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Evaluation of Co-trimoxazole in treatment of multidrug-resistant tuberculosis

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Abstract

Co-trimoxazole (SXT), a combination of sulfamethoxazole (SMX) and trimethoprim has shown in vitro activity against Mycobacterium tuberculosis. However, the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of SXT in multidrug-resistant (MDR) tuberculosis (TB) are so far lacking. Therefore we evaluated the PK and drug susceptibility along with its tolerability during treatment.

Based on drug-susceptibility testing MDR-TB patients received SXT as a part of their MDR treatment. The PK parameters of SMX, the effective component of SXT against Mycobacterium tuberculosis were evaluated. The ratio of AUC0-24h/MIC was used as the best PK/PD parameter to predict the efficacy of SMX. Adverse effects of SXT were also evaluated.

Ten patients with MDR-TB (one of whom had XDR-TB) received 480 mg of SXT with median dose of 6.5 mg/kg of SXT (Range, 6.1-6.8) qd for a median treatment period of 381 days (Range, 129-465). In two patients, the dose was escalated to 960 mg. ƒAUC0-24/MIC of SMX exceeded 25 in only one patient. SXT was safe and well tolerated except for one patient who had gastrointestinal side effects after receiving 960 mg of SXT. Additional studies are needed to find the PK/PD targets and consequently to set the optimal dose of SXT for MDR-TB treatment.

Introduction

Multidrug-resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB) are emerging in many areas around the world [1]. Also the susceptibility of *Mycobacterium tuberculosis* against current antituberculosis (anti-TB) drugs has decreased and therefore the treatment of MDR-TB has become increasingly complicated [2]. Consequently, there is an urgent need for new effective drugs with a minimum of toxicity. An old, inexpensive and well-tolerated drug like co-trimoxazole (SXT), which is registered for other indications than TB, could be a new effective agent for the treatment of MDR and XDR-TB [3].

SXT is a combination of trimethoprim (TMP) and sulfamethoxazole (SMX) in a ratio of 1:5. It is a potent antibacterial drug against a variety of pathogens causing infections in humans. SXT is currently used in the treatment of urinary tract infections, otitis media, shigellosis, chronic bronchitis and *pneumocystis carinii* pneumonitis [4].

SXT shows concentration-independent or time dependent killing. Therefore the ratio of area under the free concentration-time curve ($fAUC$) from 0 to 24 h relative to the minimal inhibitory concentration (MIC) is considered to be the important pharmacokinetic (PK)/ pharmcodynamic (PD) parameter to predict the efficacy of SXT [5]. Very little is known about the PD of SXT [5]. There are only few publications on the PK parameters of SXT of which none in TB patients [6-9] . Only two studies investigated the *in vitro* susceptibility of SXT against *M. tuberculosis* and showed promising results [3, 10]. From these studies it could be concluded that only SMX was effective against *M. tuberculosis a*nd TMP is not [3, 10,11]. One study mentioned AUC/MIC ratio of SXT that had to be exceeded 25 for effective treatment of melioidosis caused by *Burkholderia pseudomallei* [12] .The lack of data is likely due to the fact that SXT is an old drug and *in vitro* evaluation of PK/PD parameters in infection models is rather new.

In general SXT is a safe and well-tolerated drug. Gastrointestinal complications including nausea, vomiting, anorexia and diarrhea are the most common adverse effects of SMX [13, 14]. Renal side effects including hyperkalemia, slight increase in the serum creatinine level and hyponatremia occur especially in patients with renal dysfunction [15, 14,16]. Other side effects reported are hematological side effects like megalo-blastic anemia, leucopenia, thrombocytopenia and aplastic anemia in patients with preexisting megaloblastic anemia or deficiencies in folic acid stores (alcoholics, malnourished patients and pregnant women) [17].

