Pharmacokinetic parameters of 960 mg Co-trimoxazole once daily in patients with tuberculosis

Published: 17-05-2013
Last updated: 25-04-2024

Primary Objective: The primary objective of this prospective clinical trial is to determine the pharmacokinetic variability of SXT (960 mg) in patients receiving TB treatment. With these pharmacokinetic parameters, a population model and limited...

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

Summary

ID

NL-OMON40570

Source
ToetsingOnline

Brief title
Pharmacokinetics of co-trimoxazole in patients with TB

Condition

- Mycobacterial infectious disorders

Synonym
TB, Tuberculosis

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: co-trimoxazole, pharmacokinetics, tuberculosis

Outcome measures

Primary outcome

The pharmacokinetic variability of SXT (960 mg) in patients receiving TB treatment. With these pharmacokinetic parameters, a population model and limited sampling model can be developed retrospectively.

Secondary outcome

The AUC/MIC ratio and T>MIC. Furthermore, the validation of drug concentration measurement using DBS by comparing the results of blood samples routinely withdrawn from venous blood versus withdrawn by finger prick and transferred to filter paper to make dried blood spots.

Study description

Background summary

Multidrug-resistant (MDR) tuberculosis (TB) is thought to have high mortality rate. The proportion of MDR-TB among new TB cases has nearly tripled to about 3% since 2004, with levels of 22% in former Soviet republics. The spread of MDR-TB causes new challenges for the prevention, treatment and control of this deadly disease. The number of drugs to which Mycobacterium tuberculosis (the causative pathogens of tuberculosis) is susceptible has decreased. Subsequently, the treatment of MDR-TB becomes less effective, increasing the chance of treatment failure.

Therefore, there is continuing need for new drugs with minimum toxicity that is effective against M. tuberculosis. However, the management of MDR-TB could be rapidly improved by expanding the indications of established drugs. Although Co-trimoxazole (SXT) is not registered for TB, it could be a promising drug for the treatment of MDR-TB.

Co-trimoxazole (SXT) is a synergistic combination of two antimicrobial agents;

trimethoprim (TMP) and sulfamethoxazole (SMX). SXT is predominantly used for the treatment of urinary tract infections and prophylaxis and treatment of Pneumocystis jiroveci pneumonia (PCP) in HIV patients.

In available literature, no drug interactions are found between SXT/trimethoprim and other frequently used drugs in the treatment of tuberculosis (isoniazid, rifampicin, ethambutol, pyrazinamide). To evaluate the pharmacokinetic and pharmacodynamic parameters, drug -drug interactions, safety and tolerability of SXT in TB treatment we earlier performed a retrospective chart review for all patients receiving 480 and 960 mg of SXT as drug with un clear role for the treatment of (MDR) tuberculosis at the Tuberculosis Centre Beatrixoord, University Medical center Groningen, The Netherlands between (10th July 2006 to 1st July 2012).

SXT exhibits concentration independent (time dependent killing), thus 24 h AUC /MIC would be the important PK/PD parameter determining efficacy, besides the time during which the drug concentrations exceeded the MIC (T>MIC). Due to lack of information about PK-PD parameters of SXT in TB, these parameters were collected from infections with other pathogens. Improvement of treatment of melioidosis caused by Bukholderia pseudomallei by SXT is achieved when the time period in which the concentration exceeds the MIC 90 is more than 60% of the interdose interval (8). The ratio of area under the free concentration-time curve (AUC) from 0 to 24 h relative to the minimal inhibitory concentration (MIC) had to exceed 25. Depending on the PK parameters of SXT from published data and MIC of SXT against TB, we therefore assume that a suitable dose of TMP/ SMX of 160-800 mg to achieve (f AUC0-24 h) /MIC of SXT ratio should exceed 25. This, and considering the fact that Mycobacterium tuberculosis replicates significantly slower than other pathogenic bacteria, supports our hypothesis that 960 once daily should be sufficient in treating tuberculosis.

Study objective

Primary Objective:
The primary objective of this prospective clinical trial is to determine the pharmacokinetic variability of SXT (960 mg) in patients receiving TB treatment. With these pharmacokinetic parameters, a population model and limited sampling model can be developed retrospectively.

Secondary Objective(s):
The second objective is to calculate the AUC/MIC ratio and T>MIC and to validate drug concentration measurement using DBS by comparing the results of blood samples routinely withdrawn from venous blood versus withdrawn by finger prick and transferred to filter paper to make dried blood spots.

