

## PHARMACOKINETICS OF OFLOXACIN, RIFAMPICIN, ISONIAZID AND PYRAZINAMIDE WHEN ADMINISTERED ALONE AND IN COMBINATIONS

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The present study assesses the bioavailability of Ofloxacin (O) following single oral administration of the drug along with Rifampicin (R), or Isoniazid (H), or Pyrazinamide (Z) or a combination of three drugs. Information on the pharmacokinetics of O in the presence of R, H and Z based on the blood concentrations upto 8 hours, on the proportions of the doses of the drugs and their metabolites excreted in urine upto 8 hours and also the effect of O on the other anti-tuberculosis (TB) drugs in terms of absorption and interactions are extensively studied. The bioavailability indices of these drugs are assessed. The investigation was undertaken in a total of 12 male healthy volunteers and each volunteer was investigated on four different occasions at weekly intervals. A partially balanced incomplete block design was employed and the allocation of O or the drug combinations was at random. Plasma concentrations of O, R, H and Z were determined. Urinary excretion of these drugs, together with their primary metabolites was also determined. Various pharmacokinetic parameters were calculated. The results have shown that the bioavailability of O is not impaired when administered with other anti-tuberculosis drugs like R, H and Z and does not exercise any therapeutic penalty. The bioavailability of other anti-TB drugs like R, H and Z does not get affected when administered along with O. Human bioavailability studies, in general, provide direct straightforward information on the degree of absorption and biotransformation of drugs. The results of the present study indicate that the pharmacokinetic properties of O, R, H and Z as assessed after individual and combined administration of these drugs do not get affected or altered. Since there are no interactions among these drugs, the use of O in the treatment of pulmonary tuberculosis is justified.

**Kew Words :** Anti-tuberculosis drugs; Bioavailability; Drug interactions; Ofloxacin.

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### INTRODUCTION

Tuberculosis has been and continues to be the leading cause of death world wide from a single infectious agent, *M. tuberculosis*.

Though, the treatment of tuberculosis with multidrug therapy witnessed a dramatic improvement in the control of the disease, the main problem encountered in implementing these regimens is the

prolonged course of therapy and poor compliance.

The advent of the new quinolone, Ofloxacin (O), a synthetic carboxy quinolone has broadened rather unexpectedly the therapeutic efficacy against infections with mycobacteria.

Studies on the pharmacology of O have gained importance in view of the suitability of this drug for the chemotherapy of tuberculosis. This drug is reported to be as powerful as R and H and superior to streptomycin in terms of bactericidal activity. Ofloxacin appears to be as useful as ethambutol in the treatment of pulmonary tuberculosis when either drug is combined with H and R (Kohno, 1992).

Since, only limited information is currently available on the pharmacokinetic interactions of O in the presence of other anti-tuberculosis drugs, viz., R, H and Z, this study is designed to rigorously characterise the interaction potentials between O and other anti-TB drugs. Therefore, an investigation was carried out to obtain information on the plasma and urinary excretion of O alone and in combination with other anti-TB drugs mentioned above and also to study the effect of O on the other anti-TB drugs.

This investigation was carried out in collaboration with the Department of Pharmacology, Madras Medical College, Chennai.

## **MATERIALS AND METHODS**

### **Experimental design**

A partially balanced incomplete block design was adopted where the drugs were administered to the healthy volunteers, a week apart, a random.

### **Subjects**

Twelve male healthy volunteers with the mean age of 23 years (range 19-27 years) and the mean body weight of 56 kg (range

45-69 kg) were admitted to the study. The volunteers were healthy as assessed by comprehensive medical history, physical examination and laboratory profiles for diabetic, renal and hepatic functions. None of the subjects was taking any medications one week before or during the study for any ailment and also are non-alcoholics. Informed written consent was obtained from the subjects, and the study was approved by the Ethical Committee of the Centre.

### **Assay for the stated contents of the drugs**

Before starting the study, six samples of each of drugs (O, R, H & Z) were assayed for the stated contents, on five different occasions to check for the potency and the stated contents. The drugs were obtained from the same batch.