Although SXT has been administered to TB patients, data is very scarce and its role in TB treatment is still not yet clear. The objective of this study was to evaluate PK, PD and PK/PD parameters and safety/tolerability of SXT in MDR-TB patients

Patients

MDR-TB patients who were referred to the Tuberculosis Center Beatrixoord of the University Medical Center Groningen (Groningen, The Netherlands) between the 1st January 2006 and the 1st July 2012 and for whom drug susceptibility testing (DST) for SXT was performed, were eligible for evaluation. Age, gender, weight, ethnicity, underlying disease, minimum inhibitory concentration (MIC) of the *Mycobacterium tuberculosis isolate*, localization of TB, other anti-TB medications, duration of treatment with SXT and the total anti-TB regimen administration were recorded for MDR-TB patients that received SXT. Patients were subjected to routine medical care without specific study-related interventions. We describe patient data obtained during usual care, and therefore, no ethical clearance was required under Dutch Law (WMO).

Pharmacokinetics and Pharmacodynamics

Blood samples were only evaluated when obtained at steady state which was after at least three days of administration of SXT [18] . They were collected before and at 1, 2, 3, 4 and 8 h after SXT administration.

The concentrations of SMX in human plasma samples were analyzed in the laboratory of Clinical Toxicology and Drugs Analysis of the Department of Hospital and Clinical Pharmacy at the University Medical Center Groningen by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). In brief, 5 µl of each plasma sample was mixed with 750 µL precipitation reagent (methanol and acetonitrile 4:21, v/v). From the clear upper layer 5 µL was injected on a 50 mm×2.1 mm reversed phase C18, 5-µm analytical column (HyPurity Aquastar, Interscience Breda, The Netherlands) for chromatographic separation. The detector was operated in electrospray positive ionization mode and performed selected reaction monitoring (SRM) as scanning mode. The transition of *m/z* 254.1-155.9 (collision energy 25 eV) for SMX was measured with scan width of 0.5*m/z.* The recoveries ranged from 97.7% to 102.9%, depending on the concentration. The accuracy was between 97.7% and 102.9% for SMX, depending on the concentration level. The intra- and inter assay coefficients of variation were less than 5.1 % over the ranges of 5 to 100 mg/L. The lower limit of quantization was 5 mg/ L.

PK parameters of SMX, including $AUC_{0\text{-}24h}$, volume of distribution (Vd), clearance (Cl) and half life (t ½) were determined with a standard non-compartmental PK method using the KINFIT module of MW/Pharm 3.60 (Mediware, Groningen, The Netherlands). The $AUC_{0\text{-}24}$ in plasma was calculated according to the log –linear trapezoidal rule. In this case, the concentration of SMX at 24 hours after oral administration was estimated to be equal to its concentrations at zero time (before administration of the dose).

The free non-protein bound fraction of antibacterial drug is responsible for the clinical effect of these drugs [19].The free $AUC_{0\text{-}24}$ (f $AUC_{0\text{-}24}$) values estimated by multiplying the total AUC0-24 values by the fraction unbound of 0.23 which was retrieved from an earlier study [19]. Free-drug AUC 0-24/MIC ratios were calculated by dividing the f $AUC_{0\text{-}24}$ by the MIC value for SMX.

A one compartmental PK population model (POP-PK) of SMX with first order absorption without lag time was developed using an iterative two-stage Bayesian procedure (MW/Pharm 3.60) starting with pharmacokinetic estimates from previous study [8]. The individual PK parameters of each patient were calculated using KINFIT. KINPOP is used to calculate the parameters of the MDR-TB patients based on the individual concentrations of SMX and patient characteristics like body weight, age, gender and creatinine clearance [20].

To determine the MIC values, the patients' *M. tuberculosis* isolates were subjected to DST which was performed on the Middelbrook 7H10 agar dilution method at the Dutch national Mycobacterium Reference Laboratory (National Institute for Public Health and the Environment, RIVM) [21]. In accordance with European Committee on Antimicrobial Susceptibility Testing, the MIC of SXT is expressed as TMP: SMX in the ratio 1: 19.

Safety

The safety of SXT during TB treatment was evaluated by assessing the reported side effects of SXT retrospectively using a standardized data abstraction form from the Tuberculosis Centre Beatrixoord. Specific attention was paid to the side effects that could be caused by SXT like gastrointestinal side effects (nausea, vomiting and diarrhea), hepatotoxicity, and anemia and blood count abnormalities [22].

