Rifampin Pharmacokinetic in Saudi Adult TB Patients

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Introduction

Introduction:

* Tuberculosis (TB)
  * TB still one of most important health problems.
  * TB is a contagious disease, it spreads through the air.
    * Only people who are with pulmonary TB are infectious.
    * A person needs only to inhale a small number of these to be infected.
    * Left untreated, each person with active TB will infect between 10 and 15 people every year.

Introduction: (Cont.)

- TB occupies 4th place among major causes of death, and:

  - The number of new cases is estimated at 8.8 Million / Year.

  - TB kills 2 Million people each year.

  - About 99% of TB deaths and 95% of new TB cases are seen in developing countries.

  - 80% of TB patients are in the economically productive age of 15 to 49 years.

Distribution of individuals infected with tuberculosis worldwide.
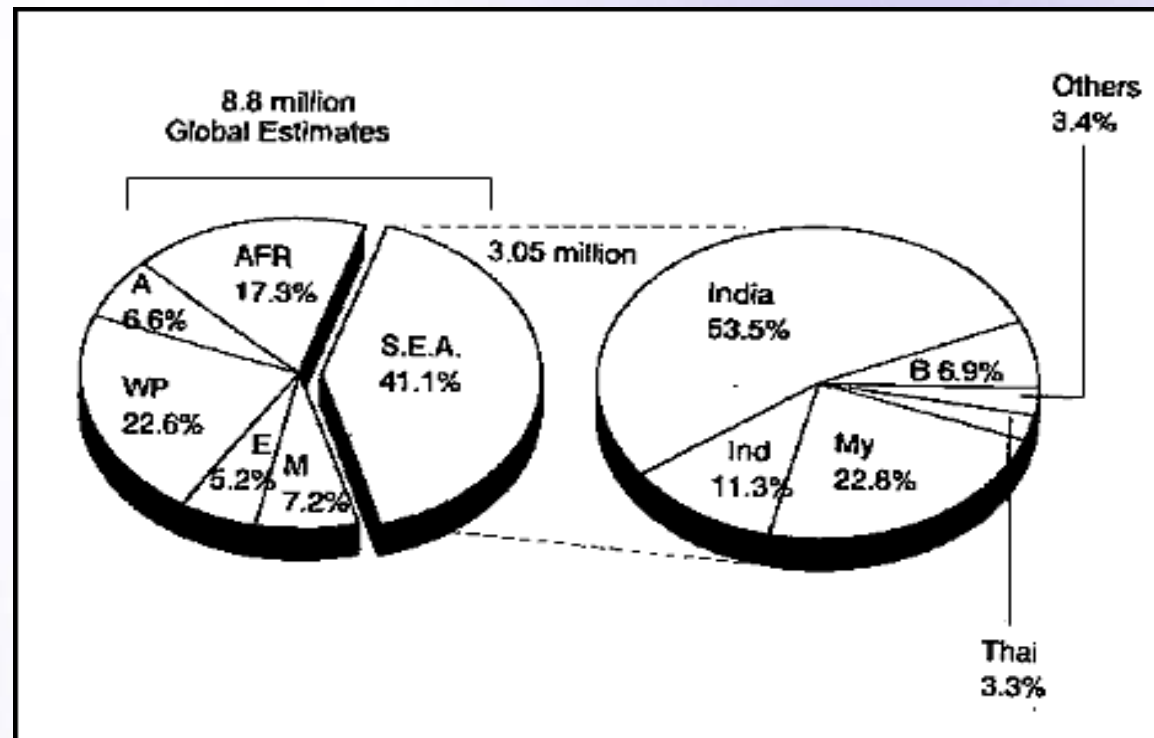
Introduction: (Cont.)

➕ TB is the largest cause of death from a single infection worldwide;

- ➢ Its infects fully one-third of the world's population,
- ➢ It is estimated that between 2000 and 2020,
  - ✓ Nearly one billion people will be newly infected,
  - ✓ 200 Million people will get sick, and
  - ✓ 35 Million will die from TB (if control is not further strengthened).

