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Determination of C_{max} and T_{max} of Fixed-Dose Combination (FDC) of Anti-Tubercular Drugs by performing High-Performance Liquid Chromatography (HPLC)

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ABSTRACT

Tuberculosis (TB) is a leading cause of mortality and morbidity around the world. Every year, more than 9 million individuals are diagnosed with active tuberculosis, and 1.6 million people die as a result of the illness. We, therefore, determined the pharmacokinetic parameter of C_{max} and T_{max} of the fixed-dose combination of anti-TB drugs in patients by performing TDM using High-Performance Liquid Chromatography (HPLC) using pharmacokinetic sampling. In 30 TB patients, plasma concentrations were determined just before and at 1, 2, 4, 8, 12, 16, and 24 h after observed drug intake to assess the peak plasma concentrations (C_{max}) and Time to achieve peak plasma concentration (T_{max}) of isoniazid, rifampin, pyrazinamide, and ethambutol. The C_{max} was below the reference range for isoniazid in 30 patients and rifampin in 24/30 patients. The C_{max} for pyrazinamide and ethambutol was not below the reference range in any of the patients. Increasing the dose of isoniazid and rifampicin may simultaneously also increase the concentration of pyrazinamide and ethambutol, which is already in between the reference range. The desired therapeutic effect of isoniazid and rifampicin may not be produced in the patients. In FDC drugs, it is impossible to withdraw a single drug that produces a side-effect, ADR, and increasing or decreasing the dose of a single drug is not possible in this formulation. So, due to the above reasons and problems, suggesting using individual drugs in the tuberculosis treatment instead of a Fixed-Dose Combination (FDC).

Keywords: *Tuberculosis, Fixed-dose combination, TDM, HPLC, C_{max}*

1. INTRODUCTION

Tuberculosis (TB) is an airborne disease caused by Mycobacterium tuberculosis (MTB) that generally infects the lungs that leads to severe coughing, fever, and chest pains[1]. Mycobacterium tuberculosis is transmitted by minute airborne droplets. These microscopic particles can float in the air for minutes to hours following expectoration[2]. Globally, tuberculosis (TB) is the second leading cause of mortality due to infectious diseases, followed by Human Immunodeficiency Virus (HIV) infection[3,4]. The prevalence of TB is 1.6 million people died due to tuberculosis (including 214 000 people with HIV) and approximately 9 million individuals would become infected with tuberculosis (TB). Tuberculosis (TB) affects people of all ages and from all nations[5,6]. DOTs therapy was first utilized in the treatment of tuberculosis in 1995[7]. DOTS treatment lasts six to nine months and consists of four drugs: isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB)[8]. The World health organization introduced a fixed-dose combination in the year 2017. A Fixed-Dose Combination (FDC) combines two, three, or four drugs in the appropriate dose on one tablet. In TB, there are two phases of treatment (Intensive and continuous phase). The drugs involved in the intensive phase such as isoniazid (75mg), Rifampicin (150mg), Pyrazinamide (400mg), and Ethambutol (275mg) in a fixed-dose combination for two months. In the Continuous phase, Rifampicin (150mg), Isoniazid (75mg), and Ethambutol (275mg) in a fixed-dose combination for four months[9-10]. As per WHO-approved FDCs for all TB patients to enhance overall outcomes and decrease MDR risk. It increases treatment adherence since most patients only need to take 3 or 4 tablets per day throughout the intensive treatment period instead of

10–12 tablets[11]. So, the current study is to determine the C_{max} and T_{max} of Fixed-Dose Combination (FDC) of Anti-tubercular drugs by performing TDM using High-Performance Liquid Chromatography (HPLC).

2. MATERIALS AND METHODS

2.1 Study designs

This study was a pilot prospective, observational study conducted over six weeks in a multispecialty tertiary care hospital with a newly diagnosed active tuberculosis infection. The samples were analyzed using the HPLC technique. The institutional committee approved the study in Tamil Nadu, India. Ethical clearance number: 1454/IEC/2018.

2.2 Study Population

The written informed consent form was obtained from the patient before starting the treatment. The inclusion criteria were patients with a newly diagnosed patient of either gender with active tuberculosis infection of greater than 18 years of age. The patients with chronic liver disease, pregnant and lactating women, renal impairment patients, extra-pulmonary tuberculosis patients, and those who were not willing to give informed consent forms are excluded from the study.

2.3 Study Method

A total of 35 patients were recruited for the study, of which four patients didn't meet the inclusion criteria. An observational study was conducted on 31 patients, of which one patient was lost the follow-up.