Hepatic injury was defined as elevation in one of the hepatic enzymes five times the upper limit of normal during the treatment with SXT (grade 3 common toxicity criteria (CTC)). These

enzymes include aspartate aminotransferase (ASAT> 200 U.L $^{-1}$), alanine aminotransferase (ALAT>225 U.L $^{-1}$) and gamma-glutamyl transpeptidase (GGT>200-275 U.L^{-1}) [23]. For other side effects the defined normal values were: anemia (hemoglobin normal range 7.5 – 9.9 mmol/L (female) and 8.7 – 10.6 mmol/L (male)), leukocyte count (4 × 10^9/L) and platelet count (150 - 350 x10^9 /L). The adverse drug reactions (ADR) in patients on multiple drug regimens like MDR-TB patients would require a standard causality assessment tool (Naranjo algorithm) [24]. Using this tool, we considered that SXT is definitely the cause of ADR if the score ≥ 9, probable if 5 to 8, possible if 1 to 4, and doubtful if the sore ≤ 0.

Statistics

Wilcoxon signed-rank test was employed in the statistical analysis when the data were not normally distributed. The POP-PK model was cross validated by developing a POP-PK model based on n-1 and by predicting the $AUC_{0\text{-}24h}$ of the subject left out during the model development. The correlation between the predicted based on the POP-PK model and calculated $AUC_{0\text{-}24h}$ was tested by means of a Bland and Altman analysis.

Results

Patients

For 17 MDR-TB patients DST for SXT was performed. Only in ten patients SXT was used as part of their TB regimen because DST showed that isolates were susceptible to SXT. In the other cases resistance to SXT (n=4) or more conventional TB drugs could be used (n=3) (Table 2). In general, these TB patients were relative young with a median age of 29 years (Inter Quartile Range (IQR), 24-31years), and had a relatively low median body mass index (calculated as weight in kilograms divided by the square of height in meters) of 21.1(IQR,

19.1-23.6). The resistance of *Mycobacterium tuberculosis* to at least isoniazide and rifampicin was diagnosed by culture. Eight patients had Pulmonary TB as the most common diagnosis in MDR-TB patients, one patient had urogenital TB and one had both pulmonary and extra pulmonary TB. SXT was prescribed as 480 mg daily. This equals to a median dose of 6.5 mg/kg (IQR, 6.1-6.8) in various combination regimens for a median period of 381 (129-465) days. The daily dose of SXT was increased arbitrary to 960 mg which equals to 14 and 13 mg/kg in two patients because of low level of SXT in blood related to MIC in these patients. All of the patients had a negative history for underlying diseases except for one patient who had diabetes mellitus. None were diagnosed with co-infection with human immunodeficiency virus. Eight of the 10 patients successfully completed the treatment with no signs of recurrence. Two patients are still on treatment at the time of writing this report; sputum culture was converted and they are in good clinical conditions. The clinical data of all 10 patients are shown in Table 1. DST was evaluated in all MDR-TB patients. Susceptibility and resistance of *M. tuberculosis* against anti-TB drugs are shown in Table 2.

Pharmacokinetics (PK) and pharmacodynamics (PD)

The steady state PK parameters of SMX could be evaluated in only 8 of total 10 patients receiving 480 mg SXT once daily because in the other two patients no plasma sampling was performed during the treatment period with SXT. The PK parameters are summarized in Table 3. The observed plasma concentration- time curves of SMX were obtained from the patients after receiving 480 mg of SXT; these are shown in figure 1.

The parameters of POP-PK model of SMX are shown in Table 4. The cross validation of this model showed that the geometric mean values of the POP-PK model (n-1) were Cl (1.28 ± 0.52)L/h/1.85 m^2, Vd (0.22± 0.03) L/Kg LBMc, Ka-po (0.44±0.18), these results were not

different from the POP-PK model (Table 4). The individual difference between the predicted based on POP-PK model and calculated values of AUC_{0-24} was underestimated by a median percentage of -0.7 (Range,-6.2-2.8). The agreement between predicted with the POP-PK and calculated AUC_{0-24h} of SMX is shown in figure 2. This figure shows that all the values of AUC were within the agreement only one was outside this agreement. The median percentage of difference between the predicted based on POP-PK (n-1) model and calculated values of AUC_{0-24} was -3.92 (Range, -6.3 -1.7).