### **Conduct of the investigation**

Each volunteer was investigated on 4 different occasions with the 4 drugs administered either alone or in combinations (O, R, H, Z, OR, OH, OZ and ORHZ) with an interval of at least one week between occasions. The drugs were administered on an empty stomach after emptying the bladder. The dosages of the drugs administered to the volunteers under investigation, were approximately 10 mg/kg body weight for R (Asojsof Caps. Pvt. Ltd.) and 35 mg/kg for Z (Lupin Laboratories); the dosages of O (Dee-Pharma Ltd.) and H (Pfizer) used were 10 mg/kg for the subjects weighing <40 kg and 15 mg/kg for subjects weighing 2 40 kg. body weight for R (Asojsof Caps. Pvt. Ltd.) and 35 mg/kg for Z (Lupin Laboratories); the dosages of O (Dee-Pharma Ltd.) and H (Pfizer) used were 10 mg/kg for the subjects weighing <40 kg and 15 mg/kg for subjects weighing >40 kg.

### **Blood sampling**

During each occasion, blood samples were drawn at 1,2,3,6 and 8 hours after drugs administration. The samples were

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centrifuged, the plasma were stored at -20°C until assay.

### Urine collection

During each occasion, urine samples excreted over the periods 0-8 hours after the administration of the drugs were collected. The volume of urine samples were measured and an aliquot was stored at -20°C until the assay of the drugs and their metabolites was performed. Urine samples were processed for R within 48 hours following collection, since R is not stable in urine (Immanuel *et al.*, 1985). The estimation of free H, isonicotinic acid and acetylisoniazid, and of Z and pyrazinoic acid, were carried out within a week, as it was found that these drugs and their metabolites are stable in urine for at least a week. The excretion of creatinine was also undertaken to check for the completeness of urine collection by each volunteer.

The % dose excreted as O, R, H and their metabolites, and of Z plus pyrazinoic acid, was calculated based on the urine samples collected upto 8 hours.

### Assay methods

Ofloxacin concentrations in plasma and urine were determined by the plate diffusion method by Prema Gurumurthy *et al.* (1998), employing a strain of *Escherichia coli*.

Plasma total R concentrations were determined by the plate diffusion method of Dickinson *et al.* (1974) employing a strain of *Staphylococcus aureus*, resistant to streptomycin and other antibiotics. Urinary excretion of total R was estimated according to the procedure described by Chandra Immanuel *et al.* (1985).

Plasma H was estimated by the spectrophotofluorimetric method of Olson *et al.* (1977). Urinary excretion of H as total INA (after conversion of the free drug and its metabolites to INA) was estimated

according to the method of Ellard and Gammon (1976).

Pyrazinamide in plasma and Z and PZC in urine were estimated by the spectrophotometric method of Prema Gurumurthy *et al.* (1980).

Pooled horse plasma and pooled normal urine were used for the preparation of standard solutions of O,R,H and Z with each assay run, appropriate blank samples were processed simultaneously. Also, fresh samples were processed in duplicate or quadruplicate after coding along with the test samples with each assay run.

The proportions of the doses of O, R, H and their metabolites, and Z and its metabolite were calculated. Creatinine estimation on all the urine samples was determined by the calorimetric method based on Jaffe's reaction (Brod *et al.*, 1948).

All estimations (plasma and urine) were undertaken after coding of the samples. The study was double-blind, i.e., neither the volunteers nor the technical personnel knew the identity of the samples and the technical personnel was also unaware of the hour of collection

Pure O, R, Z and ion exchange resin were from Sigma Chemical Company, St. Louis, MO, USA. Pure H from May & Baker Ltd., Nutrient agar and nutrient broth were products of Difco Laboratories, Detroit, MI, USA and all the other chemicals used were of analytical grade. The strain of *E. Coli* used was a clinical isolate and the strain of *S. aureus* was kindly supplied by Prof.D.A.Mitchison.

### Kinetics and statistical analyses

On each series of plasma concentrations, the pharmacokinetic variables such as the peak concentration (C-max), the time taken to attain the peak concentration (t-max), the area under the time-concentration curve (AUC), and half-life ( $t_{1/2}$ ) (using the formula

log 2/slope) were calculated from the plasma concentrations. Further, the proportions (%) of the dose excreted in the urine collected over the periods 0-8 hrs. was also calculated on the basis of the concentrations in urine.

Bioavailability of O, R, H and Z for each of the combinations has been expressed as an index (BI) and is the ratio of AUC or the proportion of the dose (%) excreted in urine with the combinations to the respective control values obtained after the administration of O, R, H and Z alone.