2.4 Administration Criteria

As per World Health Organization guidelines,

Patients with a bodyweight of 25-39 kg should take 2 FDC tablets daily, while those with a 40-54 kg bodyweight should take 3 FDC tablets daily. Patients with bodyweight between 55 and 69 kg should take 4 FDC tablets daily, whereas patients with a bodyweight greater than 70 kg should take 5 FDC tablets daily[12].

2.5 Drug administration

Patient demographic details were collected. Anti-tubercular FDC drugs (Rifampicin-150 mg, Isoniazid-75 mg, Pyrazinamide-400 mg, Ethambutol-275 mg) were administered to the patient for 45 days. As per the schedule, the patients were requested to fast overnight on the day. On the 46^{th} day, a 4ml blood sample was collected from the patient on a median cubital vein in the forearm at 1,2,4,8,12,16, and 24^{th} hours after drug administration to assess C_{max} and T_{max} FDC drugs. The Plasma drug concentration (mg/liter) of Isoniazid (H), Rifampicin (R), Pyrazinamide (P) and Ethambutol (E) Vs. time Profile (hours) curve has been recorded.

2.6 Measurement tool

The blood sample was collected and transferred into a vacutainer tube containing sodium Ethylene diamine tetraacetic acid (NA2 EDTA). The tube was closed and gently tilted up and down (frothing should be avoided) and labeled with patient identity, then the samples were centrifuged for 10 minutes at 4000 rpm (rotation per minute) to separate the plasma. After centrifugation, 2ml of plasma was transferred without any air bubbles using a micropipette (1000µl) by placing the tip (Tarsons Micro tip, 200-1000µl) of the pipette under the surface of the plasma.

2.7 Preparation of Patient's Plasma samples

Then 2ml of Acetonitrile solution was added to the plasma. The mixture was centrifuged again for 20 minutes at 2000 rpm. The clear supernatant liquid was filtered with 20µm Whatman filter paper using a funnel and then transferred into a 10ml conical flask. The solution was made up of an Acetonitrile-HPLC water mixture.

The final solution was mixed using an ultrasonicator for about 20 minutes. Finally, the solution was injected into the HPLC column for analysis.

2.8 Simultaneous estimation of a fixed-dose combination of Anti-tubercular drugs (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) samples by high-performance liquid chromatography (HPLC) method

2.9 Reagents and chemicals

RIF, INH, PYZ, and EMB reference standards were obtained as gift samples. Ultrapure water was obtained from a Milli-Q RO system. The analytical grade (Phosphate buffer) and HPLC grade (Acetonitrile) chemicals with more than 95% purity were used in the study.

2.10 Chromatographic Conditions

Agilent technologies HPLC (autosampler) system was used for the analysis. The stationary phase consists of the ZORBAX eclipse plus C18 column (100 x 4.60mm). The mobile phase was composed of acetonitrile: phosphate buffer (pH 3.7) in a ratio of 2:98 % v/v, with a sample volume of 10 µl using Rheodyne injector and absorbance was detected at 286nm and 518

nm using PDA-detector in OPEN LAB data station.

The mobile phase was filtered through a 0.22µ membrane and degassed using Ultrasonicator. The HPLC analysis was carried out at room temperature of about 20ºC[13].

2.11 Preparation of standard solutions

A stock solution was prepared by dissolving 100 mg of rifampicin in 100 ml of Acetonitrile: Phosphate buffer in a 2:98 (v/v) ratio, representing 1000µg/ml of Rifampicin concentration. Further this stock solution was used to prepare the standard solutions containing 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 30, 40 and 50µg/ml of rifampicin using HPLC water and Acetonitrile: Phosphate buffer (2:98 v/v).

Similarly, a stock solution of isoniazid, pyrazinamide, and ethambutol was prepared separately by dissolving 100 mg of drug in 100 ml of Acetonitrile: Phosphate buffer in a 2:98 (v/v) ratio, representing 1000µg/ml concentration. Further, this stock solution was used to prepare the standard solutions containing 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 30, 40, and 50µg/ml of isoniazid, pyrazinamide, and ethambutol using HPLC Water and Acetonitrile: Phosphate buffer (2:98 v/v)[14].

2.12 2.6 Analysis of Data

The plasma concentrations of isoniazid, pyrazinamide, rifampicin, and ethambutol were quantified using the HPLC technique. The pharmacokinetic parameters of C_{max} and T_{max} were calculated using the Win Nonlin Standard Version 5.01 software. The results were compared statistically by ―GraphPad Prism software.

