STUDY THE RIFAMPICIN REDUCES PLASMA CONCENTRATIONS OF MOXIFLOXACIN IN PATIENTS WITH TUBERCULOSIS

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ABSTRACT :
Tuberculosis (TB) is an infectious disease usually caused by the bacterium Mycobacterium tuberculosis (MTB).[1]Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms, known as latent tuberculosis. This study aimed to calculate the incidence of AKI due to anti-TB drugs and analyze the outcomes and predictors of renal recovery. Study subjects were patients with pulmonary TB who were in the last month of the continuation phase of TB treatment. All study subjects had a body weight >35 kg, were 18–55 years of age, and had normal electrocardiogram findings. Subjects were excluded from the study if they were pregnant or lactating; had a relevant history or condition that might interfere with drug absorption, distribution, metabolism, or excretion; had heart rhythm disturbances; 15 subjects were included in the study. All patients had abnormal radiograph findings and had cultures positive for M. tuberculosis at initiation of TB treatment. The mean age of the 15 study subjects who completed the study (6 of whom were female) was 30 years (range, 20–55 years), and the mean weight of the subjects was 55 kg (range, 38–80 kg) at the first day of pharmacokinetic assessment. We showed a 31% decrease in exposure to moxifloxacin when combined with intermittently administered rifampicin and isoniazid in patients with TB. A higher dose of moxifloxacin may possibly overcome the effect of rifampicin on the pharmacokinetics of moxifloxacin. Additional studies are warranted to assess the pharmacokinetics, dynamics, and tolerability of a higher dose of moxifloxacin when combined with rifampicin or other rifamycin derivatives.
Key words: Mycobacterium, moxifloxacin, rifampicin

I.INTRODUCTION

Tuberculosis (TB) is an infectious disease usually caused by the bacterium *Mycobacterium tuberculosis* (MTB).[1]Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms, known as latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. The classic symptoms of active TB are a chronic cough with blood-containing sputum, fever, night sweats, and weight loss.[1] The historical term "consumption" came about due to the weight loss.[2] Infection of other organs can cause a wide range of symptoms.[3]

Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze.[1][4]People with latent TB do not spread the disease. Active infection occurs more often in people with HIV/AIDS and in those who smoke.[1] Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests.[5]

Prevention of TB involves screening those at high risk, early detection and treatment of cases, and vaccination with thebacillus Calmette-Guérin vaccine.[6][7][8] Those at high risk include household, workplace, and social contacts of people with active TB.[8] Treatment requires the use of multiple antibiotics over a long period of time.[1] Antibiotic resistance is a growing problem with increasing rates of multiple drug-resistant tuberculosis (MDR-TB).[1]

One-third of the world's population is thought to be infected with TB.[1] New infections occur in about 1% of the population each year.[9] In 2014, there were 9.6 million cases of active TB which resulted in 1.5 million deaths. More than 95% of deaths occurred in developing countries. The number of new cases each year has

decreased since 2000.[1] About 80% of people in many Asian and African countries test positive while 5–10% of people in the United States population tests positive by the tuberculin test.[10] Tuberculosis has been present in humans since ancient times.[11]

SIGNS AND SYMPTOMS:

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis).[3] Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB.[3]

General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue.[3]Significant nail clubbing may also occur.[13]

Pulmonary

If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases).[11][14] Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain "asymptomatic").[11] Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery or aRasmussen's aneurysm, resulting in massive bleeding.[3][15] Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones.[3] The reason for this difference is not clear.[10] It may be due either to better air flow,[10] or to poor lymph drainage within the upper lungs.[3]

Extrapulmonary

In 15–20% of active cases, the infection spreads outside the lungs, causing other kinds of TB.[16] These are collectively denoted as "extrapulmonary tuberculosis".[17] Extrapulmonary TB occurs more commonly inimmunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases.[17] Notable extrapulmonary infection sites include thepleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (inurogenital tuberculosis), and the bones and joints (in Pott disease of the spine), among others. When it spreads to the bones, it is also known as "osseous tuberculosis",[18] a form of osteomyelitis.[10] Sometimes, bursting of a tubercular abscess through skin results in tuberculous ulcer.[19] An ulcer originating from nearby infected lymph nodes is painless, slowly enlarging and has an appearance of "wash leather".[20] A potentially more serious, widespread form of TB is called "disseminated tuberculosis", also known as miliary tuberculosis.[3] Miliary TB makes up about 10% of extrapulmonary cases.[21]

This study aimed to calculate the incidence of AKI due to anti-TB drugs and analyze the outcomes and predictors of renal recovery.