Introduction: (cont.)

✹ Rifampin

　✚ It is used in the treatment of tuberculosis, for which is considered a first line agent.

　　➢ Asymptomatic carriers of Neisseria meningitis.

　　➢ Prophylaxis against H. influenzae type B.

　　➢ Hansen's disease (leprosy).

　　➢ Atypical mycobacterial infection, and

　　➢ Saphylococcal infection.

Introduction: (cont.)

- Rifampin could be Bactericidal or bacteriostatic.

- Inhibits bacterial and mycobacterial RNA synthesis.

- Absorbed rapidly from the GI tract .

- Metabolized in the liver to an active metabolite, *desacetyl-rifampin*, via deacetylation.

Introduction: (cont.)

✚ Rifampin pharmacokenitic:-

➢ V_d (Population value) $= 0.6$ L/kg.

➢ Therapeutic conc. $= 0.5 - 10$ ug/ml .

➢ $T_{1/2} = 3$ hr .

➢ Peak serum concentrations (of 6 to 8 ug/ml) occurring 1.5 to 2 h after ingestion.

Introduction: (cont.)

- Patients with mycobacteria have altered pharmacokinetic profiles for antimycobacteria drugs :-
    - Malabsorptions / reabsorbtion
- Therapeutic drug monitoring (TDM)
    - Optimize therapy to achieve success.
    - Management of interaction.
    - Monitor and evaluate drug compliance.
    - Minimize toxicity.

Study objective

Study objective :

1- Investigate the pharmacokinetic of *Rifampin.*

2- Study the intrasubject and intersubject variability and the effect of drug level on therapy or treatment failure.

3- Study the effects and magnitude of patient demographics data, concomitant drugs, and diseases on *Rifampin* plasma level, and on therapy in general.

Methodology

Methodology:

➕ Patient:

➢ Study population:

✓ Saudi adult patients who admitted to King Khalid university hospital between 15-9-2000 to 1-12-2000 with pulmonary tuberculosis disease.

✓ Treatment was initiated, and patients were asked to avoid food for at least 2 hours before dose.

Methodology: (cont.)

➤ Study population: (cont.)

✓Relevant demographic, clinical, and laboratory information for each patient, including all concurrent illness and medications.

✓Clinical and bacteriological outcomes, as available from routine follow-up were recorded.

Methodology: (cont.)

➢Inclusion criteria:

✓Patients were included in this study if they were older than 18 years, and were diagnosed with active pulmonary tuberculosis by clinical criteria and positive culture.

Methodology: (cont.)

➢ Exclusion criteria:

✓ Patients were excluded if they were pregnant or nursing, had renal insufficiency, hepatic insufficiency, or gastrointestinal disease.

Methodology: (cont.)

- **Sampling:**

  - Blood sample were drawn from each patient at 2 hr after administration of Rifampin 600 mg.

  - Samples collected in plain vacuum tube, then the samples centrifuged at 3000 rpm for 10 min.

Methodology: (cont.)

➢ Plasma decanted in coded polypropylene tube containing 0.5 mg ascorbic acid per 1 ml plasma.

➢ The samples were stores frozen at - 70'C pending analysis.

Methodology: (cont.)

- Method of analysis:

  - New reversed-phase high-performance liquid chromatographic (HPLC) method was developed for this study:

    - ✓ To improve sensitivity and specificity

    - ✓ Many of the other methods involved :

      i. Very lengthy, and

      ii. Time consuming sample extraction

Methodology: (cont.)

- **Method of assay :** (cont.)
  - The chromatographic condition utilized were arrived at after investigation:
    - Several mobile phase.
    - Several internal standard.
  - The retention times of rifampin and internal standard were 7.5 and 1.2 min, respectively.

Methodology: (cont.)