3. RESULTS

Thirty-one patients with active tuberculosis have been enrolled in the study. The age of the patients ranged from 35–45 years, with a mean, standard deviation value of 40.6±3.39. The mean, standard deviation value of the bodyweight of the patients is found to be 46.8±5.28 kg, which is a range of 37–57 kg. The height of the volunteers ranged from 158-172 cm.

During the review, 01 patient were lost their follow-up. The peak plasma concentration (C_{max}) of TB drugs can be achieved on the 46th day. The drugs were administered for 45 days, and a blood sample(s) were collected on the 46th day after drug administration (i.e., approximately six weeks). According to these concentrations, the pharmacokinetic parameters of C_{max} and T_{max} of isoniazid, rifampicin, pyrazinamide, and ethambutol were calculated as mean, standard deviation and shown in Tables 2, 3, 4, 5, and 6, respectively. The reference ranges for C_{max} were 3 to 5 mg/liter for isoniazid, 8 to 24 mg/liter for rifampin, 20 to 50 mg/liter for pyrazinamide, and 2 to 6 mg/liter for ethambutol, respectively.

The mean, standard deviation value of the C_{max} of FDC drugs was obtained from 1, 2, 4, 8, 12,

16 and 24 hours. The mean, standard deviation of C_{max} of isoniazid was found to be 2.162±0.12, 2.521±0.10, 1.426±0.14, 0.344±0.11, 0.086±0.02, 0.032±0.01 and 0.004±0.001 mg/liter, which is less than the reference value (3 to 5 mg/liter) of isoniazid. The peak plasma concentration of isoniazid was below when compared with the reference range.

The mean, standard deviation value of the obtained C_{max} of rifampicin was found to be 7.217±0.21, 8.365±0.25, 4.491±0.18, 1.121±0.15, 0.287±0.10, 0.072±0.02, 0.004±0.002

mg/liter is below the reference value (9 to 24 mg/liter) of rifampicin. The rifampicin peak plasma concentration in 24 patients (80%) was below the reference range.

The mean, standard deviation value of the obtained C_{max} of pyrazinamide was found to be 30.712±1.24, 38.773±0.87, 33.201±0.75, 26.146±0.81, 15.120±0.65, 12.174±0.47,

5.761±0.91 mg/liter, which is between the reference value (20 to 50 mg/liter) of pyrazinamide. The peak plasma concentration of pyrazinamide was within the reference range.

The mean, standard deviation value of the obtained C_{max} of ethambutol was found to be 2.864±0.24, 3.368±0.14, 2.521±0.11, 1.261±0.09, 0.634±0.12, 0.273±0.08,

0.068±0.03mg/liter is between the reference value (2 to 6 mg/liter) of ethambutol. The peak plasma concentration of ethambutol was within the reference range.

The Mean Standard Deviation value of the obtained T_{max} of isoniazid, rifampicin, pyrazinamide, and ethambutol was found to be 1.21±0.1174 hr, 1.33±0.1424 hr, 1.23±0.1388 hr, 1.51±0.0743 hr.

4. DISCUSSION

This study shows important data on the pharmacokinetic parameter (C_{max} and T_{max}) of a fixed-dose combination of anti-tubercular drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) based on 24-hour pharmacokinetic sampling in TB patients. Isoniazid and rifampicin are the first-line agents in the treatment of tuberculosis. The concentration of both the drugs must reach the therapeutic index to show their efficacy in the treatment. In our study, isoniazid and rifampicin have failed to

reach the minimum therapeutic concentration. So, to overcome the above problem, the dose of isoniazid and rifampicin needs to be increased. Similar results were found with the study conducted by *Alma Tostmann et al*., which shows that the plasma concentration of isoniazid and rifampicin was below the reference range[15].

On the other hand, the C_{max} of the other two drugs in the combination, i.e., Pyrazinamide and Ethambutol, are within the reference ranges. It crosses the minimum therapeutic concentration to reach the therapeutic index. Similar results were found with the study conducted by *Alma Tostmann et al*., which shows that the plasma concentration of pyrazinamide and ethambutol was within the reference range[15].

Previous research has shown that consuming high cholesterol or carbohydrate food immediately before taking isoniazid affects the rate of absorption and greatly reduces the C_{max} of isoniazid by 20% to 51%[16-17]. When taken immediately after a meal, the C_{max} of rifampicin can be lowered by up to 36%[18]. Food does not influence the C_{max} of Pyrazinamide or Ethambutol[19].