II. EXPERIMENTAL WORK

Subjects. Study subjects were patients with pulmonary TB who were in the last month of the continuation phase of TB treatment. All study subjects had a body weight >35 kg, were 18–55 years of age, and had normal electrocardiogram findings. All patients had a satisfactory response to treatment, and none had sputum smear results positive for TB after 2 months of treatment. Subjects were excluded from the study if they were pregnant or lactating; had a relevant history or condition that might interfere with drug absorption, distribution, metabolism, or excretion; had heart rhythm disturbances; had a history of seizures or epilepsy; had a glucose 6 phosphate dehydrogenase deficiency; had hypersensitivity to quinolones; had experienced tendon disorders related to fluoroquinolone treatment; had hypokalemia; or had use of any drug that might interact with moxifloxacin.

Study design. This study was an open-label, multiple-dose, 1-arm, 2-period, fixed-order pharmacokinetic interaction study and was performed in an outpatient clinic in OM SAI HOSPITAL Hyderabad. According to the National Tuberculosis Program, the continuation phase of TB treatment consists of 600 mg of isoniazid and 450 mg of rifampicin, both administered 3 times per week. The dose of rifampicin is lower than the usual 600-mg dose because of the low mean body weight. Because all patients were in the last month of TB treatment, steady state for rifampicin and isoniazid was already achieved at the start of the study. In addition to regular TB treatment, subjects were given 400 mg of moxifloxacin every day for 5 days to attain steady state of this drug. After completion of TB treatment and a washout period of 1 month, patients received 400 mg of moxifloxacin per day for another 5 days.

Experimental procedures. Steady state pharmacokinetic parameters were assessed on the last day in both phases. Patients were asked to refrain from any food intake from 11 PM the preceding night until standardized lunch was provided, 4 h after intake of study medication. Study drugs (moxifloxacin in phase 1 and phase 2, plus rifampicin and isoniazid in phase 1 only) were taken together on an empty stomach.

Plasma concentrations. Moxifloxacin plasma concentrations were measured by means of a validated high-performance liquid chromatography method with fluorescence detection. Accuracy was >95% for the moxifloxacin standard concentrations of 0.074 mg/L, 0.15 mg/L, 0.74 mg/L, and 7.4 mg/L. Intraday precision and between-day precision (expressed as coefficient of variation) ranged from 1.4% to 5.4% and from 0.2% to 3.9%, dependent on the concentration. Ninety-eight drugs were tested for interference. The lower and upper limits of quantitation were 0.03 mg/L and 10.0 mg/L, respectively. Moxifloxacin in plasma is stable at -20°C and -80°C for at least 12 months.

Tolerability and safety. Tolerability and safety were assessed on days 1, 3, and 5 in both study phases. Patients were actively questioned about the occurrence of the known adverse effects of moxifloxacin. Clinical chemistry and hematological tests and evaluations of vital signs (i.e., heart rate and blood pressure) and electrocardiograms were performed on the same days. All possible adverse events were graded according to the Common Toxicity Criteria, version 2.0 [15].

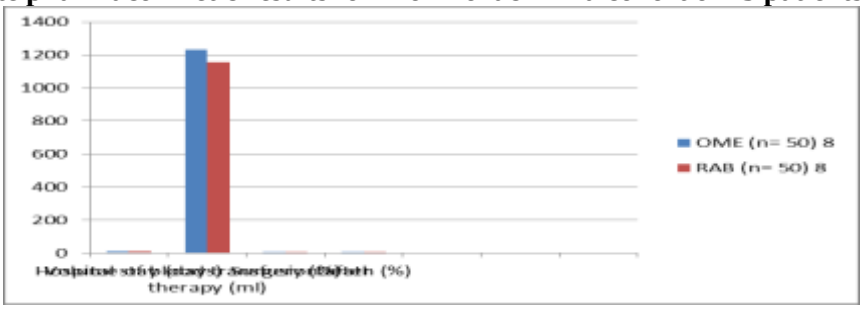
Pharmacokinetic and statistical analysis. All pharmacokinetic evaluations for rifampicin and moxifloxacin were performed using noncompartmental methods with WinNonLin software, version 4.1 (Pharsight). The highest observed plasma concentration was defined as C_{max}, with the corresponding time as t_{max}. C_{min} was the plasma concentration at 24 h after intake of study medication. The $AUC_{0–24\ h}$ was calculated using the log-linear trapezoidal rule from 0 up to the last concentration. The terminal log-linear period (log C vs. t) was based on the last data points ($n \geqslant 3$).