## **RESULTS AND DISCUSSION**

Ofloxacin seems to be absorbed completely after administration of a single oral dose of 600 mg. Peak plasma concentrations were attained rapidly within 1.25-1.80 hours. The mean serial plasma concentrations of O when administered alone and in combination with other anti-TB drugs namely R, H and Z is shown in Figure 1. C<sub>max</sub> values of O following the single oral dose were 7.14, 6.98, 7.19, 6.06 and 6.38 µg/ml respectively when O was given alone and in combination viz. OR, OH, OZ and ORHZ. The differences between these groups in the mean O concentrations when administered alone and in combination were not statistically significant. The plasma concentrations of O are generally well in excess of the MIC values for Gram + ve bacteria within the spectrum of activity of O.

Several pharmacokinetic variables, such as peak concentration, coverage, area under the time concentration curve (AUC) and half-life were calculated based on the plasma concentrations of O at different time points (Table 1). When O was administered in combination with all the other three drugs, a significant difference in the coverage was observed. The corresponding values for the groups, O alone, OR, OH, OZ and ORHZ being 20.27, 23.51, 24.45, 24.37 and 34.46 µg/ml.hrs. respectively.

Similarly, the half-life of O is not altered when administered with R, H and Z alone. When O is administered with all the three anti-tuberculosis drugs, the half-life of O is significantly increased. The half-life of O ranges from 5.29, 6.02, 6.08, 6.51 and 10.00 hours, when O was administered alone and in combination with R, H, Z alone and with all the three drugs (O,R,H and Z). There are no significant differences in the AUC (area under the time-concentration curve) of O when administered alone and in combination with other anti-tuberculosis drugs. The auc VALUES OF o BEING 27.49, 31.51, 32.08, 27.86 AND 27.98 µg/ml.hours respectively when O alone, OR, OH, OZ and ORHZ were given.

The mean proportions of the dose excreted as O in urine, collected over the 0-8 hr. period and after the administration of O either alone or in combination with various anti-tuberculosis drugs are given in Figure 2. The proportions (%) of the dose excreted as O in urine were 40.98, 37.20, 46.83, 39.29 and 35.68% respectively of O alone, OR, OH, OZ and ORHZ which were statistically non-significant between the groups. Thus, the bioavailability of O is not affected by the coadministration of other anti-TB drugs. While investigating the effect of R,H and Z on O, it was also felt essential to find out whether O will be affecting the bioavailability of other drugs, since O alone is not administered to tuberculosis patients but and always in combination with other potent drugs like R,H and Z.

The mean serial plasma concentrations of R at different time points after oral administration of the drug was given in Figure 3. The C<sub>max</sub> values of R were 11.71, 9.62 and 9.18 µg/ml respectively when R was given alone, in combination with O alone and together with all the three drugs namely, O, H and Z respectively. The differences in the plasma peak concentrations between the groups were non-significant, although the highest concentrations of R were obtained after the second hour when R was given alone and

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in the third hour when combined with O, H and Z.

Based on the plasma concentrations of R at different time points, several pharmacokinetic variables were calculated and half-life, when given alone and in combinations, remain unaltered and it was non-significant, indicating that there are no drug interactions when R was combined with O and other anti-tuberculosis drugs.

The mean proportions (%) of the dose excreted as total R in urine were 16.08, 14.49 and 14.77% respectively when R was administered alone or in combination with O and when all the four drugs are given (Figure 4). The results have shown that the differences between the means of the different groups the means of the different groups containing R were not statistically significant.

Computing the results obtained for H, the mean serial plasma concentrations of H, when given alone and in combination with O alone or with all the other drugs namely O, R and Z at different time points are given in figure 5. The mean peak concentrations of H in plasma are 11.80, 11.57 and 13.77 µg/ml respectively when given alone, with O and with all the other three drugs. Isoniazid was rapidly absorbed in the first hour itself when given either alone or in combination (OH and OHRZ). There are no significant differences in the concentrations of H between the groups.

Similar to R, there are no significant differences in the various pharmacokinetic differences in the various pharmacokinetic parameters calculated (Table 3) based on the mean serial plasma concentrations of H at different time points, between the groups. There are marked increases in the AUC of H when H was given with all the other three anti-tuberculosis drugs ( $p < 0.021$ ). Whereas when H was given with O alone, there are no significant differences in the AUC, coverage, half-life, T-max and C-max.