Although after drug administration, if the patient experiences any adverse hypersensitivity reaction. It is difficult to determine which drug (one of the four drugs) is responsible for the adverse effect. Similarly, in African nations, a pharmacokinetic study is conducted by Chideya conducts. *et al.*and *Tappero. et al.* reported an even higher proportion of individuals with C_{max} values below the standard range for isoniazid (30% in Botswana [20,21]and 89% in Kenya[22]) and rifampicin (69% in South Africa[23]), 78 to 84% in Botswana, and 90% in Kenya), despite administration of drugs on an empty stomach. In our study, the average Tmax values for the TB drugs about 1 h for isoniazid, rifampin, pyrazinamide, and ethambutol were shown in Table.6.

Overcoming the above problem, we should increase the dose of isoniazid and rifampicin. In FDC formulation it is not possible to increase the dose for both drugs separately. It may also simultaneously increase the concentration of pyrazinamide and ethambutol, which is already in between the reference range. Therefore, it may lead to adverse effects due to the increased concentrations of pyrazinamide and ethambutol in the blood. The C_{max} of pyrazinamide and ethambutol may reach the maximum therapeutic concentration range and the toxic range, eventually producing adverse effects.

Table 1: Demographic details of the Pulmonary TB Patients enrolled in the study

Characteristics	**Value** **(Mean ± Standard deviation)**
Male (%)	83%
Age in years	40.6±3.39
Weight in kg	46.8±5.28
Height in cm	166.9±3.59

Table 2: Plasma concentration(mg/L) of isoniazid in pulmonary TB patients at 1,2,4,8,12,16,24 hr after intake of Anti-Tuberculosis FDCtablets.

Isoniazid (75 mg) **(Time/hr)**	**Plama drug concentration C_{max}** **(Mean ± Standard deviation)**
1 hr	2.162 ± 0.12
2 hr	2.521 ± 0.10
4hr	1.426 ±0.14
8hr	0.344 ± 0.11
12hr	0.086 ± 0.02
16hr	0.032 ±0.01
24hr	0.004 ± 0.001

Table 3: Plasma concentration (mg/L) of rifampicin in pulmonary TB patients at 1,2,4,8,12,16,24 hr after intake of Anti-Tuberculosis FDCtablets.

Rifampicin(150 mg) (Time/hr)	**Plama drug concentration Cmax (Mean ± Standard deviation)**
1hr	7.217 ± 0.21
2hr	8.365 ± 0.25
4hr	4.491 ± 0.18
8hr	1.121 ± 0.15
12hr	0.287 ± 0.10
16hr	0.072 ± 0.02
24hr	0.004 ± 0.002

Table 4: Plasma concentration(mg/L) of pyrazinamide in pulmonary TB patients at 1,2,4,8,12,16,24 hr after intake of Anti-Tuberculosis FDCtablets.

Pyrazinamide (400 mg) (Time/hr)	**Plama drug concentration C_{max} (Mean ± Standard deviation)**
1hr	30.712 ±1.24
2hr	38.773 ±0.87
4hr	33.201 ± 0.75
8hr	26.146 ± 0.81
12hr	15.120 ± 0.65
16hr	12.174 ± 0.47
24hr	5.761 ± 0.91

Table 5: Plasma concentration (mg/L) of ethambutol in pulmonary TB patients at 1,2,4,8,12,16,24 hr after intake of Anti-Tuberculosis FDCtablets.

Ethambutol (275 mg) (Time/hr)	**Plama drug concentration Cmax (Mean ± Standard deviation)**
1hr	2.864 ± 0.24
2hr	3.368 ± 0.14
4hr	2.521 ± 0.11
8hr	1.261 ± 0.09
12hr	0.634 ± 0.12
16hr	0.273 ± 0.08
24hr	0.068 ± 0.03

Table 6: T_{max} of pulmonary TB patients after intake of Anti-Tuberculosis FDC tablets

FDC drugs	Tmax (Mean ± Standard deviation)
Isoniazid Rifampicin Pyrazinamide Ethambutol	1.21 ± 0.1174 1.33 ± 0.1424 1.23 ± 0.1388 1.51 ± 0.0743

5. CONCLUSION

This study showed that the peak plasma concentration (C_{max}) of Isoniazid and Rifampicin is below the reference range in the Fixed-Dose Combination of Anti-tubercular drugs. The desired therapeutic effect of isoniazid and rifampicin might not have been produced in the patients. In FDC drugs, it is not feasible to increase or decrease the dose of a single drug. Similarly, it is not feasible to withdraw a single drug that produces a side-effect or ADR. For the above reasons and problems, this study suggests using individual drugs in the treatment of tuberculosis instead of a Fixed-Dose Combination (FDC).

6. LIMITATIONS

This study was conducted with a smaller sample size in a single study center. Therefore, future studies with a large sample size are required.

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