III.RESULTS AND DISCUSSION

Patients. 15 subjects were included in the study. The diagnosis of TB in the study subjects was based on the following clinical symptoms: history of cough (in 100% of subjects), shortness of breath (50%), fever (60%), night sweats (65%), and weight loss (65%). All patients had abnormal radiograph findings and had cultures positive for *M. tuberculosis* at initiation of TB treatment. The mean age of the 15 study subjects who completed the study (6 of whom were female) was 30 years (range, 20–55 years), and the mean weight of the subjects was 55 kg (range, 38–80 kg) at the first day of pharmacokinetic assessment. Type 2 diabetes was present in 1 patient, but the patient did not take antidiabetic medication. Adherence was excellent in all subjects: all 15 patients were 100% adherent.

pharmacokinetic parameter	Geometric mean value (range)		Geometric mean ratio of period 1 to period 2 (90% CI)
	phase 1	phase 2	
AUC 0-24hr mg X h/L	32.2(25.1-55.5)	46.1(37.2-60.5)	0.71(0.65-0.74)
Cmax mg/L	3.1(2.5-4.5)	4.2(3.4-6.0)	0.65(0.64-0.73)
cmin, mg/L	0.36(0.18-0.78)	0.62(0.51-1.1)	0.34(0.31-0.48)
Tmax,h	2.0(0.4-6.0)	1.02(0.5-3.0)	0.002
CL/F,L/h	11.8(7.2-16.0)	7.6(6.6-10.8)	1.42(1.35-1.54)
Vo/F,L	121(83-187)	112(8.4-179)	1.03(0.98-1.09)
T1/2,h	6.8(5.0-9.6)	8.2(7.4-14.0)	0.62(0.68-0.75)

Table 1: Steady state pharmacokinetic results for Moxifloxacin in a cohort of 15 patients.



Graph1: Steady state pharmacokinetic results for Moxifloxacin in a cohort of 15 patients.

Pharmacokinetics and safety of moxifloxacin and rifampicin. The geometric mean for the ratio $AUC_{phase\ 1}$: $AUC_{phase\ 2}$ of moxifloxacin was 0.71 (90% CI, 0.65–0.74). Similar figures were shown for moxifloxacin

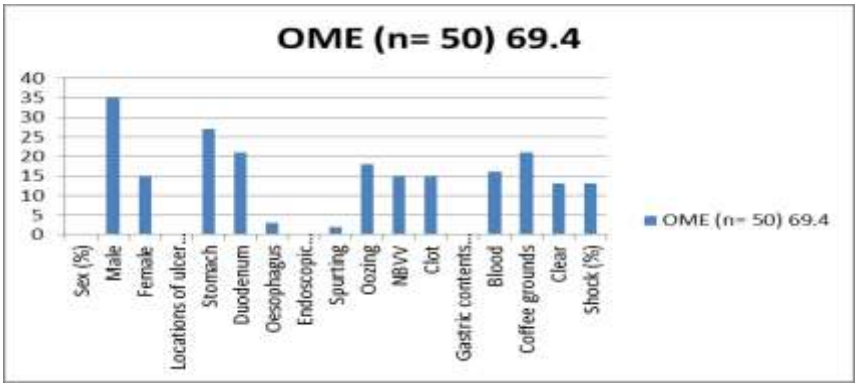
C_{max} (table 1). Moxifloxacin C_{min} showed a stronger decrease (geometric mean ratio, 0.38) when coadministered with rifampicin and isoniazid. As a result, bioequivalence for the combination of rifampicin, isoniazid, and moxifloxacin, compared with moxifloxacin alone, cannot be concluded. Moxifloxacin exposure decreased in all but 1 subject (figure 2). Moxifloxacin t_{max} was prolonged when combined with rifampicin and isoniazid (P = .003; figure 3). A relatively small interindividual variability in pharmacokinetic parameters for moxifloxacin was observed, which has been described elsewhere [25].