The drug susceptibility testing shows that MICs values of SMX for *M. tuberculosis* varied with median ranges of 9.5 (IQR, 4.8-25) mg/L.

The ratios of $\int AUC_{0-24h}$/MIC of SMX in each patient are presented in Table 5. The geometric means of AUC/MIC and $\int AUC_{0-24h}$/MIC ratios after receiving 480 mg for SMX were 48.4 (IQR, 34.8-71.3) and 11.1 (IQR, 8 -16.4) respectively. One of the eight patients that received 480 mg of SXT had $\int$AUC0-24h/MIC ratio of SMX greater than 25.

Safety

In general, SXT was well tolerated. However, there were some mild side effects including abdominal complaints with diarrhea and vomiting in one patient (Naranjo score=4). Elevations in hepatic enzymes (ASAT and ALAT) were observed in two patients that are receiving 480 and 960 mg of SXT respectively (Naranjo scores= 5). In these two patients the values of ALAT during treatment with 480 mg were 47.50 and 48 U.L -1 (baseline 29) and with 960 mg of SXT were 46 and 71 U.L -1 (baseline 43). The values of ASAT after receiving 480 and 960 mg of SXT were 48 and 99 $U.L^{-1}$ respectively compared with baseline 35. Although the hepatic enzymes were two times higher than base line, the values of ASAT and ALAT did not exceed 5 times the upper limit of normal. The median hemoglobin level in patients before treatment

with 480 mg SXT was 7.6 mmol/L (range: 7.6 to 8 mmol/L) and during treatment was 7mmol/L (range: 6.6- to 7.2 mmol/L); the difference was significant (P=0.002) but probably, clinically not relevant. The value of Naranjo score for low hemoglobin level is 3 or 4. One patient developed leucocytopenia after receiving 480 and 960 mg of SXT. Leucocyte counts were 2.2×10^9/L and 3.2×10^9/L respectively in comparison to a baseline value of 4.2 (Naranjo score=3). Besides, one patient developed mild thrombocytopenia with a thrombocyte count of 146 x109 /L and of 247 at baseline (Naranjo score = 3).

Discussion

No earlier study described the PK, PD and PK/PD parameters of SXT in MDR-TB patients. It is interesting is that the PK parameters of SMX in TB patients including AUC 0-24h, Vd and Cl are lower than the values observed in patients with meningitis, HIV infections or those suffering from bacterial skin infection (Table 6) [6-9]. Low drug exposure may be explained by decreased intestinal absorption resulting in low serum concentrations of antituberculous drugs. Other factors such as alcohol abuse, smoking, weight loss, albumin and hemoglobin could be the possible reasons for reduced permeability via paracellular intestinal transport [25]. To further explore the PK parameters in MDR-TB patients, we made a population model. This model showed no significant difference between the calculated and predicted AUC according to Bland-Altman analysis and this difference was also statistically insignificant *(P*=0.78). Thus, MDR-TB patients seem to display a consistent PK profile for SMX. Therefore this developed model could be used to assess drug exposure in a prospective study to evaluate the safety and efficacy and find the suitable dose of SXT as part of a TB-regimen.

The MIC value of SMX in this study was in accordance with previous study that mentioned that SMX inhibits 80% growth of all 117 isolates at an MIC 19 mg/L [10].

