moxifloxacin (MFX) is a fluoroquinolone with a high in vitro and in vivo bactericidal activity against Mycobacterium tuberculosis. A daily dose of 600-800 mg MFX should be considered for optimal killing of the involved mycobacteria and suppression of drug resistance, which is higher than the currently used dose of 400 mg once daily. In general, safety data to support switching to the suggested higher dose are limited.

Study objective

Primary Objective:

The main objective of this prospective clinical trial is to compare pharmacokinetics and safety and tolerability of a standard dose (400 mg) with an escalated dose of 600 and 800 mg MFX.

Secondary Objectives:

* To evaluate limited sampling strategies based on a pharmacokinetic population model to predict MFX AUC0-24h
* To evaluate the correlation between MFX concentration (mg/L) and QT interval (msec)
* To evaluate a genetic risk score for the prediction of MFX induced QT prolongation

Study design

In a prospective clinical trial the pharmacokinetic parameters and safety/tolerability of three dosages of MFX will be evaluated (400 mg; 600mg; 800mg). For this trial patients will be included, who will receive MFX as part of their TB regimen, at the Tuberculosis Centre Beatrixoord, University Medical Center Groningen, The Netherlands. MFX (400 mg) will always be started in the interest of the patients* TB treatment and not in the interest of the study.

During seven days patients will receive 400 mg MFX once a day. On the 8th day the dose of MFX will be escalated to 600 mg, and the 15th day the dose of MFX will be escalated to 800 mg MFX once a day. Once included in the study, each dosing step is evaluated for proceeding to the next dose. This prevents potential toxic exposure or increased risks on QT prolongation. The evaluation

criteria are vital signs and pharmacokinetic parameters.

Intervention

Patients will start on a standard dose of MFX 400 mg once daily. After 8 days the dose will be increased to 600 mg once daily and on the 15th day of treatment, the dose of MFX will be escalated to 800 mg. In patients who have been treated with rifampicin (RIF) in the past three weeks prior to start of MFX treatment an additional washout period of 3 weeks to reduce the rifampicin induced enzymatic activity will precede the dose escalation.

Study burden and risks

Three pharmacokinetic curves will be obtained (400 mg; 600 mg; 800 mg). One additional blood sample will be obtained to genotype genetic variants that modulate QT interval. Blood samples will be taken from an indwelling intravenous (IV) catheter. Every day of treatment a 3-lead ECG will be recorded. At baseline and on the 7th, 14th, 21st day ambulatory monitoring (Holter) will be performed. The patient may experience mild discomfort due to indwelling IV catheter or during (ambulatory) ECG monitoring. The patient may experience side effects of the study drug (diarrhoea, vomiting) at higher dosage but these are expected to be rare. The potential benefit for participating in this study is that treatment can be continued with an optimized dosage (based on AUC0-24h/MIC ratio) of MFX compared to standard treatment of 400 mg once daily. The results of this will contribute to optimization of TB treatment with MFX and may result in a phase III study comparing standard dosing with individualised dosing.

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

1) Patients with TB, with Mycobacterium tuberculosis (or M. africanum) by culture
2) Starting treatment with MFX in a dose of 400 mg as part of their TB treatment

Exclusion criteria

1) Contra-indication for moxifloxacin; baseline QTc-interval > 450 msec
2) History of resuscitation
3) History of ventricular tachycardia (including Torsades de Pointes)
4) Family history of sudden cardiac death or Torsades de Pointes
5) Additional risk factors for Torsades de Pointes (including known heart failure, Left ventricular hypertrophy)
6) Use of concomitant treatment with QT/QTc prolonging drugs (including anti-dysrhythmics class IA and III, antipsychotics, tricyclic antidepressants or the antihistaminic drug terfenadine)
7) Abnormal electrolytes (K, Mg, Na, Ca)
8) Abnormal cardiac repolarisation on screening/baseline ECG
9) History of adverse events to fluoroquinolones
10) HIV co-infection
11) RIF treatment during last 3 weeks before start of the study. After a washout period of 3 weeks the patient can be included.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-11-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-01-2011
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
Other	clinical trials.gov
EudraCT	EUCTR2010-023491-25-NL
CCMO	NL34348.042.10