Study design

In a prospective clinical trial the pharmacokinetic parameters of 960 mg co-trimoxazole will be evaluated. For this trial patients will be eligible for inclusion who are referred for TB-treatment to Tuberculosis Centre Beatrixoord, University Medical Center Groningen, The The patients will receive 960 mg once a day for four to six consecutive days. This specific range of three days is for practical reasons, since it is preferred to perform this study during office hours.

Blood samples will be collected before the start of this study (1x 2 ml) and (8 x 2 ml) on the 4th, 5th or 6th day before administration and from start of administering SXT at intervals of 1h, 2h, 3h, 4 h, 5h, 6h and 8h hours. Parallel with the sampling of venous blood finger prick (0.1 ml) will be taken to make a DBS at 1h, 5h and 8h after administration.

There are no published data that showed whether protein binding of sulfamethoxazole is concentration or non- concentration dependent. Therefore the unbound concentration in plasma ultra filtrate will be measured in the sample at three different time points. The plasma concentrations of sulfamethoxazole can be determined using a validated liquid chromatography-tandem mass spectrometry (LS-MS/MS). sulfamethoxazole and metabolite were measured by protein precipitation, followed by LC with tandem mass detection.

The area under the concentration-time curve up to 24 h post dosage (AUC 0-24h) for plasma will be determined with a standard non- compartmental pharmacokinetic method using KINFIT module of MW Pharm 3.60 (Mediware, The Netherlands). The AUC 0-24h will be calculated according to the log-linear trapezoidal rule. In addition, several limited sampling strategies will be evaluated based on a population one -compartment model, with first-order absorption pharmacokinetics without lag time using the sulfamethoxazole dose, the body surface area of the participants and the observed SXT plasma concentrations, using an iterative two-stage Bayesian procedure. The population pharmacokinetic model will be cross validated by developing a model based on n-1. Limited sampling model (LSM) will be calculated using Monte Carlo data simulation. The correlation between predicted SXT AUC0-24h and observed AUC0-24h will be investigated by Bland-Altman analysis. The predictive performance of the final model will be prospectively tested with SXT profiles of TB patients receiving 960 mg once daily. AUC0-24h/MIC ratio of bound and unbound drug and T>MIC will be calculated. To calculate MIC values, the drug susceptibility test of the available M. tuberculosis isolates is performed with the Middlebrook 7H10 agar dilution method at the Dutch national Mycobacterium Reference Laboratory (National Institute for Public Health and the Environment, RIVM).

The results from the analysis of DBS and the analysis of venous blood will be compared to evaluate whether DBS method is reliable for routine TDM and clinical pharmacokinetics. A DBS will be produced from venous samples (about

0.05 ml) to evaluate the differences between the drug concentration in venous blood and capillary blood.

Intervention

After exclusion of patients that cannot participate in this study, evaluation of medical chart (including age, sex, weight, length, ethnicity, co-morbidity, type of diagnosis, localization of TB, medical history, dose and duration of TB co-administered medications) will be done at day 1 of the study. After evaluation of baseline parameters, the attending physician (pulmonologist) will start with 960 mg for four to six consecutive days in the participating TB patients.

Study burden and risks

There are low risks from using SXT in this study because of the short study time and low dose of SXT. Mild, no serious side effects may occur because SXT in general is a safe and well tolerated drug. The patients could have mild discomfort during the use of an indwelling IV catheter or due to the finger prick to make a DBS.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

TB patients with Mycobacterium tuberculosis (or mycobacterium africanum) by culture or molecular testing for InhA, KatG and rpoB.

Exclusion criteria

• Patients younger than 18 years or older than 64 years.
• Pregnancy and breast feeding.
• Patients with hypersensitivity to sulfonamide or trimethoprim.
• Concomitant treatment with vitamin K antagonist (acenocoumarol).
• Patients with preexisting renal dysfunction or concomitant treatment of angiotensin converting enzyme inhibitors and potassium-sparing diuretics that may exacerbate the hyperkalemic effect of SXT.
• Patients treated with dofetilide, methotrexate, phenytoin, sulfonylureas (glibenclamide, gliclazide, glimepiride or tolbutamide).
• Patients that have gastrointestinal complaints like diarrhea and vomiting (observed)
• Patients that have experienced an adverse effect to SXT or similar antibiotic drugs.
• Patients with HIV or AIDS.
• Patients with severe damage to the liver parenchyma.
• Patients with anemia, thrombocytopenia and agranulocytosis

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):	08-10-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	17-05-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-08-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
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	EUCTR2013-001184-24-NL
CCMO	NL43475.042.13