The PK-PD parameter (AUC_{0-24}/MIC) best predicting of SMX efficacy has not been firmly established. According to an earlier single study, the $\int$ AUC $_{0-24}$/MIC of SMX had to exceed 25 for adequate treatment of melioidiosis [12]. From the results, it can be seen that only in 1 of 8 patients, $\int$ AUC $_{0-24}$/MIC ratio of SMX was > 25. However, this ratio could be lower than 25 and still be effective in TB treatment. Especially the magnitude of this parameter may vary for different bacterial species. For example the AUC_{0-24}/MIC ratio for fluoroquinolone is different against *Pseudomonas aeruginosa* and other gram-negative bacilli [26]. The lower ratio might be acceptable in patients receiving multidrug treatment for MDR-TB. Other drugs might decrease this ratio as shown in a murine aerosol infection model from previous study in which the AUC_{0-24}/MIC ratio of rifampicin that correlated with efficacy decreased when administered in combination with moxifloxacine [27]. Therefore the interpretation of the value of the AUC_{0-24}/MIC for SMX in our MDR-TB-patients at this time is difficult. The dose of SXT given to the MDR-TB patients was low compared to commonly used dosages for other infectious diseases. However one has to keep in mind that the more conventional dosages of SXT are for the treatment of fast replicating bacteria and is often given as mono therapy. In our case the aim is slow growing *M. tuberculosis* in combination with other antimicrobial agents. For future study of SXT for MDR-TB it's can be advised to also explore higher dosages to achieve higher drug exposure but tolerability may be a problem during prolonged treatment.

The TB patients with HIV infections can have drug–drug interaction (DDI) when rifampin (RIF) is co-administered with SXT as mentioned in previous study [8] but this is of no concern in MDR-TB. Indeed, RIF decreases the concentrations of TMP and SMX significantly in serum but again, SXT would not be prescribed in individuals that can be treated with RIF and non received RIF before starting the treatment with SXT.

Although our sample size was low, this retrospective study confirmed the safety of SXT in accordance with earlier studies that showed that SXT was safe and well tolerated when it was

used as prophylaxis in adults with HIV infection who have pulmonary TB [28, 29]. SXT was well tolerated in MDR-TB patients and was not discontinued in any of 8 patients till the end of treatment and in 2 patients that are still on treatment. Only one patient has gastrointestinal complaints as a possible side effect of SXT following administration of 960 mg of SXT daily. Therefore the dose was lowered to 480 mg till the end of treatment. In our patients, the maximum Naranjo score of 5 was reached, in other words there is a probable relationship between the observed side effects and SXT. However hematological side effects including anemia, leucocytopenia and thrombocytopenia during treatment could be due to other antituberculosis drugs like linezolid [30, 31].

The main limitation of this study is that there is a lack of data on the target (AUC/MIC value) to be reached to predict the efficacy of SXT in the treatment of TB. In the future, a prospective study is needed to evaluate the PK and PD parameters of SXT in TB-patients. To determine $fAUC_{0\text{-}24}$/MIC ratio of SMX for effective treatment along with suppression of the emergence of drug resistance, an *in vitro* infection model could be the suitable strategy as reported previously for moxifloxacin [32]

Comparing SXT with other drugs not registered for TB treatment but used in MDR-TB regimen, it has the great advantage that it is cheap and readily available all over the world.

These are the first results on the inclusion of SXT in MDR-TB treatment in which drug susceptibility testing and SXT concentration measurements were combined. Based on our preliminary data we showed that SXT has a favorable PK profile in TB patients.

Further in vitro PK and PD studies like a hollow fiber infection model or mouse model is warranted to establish target AUC/MIC value to predict the efficacy of SXT and consequently to set the optimal dose in the treatment of MDR-TB treatment. Preferably, PK/PD parameters of SXT, MIC of SXT should be measured alone and in the presence of other antituberculous drugs to detect the possible synergism between these drugs. According to the clinical

outcome that showed no treatment discontinuation or serious side effects, the consistent PK values and relative low MIC values, this study could be the starting point for further exploration of SXT for MDR-TB treatment.