The geometric mean values for $AUC_{0–24\ h}$: MIC and C_{max} : MIC for moxifloxacin in phase 2 approached the desired values for fast growing bacilli (geometric mean values, 93.4 [range, 74.4–121] and 9.0 [range, 6.8–12.1], respectively), in contrast with the values in phase 1 (geometric mean values, 60.7 [range, 50.3–111] and 5.5 [4.9–9.1], respectively; P < .01). When moxifloxacin was given alone (in phase 2), 7 (47%) of 15 participants reached an $AUC_{0–24\ h}$: MIC that was >100, compared with only 1 patient (5%) when moxifloxacin was combined with rifampicin and isoniazid in phase 1. Results were similar with respect to the C_{max} : MIC ratio. The median time during which the moxifloxacin concentration was greater than the MPC was 4.5 h (range, 2.5–7.5 h) when given alone in phase 2, compared with 2.6 h (range, 0–7.5 h) when combined with rifampicin and isoniazid (P < .01).

The pharmacokinetic parameters of rifampicin and its main metabolite (desacetylrifampicin) are shown in table 2. No significant correlation was found between exposure to rifampicin ($AUC_{0–24}$) and the ratio of $AUC_{phase\ 2}$: $AUC_{phase\ 1}$ for moxifloxacin (Pearson correlation coefficient, 0.168; P = .493). The 1 diabetic patient showed average exposure to rifampicin, although plasma rifampicin concentrations have been found to be reduced in patients with type 2 diabetes [26]. The patients experienced only grade I adverse events, and no laboratory abnormalities were detected.

Drug or metabolites, Pharmacokinetic parameter	**Geometric mean value(range)**
Rifampicin	
AUC 0-24hr mgX h/L	32.6(10.4-55.4)
Cmax Mg/L	6.2(2.4-11.5)
Cmin Mg/L	0.31(0.23-0.87)
t max, h	2.1(1.5-6.0)
Cl/F, L/h	12.2(8.1-45.6)
V0/F, L	35.7(23.9- 91.8)
t1/2, h	1.8(1.4-3.1)
Desacetylrifampicin	
AUC 0-24hr mgX h/L	4.6(0.0-7.1)
Cmax Mg/L	1.2(0.0-1.5)
Cmin Mg/L	0.25(0.0-0.39)
t max, h	4.8(0.0-6.0)
t1/2, h	2.01(0.0-3.1)
Ratio of Desacetylrifampicin to rifampicin	
AUC 0-24hr mgX h/L	0.21(0.0-0.26)
Cmax Mg/L	0.18(0.0-0.21)

Table 2: Pharmacokinetic results for rifampicin And metabolites in 15 patients



Group 2: Pharmacokinetic results for rifampicin And metabolites in 15 patients

The interaction is expected to result from an increase in phase II metabolism caused by rifampicin, because moxifloxacin does not undergo phase I oxidative metabolism [13]. No interference of isoniazid in the metabolism of moxifloxacin is anticipated, because isoniazid is only known to affect cytochrome P450–mediated metabolism [27]. Rifampicin is known to be a very strong inducer of CYP-P450 isoenzymes. It is probably less well known that this drug also induces phase II metabolism. More specifically, rifampicin induces uridine diphoshate glucuronosyltransferase and sulphotransferase, thereby reducing plasma concentrations of rofecoxib, mycophenolate mofetil, lamotrigine, zidovudine, and propafenone [13, 28–34]. A similar mechanism may be involved in the interaction with moxifloxacin, because this drug undergoes phase II biotransformation and will be excreted as a sulpho-compound or as glucuronide via the kidneys (2.5% and 14%, respectively) and the feces (34% and 14%, respectively) [35]. Recently, it was found that, in healthy volunteers, rifampicin mainly induces the sulphation pathway of moxifloxacin [36]. of note, the difference in t_{max} between phases could be suggestive for a role of P-glycoprotein. The expression of P-glycoprotein in intestinal cells is induced by rifampicin, and moxifloxacin could be a substrate of this protein [37]. However, induced sulphation or glucuronidation could also cause this difference.