- **Method of assay :** (cont.)
  - ➢ Quantitation of Rifampin in plasma was determined by:
    - ✓ The slope of the calibration curve (standard curve).
    - ✓ Peak-area ratio for Rifampin and the internal standard (tetracycline HCL).
  - ➢ The calibration curves were described by:
    - ✓ Y= 0.0459 (+/- 0.011) + 0.0347(+/- 0.0349)X
    - ✓ r = 0.98 (+/- 0.02)

Methodology: (cont.)

Method of assay: (cont.)

➤ Sample preparation and analysis were conducted at room temperature.

➤ For preparation of sample for injection onto HPLC system, the internal standard (tetracycline HCL, 1 mg/ ml) was added to plasma sample.

Result

Result :

- Eight patients received standard therapy for TB had serum level drown during the study period.

- Serum level were evaluated at 2 hr after observed ingestion of the drug.

- Only one patient diabetic on diet control,one with sickle cell, and one with osteoporosis.

Patient Demographic Data

	Mean	Std. D	Range
Age (year)	40	+/-18.3	22-66
Weight (kg)	63.6	+/-15.1	41-83
Height (cm)	162	+/-11.2	144-174
Dose (mg/kg)	9.9	+/-2.5	7.2-14.6
App.Rif. Clearance (ml/hr/kg)	134.7	+/-75.3	58.6-264.2

Patient Demographic Data

	MALE	FEMAL
Age (yrs)	33 +/-16.8 (22 – 58)	47 +/-19.1 (24 – 66)
Weight (kg)	68.8 +/-16.5 (53 – 83)	58.5 +/-13.8 (41 – 70)
Height (cm)	167.3 +/-5.0 (162 – 172)	156.8 +/-13.9 (144 – 174)

Patient Clinical Data:

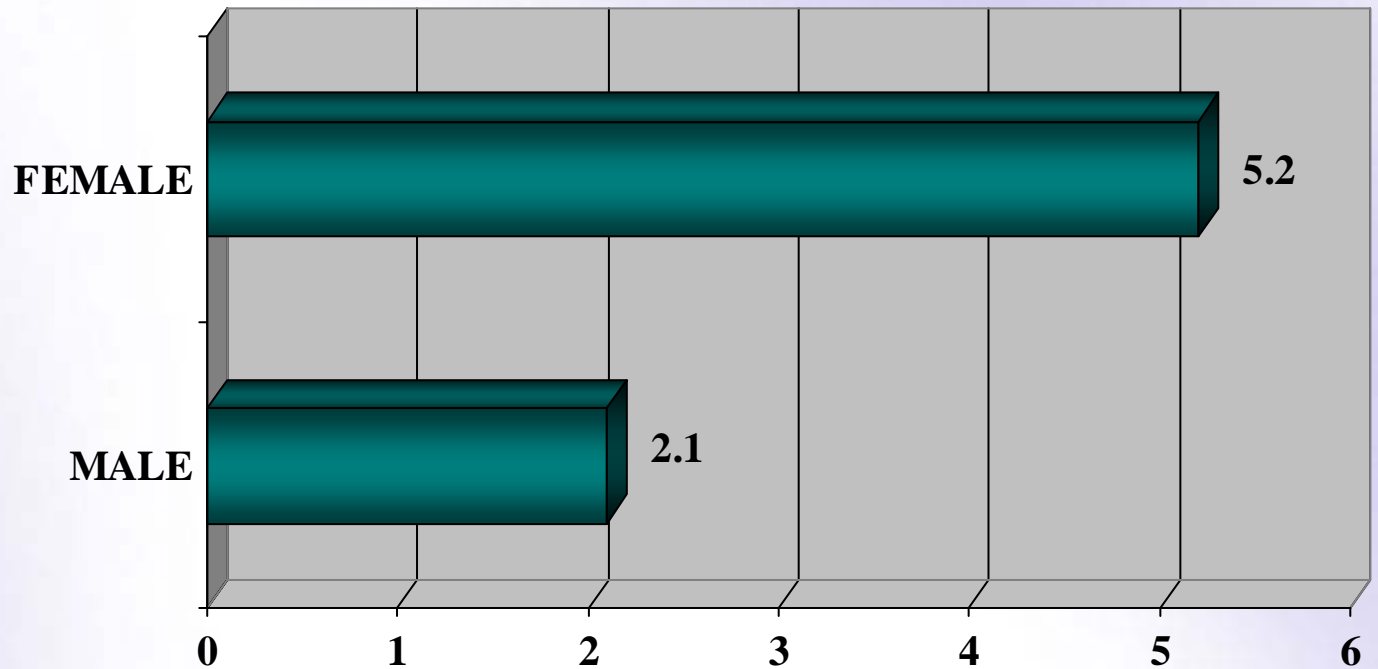|	Minimum	Maximum	Mean
ALBUMIN	23.00	37.00	30.5
T_BILIRU	6.00	30.00	12.0
D_BILIRU	1.00	11.00	3.87
HEMOGLOB	19.00	63.00	44.25
Alk. PHOS	47.00	225.00	121.37
AST	13.00	99.00	35.87
SR_CREAT	50.00	91.00	70.62
BUN	1.40	5.40	3.60
CONC_PL	1.14	7.90	3.90