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Figure 1

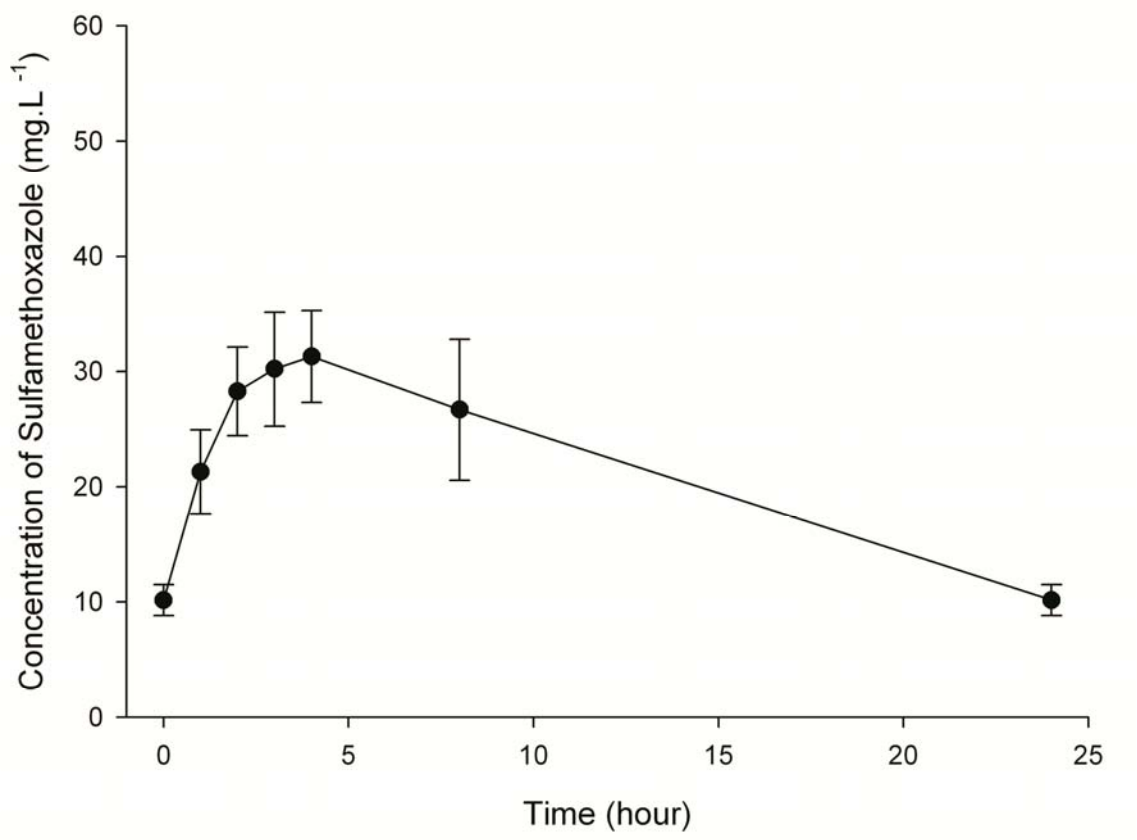
Concentration of Sulfamethoxazole (mg.L -1)
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (hour)