The $AUC_{0-24\ h}$ and C_{max} of moxifloxacin showed mean decreases of 31% and 32%, respectively. This reduction in plasma concentrations can be characterized as modest, and similar reductions in AUC (27%) and t_{max}were found in a similar study involving healthy subjects [36]. Strikingly, C_{max} was found to be unaffected by rifampicin in this study [36]. In the current study, the reduction of moxifloxacin plasma concentrations occurred almost uniformly, in all but 1 of the study subjects. Daily dosing of rifampicin instead of intermittent dosing could possibly amplify the extent of this interaction. For gram-negative, fast-growing bacteria, the greatest bactericidal effect and a decreased probability of development of resistance to fluoroquinolones occurs at $AUC_{0-24\ h}$: MIC and C_{max} : MIC ratios of $\geqslant$100 and $\geqslant$10, respectively [17, 18, 23], in which $AUC_{0-24\ h}$ and C_{max} values refer to total (i.e., both protein-bound and unbound) concentrations [18–22]. For *M. tuberculosis*, which is a slowly duplicating organism with the capacity for dormancy, the pharmacodynamic parameters for optimal fluoroquinolone activity are less well defined [21]. Recently, the activity of moxifloxacin against *M. tuberculosis* has been found to be best described by the ratio between AUC and MIC [17, 20]. Nuermberger and Grosset [21] showed that even the potent quinolone moxifloxacin, when used in TB treatment, does not reach The ideal pharmacodynamic values for activity against gram-negative bacilli. Apart from this, an MPC has been defined [24], above which plasma concentrations should be maintained to prevent the emergence of resistance. It has been demonstrated that only a few quinolones (moxifloxacin among them) achieve brief periods of concentrations above the MPC [24]. In line with this, previous research using an aerosol model concluded that a moxifloxacin dosage of 800 mg per day (instead of 400 mg per day) is likely to achieve excellent antimicrobial activity against *M. tuberculosis* and suppress drug resistance [38]. It should be acknowledged that the clinical relevance of these pharmacodynamic parameters in patients receiving multidrug treatment of TB remains unclear. Presumably, the same interaction between rifampicin and moxifloxacin is occurring in the murine model of TB treatment, and even so, the substitution of moxifloxacin for isoniazid markedly improves the activity of treatment. Therefore, it should be concluded that the clinical relevance of the interaction between rifampicin and moxifloxacin is unknown at this time, and this applies to the administration of this drug combination to shorten the duration of TB treatment, as well as for other clinical situations in which this combination is used.

On the basis of the current study, we would propose that follow-up pharmacokinetic studies be performed to assess whether an increase in the dose of moxifloxacin to 600 mg or 800 mg compensates for the decrease in

plasma levels caused by (daily) coadministration of rifampicin. In addition, a study of the pharmacokinetic interaction between moxifloxacin and rifapentine (another rifamycin) is warranted, considering that clinical trials involving this combination are underway. Finally, additional research should be performed to explore the activity and tolerability of higher doses of moxifloxacin, even in the absence of rifampicin coadministration.

Our study is limited by the design of the study, which did not allow discrimination between an effect on the moxifloxacin metabolism of rifampicin or isoniazid. In addition, the MIC and MPC values of *M. tuberculosis* for moxifloxacin were not determined but were based on previous findings. Therefore, pharmacodynamic ratios were partly derived. Furthermore, this study was not designed to assess the impact of moxifloxacin on the pharmacokinetics of rifampicin. Such an effect is not expected, because moxifloxacin does not induce any metabolism.

CONCLUSION

we showed a 31% decrease in exposure to moxifloxacin when combined with intermittently administered rifampicin and isoniazid in patients with TB. A higher dose of moxifloxacin may possibly overcome the effect of rifampicin on the pharmacokinetics of moxifloxacin. Additional studies are warranted to assess the pharmacokinetics, dynamics, and tolerability of a higher dose of moxifloxacin when combined with rifampicin or other rifamycin derivatives.

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