Rifampin Plasma Level
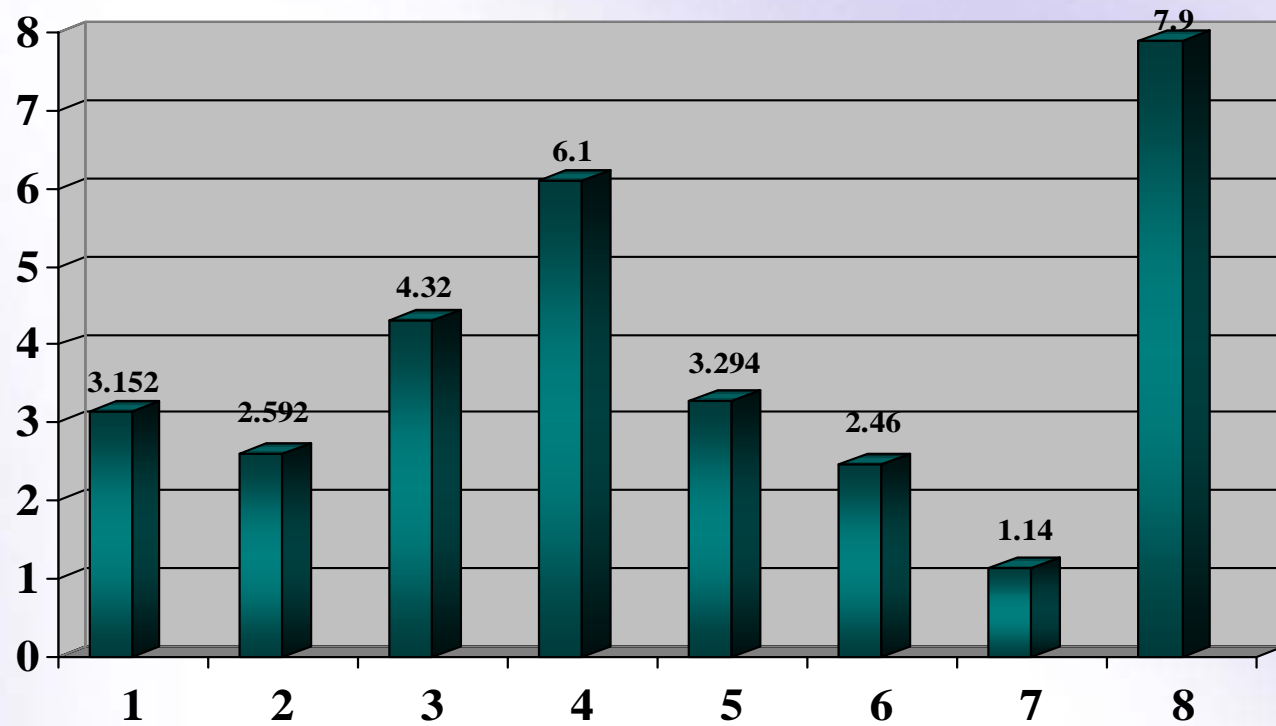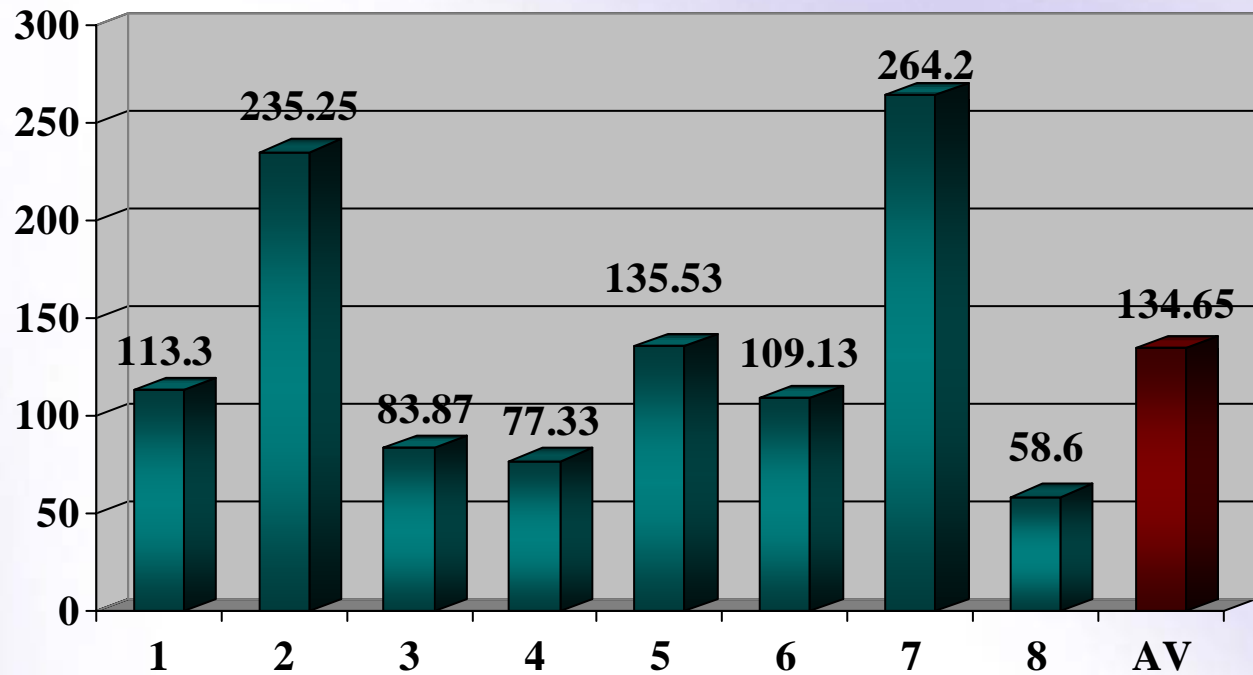
Male vs. Female Plasma Level
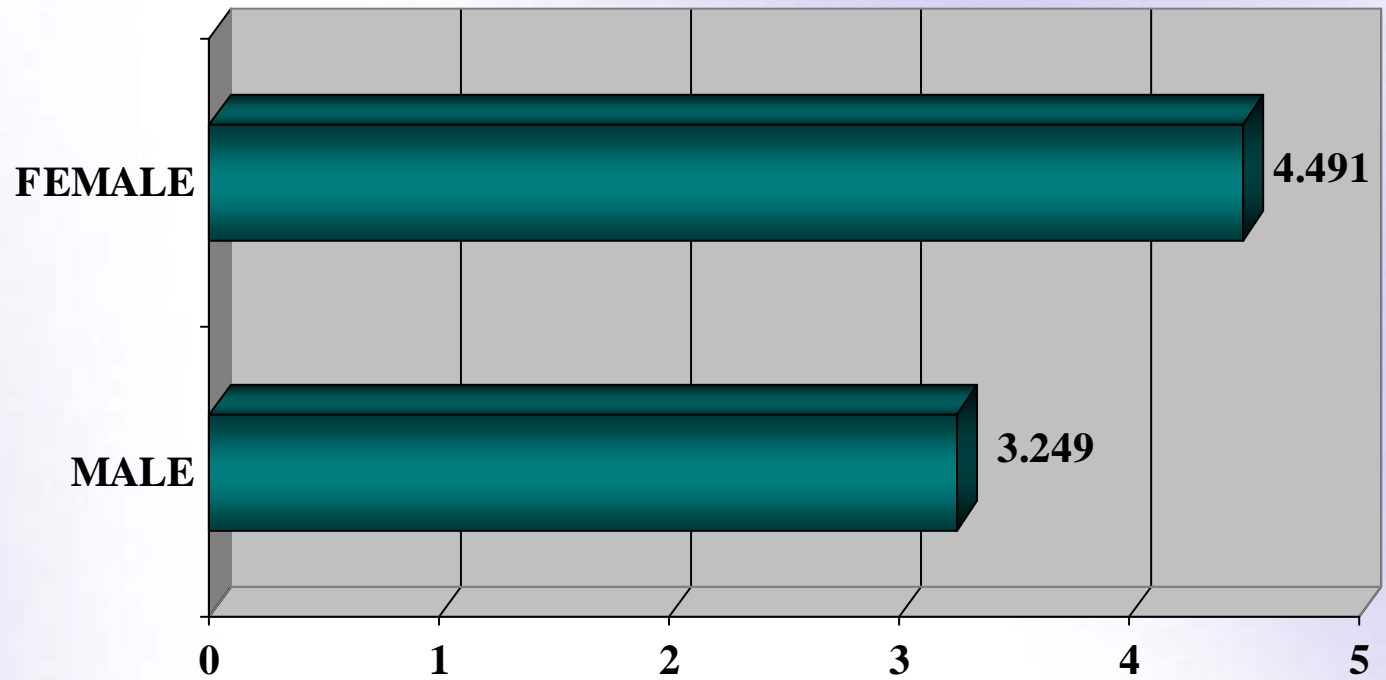
Male vs. Female Plasma Level

Low Serum Antimycobacterial Drug Level in Non-HIV infected tuberculosis Patients ; CHEST/ 113/ 5/ MAY 1998

Apparent clearance for patient on Rifampin
ml/hr/kg

Comment

Discussion:

- Our result have showed no statistical significant effects ($p > 0.05$) were detected of either age, gender, clinical body function or other concurrent illness and medications.

- These result suggest that malfunction in the GI tract properly cause the low plasma concentration of Rifampin.

Discussion: (cont.)

- In general, low plasma concentration of Rifampin highlights a potential clinical problem:

  - ➢ Slow/delayed clinical response to therapy.

  - ➢ Early relapse with failure to cure.

  - ➢ Treatment failure associated with acquired multi-drug resistant tuberculosis.

Discussion: (cont.)

- A limitation of this pilot study is that :

  - Only one blood sample was collected and analyzed.

  - Samples were collected 2 hours after dosing to approximate the t max for Rifampin.

  - The short time of the study and resources availability limits the recruitment more patients in this study.

Discussion: (cont.)

- This is a pilot study involving a limited number of patients and blood draws. The data were unusual and potentially worth studying in the future.

- Despite the efforts, the study sample may not represent the full spectrum of Saudi pulmonary TB patients.