Figure 2

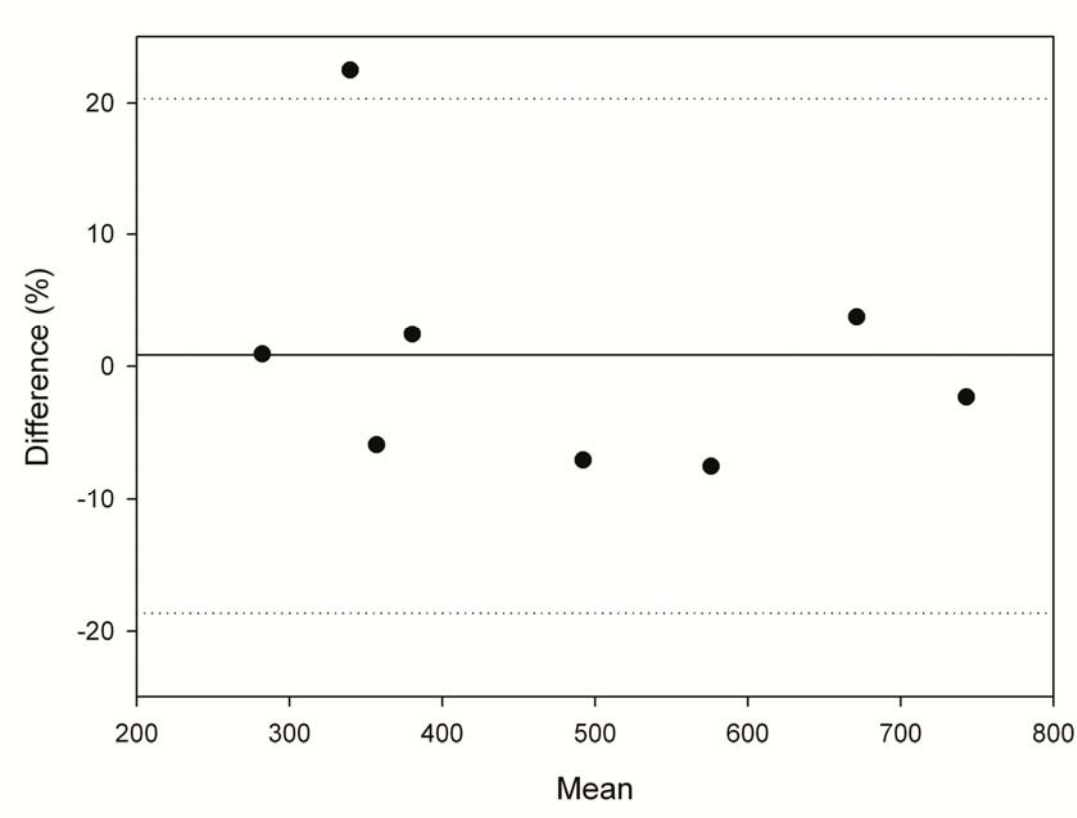

Table 1: Characteristics of MDR-TB patients receiving SXT at baseline

Patient	sex	BMI ($kg/m^{2)}$	Duration of treatment (day) (SXT)	Total duration of treatment (day)	Ethnicity	co- morbidities and intoxications	Localization of TB	Other Anti- TB drugs
1	m	18.6	531	546	Hindustani	smoking, soft drugs	pulmonary	E,AM,MOX,PTH, LZD, CFZ, Doxy
2	f	21.5	191#	202#	African	none	Pulmonary and extra pulmonary	MOX, KM, ERTA
3	m	22.1	501	705	Russian	alcohol abuse	pulmonary	Z, KM, LZD, CFZ, CLM, CM
4	f	18.1	412	548	Asian	none	pulmonary	E, AM, MOX, PTH, LZD, CFZ, CPX
5	f	19.3	154	191	Russian	none	pulmonary	MOX, LZD, AMX/CL, ERTA
6	m	20.7	350	365	Asian	smoking	pulmonary	E,AM,MOX, LZD, CFZ CPX ,Doxy
7	f	27.2	453	566	African	none	pulmonary	AM, MOX, CS, LZD
8	f	31	52	55	African	diabetes mellitus	extra pulmonary	AM, KM, MOX, LZD, CLM, ERTA
9	m	19.0	56	62	Russian	alcohol abuse, drug abuse, smoking	pulmonary	MOX, LZD, CLM, ERTA
10	m	21.1	44 #	41#	African	none	extra pulmonary	CLM, ERTA, LZD, KM

#Patients still on treatment. BMI: body surface area; m: male; f: female; Anti-TB; antituberculosis; E: ethambutol; SXT; Z: pyrazinamide; KM: kanamycin; AM: amikacin; CM: capreomycin; CPX: ciprofloxacin; CS: cycloserine; CLM; clarithromycin; MOX: moxifloxacin; CFZ: clofazimine; PTH: prothionamide; Doxy: doxycycline, ERTA: ertapenem; amoxicillin+clavulanic acid (Augmentin): AMX/CL; LZD: linezolid.

Table2. Susceptibility and Resistance to anti TB drugs (n=17)

	R	S	I
Group 1: First-line oral agents			
Isoniazide	17 (100)		
Ethambutol	14 (82.4)	2 (11.8)	1(5.9)
Rifampicin	17 (100)		
Pyrazinamide	9 (53)	8 (47)	
Rifabutine	13 (76.5)	3 (17.6)	1(5.9)
Group 2: Injectable anti-TB-medication			
Amikacine	7 (41.2)	10 (58.8)	
Kanamycin	2 (11.8)	4 (23.5)	
Streptomycin	15 (88.2)	2 (11.8)	
Capreomycin	5 (29.4)	10 (58.8)	
Group 3: Fluoroquinolones			
Ofloxacin	1 (5.9)		
Moxifloxacin	3 (17.6)	13 (76.5)	1(5.9)
Ciprofloxacin	4 (23.5)	12(70.6)	
Group 4: Other bacteriostatic second line agents			
Protionamide	4 (23.5)	12 (70.6)	
Cycloserine	1 (5.9)	7 (41.2)	
Group 5: Antituberculosis drugs with unclear efficacy			
Linezolid	13 (76.5)	3(17.6)	
Clofazimine		11 (64.7)	
Clarithromycin	2 (11.8)	5 (29.4)	
Augmentin	9 (53)	4 (23.5)	
Imipenem	2(11.8)		
Others			
Co-trimoxazole	4 (23.5)	13 (76.5)	
Ertapenem		7 (41.2)	
Tigecycline	7 (41.2)	1 (5.9)	
Meropenem	1 (5.9)		

R: resistance; S: susceptibility; I: intermediate susceptibility. Data are presented as absolute values (%) of MDR-TB patients susceptible, resistant and intermediately-susceptible to Anti-TB drugs.

Table 3. Pharmacokinetic parameters of SMX at steady state after oral administration of 480 mg of SXT (n=8).

Pharmacokinetic parameter	SMX (400 mg)
AUC 0-24 (mg.h.liter^{-1})	371.5 (360-574.8)
Cl (ml/min/kg)	0.19 (0.14-0.25)
V (L/kg)	0.15 (0.13-0.22)
t ½ (h)	10.1 (8.7 -10.8)

Pharmacokinetic data are presented as median (interquartile range). AUC 0-24: area under the concentration-time curve up to 24 h post dosage; Cl: clearance; V: volume of distribution; t ½: half-life.

Table 4. Population pharmacokinetic model parameter values of SMX (n=8)

Parameter	Values
Cl (L.h/1.85 m ^{2})	1.14 ± 0.43
Vd (L.Kg^{-1} LbMc)	0.24 ± 0.05
Ka (h-^{1})	0.43 ± 0.17
F	1

Data are expressed as geometric mean ± standard deviation. Cl: apparent clearance; Vd: volume of distribution; Ka: absorption rate constant; F: bioavailability;

Table 5. ƒAUC$_{0\text{-}24}$/MIC ratio of SMX after receiving 480 mg and 960 mg of SXT (n=8).

Patient no.	MIC (mg/L)	AUC0-24 (mg .h/L) 400 mg SMX	ƒAUC0-24/MIC 400 mg SMX	AUC0-24 (mg .h/L) 800 mg SMX	ƒAUC0-24/MIC 800 mg SMX
1	25	376	3	774	7
2	4.75	297	14	-	
5	9.5	658	16	991	24
6	25	509	5	-	-
7	4.75	597	29	-	-
8	4.75	367	18	-	-
9	19	752	9	-	-
10	4.75	281	14	-	-

AUC 0-24: area under the concentration-time curve up to 24 h post dosage; MIC: minimum inhibitory concentration; ƒAUC$_{0\text{-}24}$/MIC: protein unbound (free) AUC from 0 to 24 h relative to the minimal inhibitory concentration (MIC).

Table6. Pharmacokinetic parameters of SMX for the treatment of different infections from previous studies.

Infection	Dosage regimen	T ½ (hr)	Vd (L/kg)	Cl (ml/min/kg)	AUC (mg/L/hr)	Refere-nce
Bacterial skin disease (N=12)	Single dose 0.23 g (PO)	10.0±1.1	N/A	N/A	1295±823	[9]
Normal meninges (N=9)	25 mg/kg over 120 min (IV)	9.8±1.5	0.30±0.04	0.36±0.03	1,160±103	[6]
AIDS (N=8)	75 mg/kg daily (IV)	15.5±7.4	0.5± 0.3	0.40±0.12	N/A	[7]
HIV (N=10)	800 mg once daily (PO)	N/A	N/A	N/A	574.2 (342.6-796.3)	[8]

N: number of patients; PO: orally; IV: intravenously; N/A: not available. The values are shown in mean (±SD) except in HIV patients that shown in medians (range).

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