Isoniazid is estimated in the urine as its metabolite, isonicotinic acid (INA). The proportions (%) of the doses excreted in urine as INA are 59.49.32 and 44.68% respectively when H is given alone or with O and with all the other three drugs in combinations. The results show that there are not significant differences in the proportions of the doses excreted when given either alone or in combination with O and other drugs (Figure 6).

The mean serial plasma concentration of Z at different time points after a single oral administration of Z is given in figure 7. The highest concentrations of Z are obtained in the third hour (ranges from 2.5 - 3.5 hours), when given alone and in combinations of Z are 47.62, 50.90 and 49.58 µg/ml respectively when Z is given alone, along with O and with all the other three drugs (viz. O, H and R). The results indicate that the bioavailability of Z is not affected when administered along with other antituberculosis drugs, particularly with O. The differences between the groups in the Z concentrations are not significant statistically.

Based on the plasma estimates of Z, pharmacokinetic parameters are calculated (Table 4). The AUC remains the same when Z is administered with other drugs, whereas the coverage and half-life of Z are significantly increased when administered with all the three antituberculosis drugs. This is not due to O because when Z administered with O, statistically there is no significant difference when compared to the group which received Z alone. Moreover the significant increase in AUC and half-life in the group, which received all the four drugs, may be due to population size and hence the variability. Thus, the results indicate that there are no drug interactions when Z is administered with O.

The mean proportions of the dose excreted in the urine as Z and PZC, collected over periods 0-8 hr. after the administration, either alone or in combinations, are given in

Figure 8. Pyrazinamide gets excreted via kidneys as Z and its metabolite PZC. The proportions of dose excreted as Z are 6.27, 4.34 and 10.43% and as PZC, 14.46, 11.09 and 11.44% respectively when Z is administered alone, in combination with O either alone and together O, R and H. The data clearly show that there are no significant differences in the excretion of the dose as Z and PZC, when Z is given alone and in combination with O.

Tuberculosis has been declared a global emergency by the WHO. This unprecedented declaration has prompted predominantly by two developments; the resurgence of tuberculosis in the west and a number of outbreaks of multi-drug resistant tuberculosis (MDR-TB) in many parts of the world.

Tuberculosis requires effective chemotherapy, which can be achieved with regimens containing a number of drugs given separately or in fixed dose combinations.

Tuberculosis research centre has been conducting controlled clinical trials in the chemotherapy of tuberculosis. The management of MDR-TB is a challenging problem. The treatment is less effective, more toxic and much more expensive compared to treatment of drug susceptible to tuberculosis. Therefore, the prevention of the emergence of drug resistance is of paramount importance. There is an urgent need for research to develop drugs with antimycobacterial activities.

Recently, O had proved to be a particularly valuable addition to the available anti-tuberculosis drugs. Ofloxacin is a fluorinated quinolone with a broad spectrum of activity against Gram +ve and Gram -ve bacteria (Sato *et al.*, 1982). The effectiveness of O against *Mycobacterium tuberculosis* was studied by Crowle *et al.*, 1988 and their results confirm its clinical usefulness as published by others that it should be an useful anti-tuberculosis drug

with a minimum inhibitory concentration of 1.0 µg/ml.

Earlier studies reveal the rationale for combining O with other anti-tuberculosis drugs and the improvements that can be expected to result from its use in anti-tuberculosis chemotherapy. Human bioavailability studies provide direct, straightforward information about the drugs whose vital role in chemotherapy is well established.

The pharmacokinetics of O are assessed by almost its complete bioavailability (95-100%). The studies conducted by Lode *et al.*, 1987, confirm these findings. Even when O is administered together with other anti-tuberculosis drugs, the pharmacokinetic properties of O is not modified and does not exercise any therapeutic penalty.

The results of this study correlate with the hypothesis of complete independence between the drugs, as witnessed by a lack of negative pharmacokinetic drug interactions. Thus, our findings suggest that O and other anti-tuberculosis drugs do not interfere with each other in terms of absorption, distribution and metabolism.

It needs to be emphasized that the methods employed for the estimation of O, R, H and Z and their metabolites in plasma and urine are very simple, precise, sensitive, specific, reproducible and do not require sophisticated equipments. Good bioavailability leading to adequate plasma and tissue concentrations of O (and other drugs) is an absolute prerequisite for the success of treatment of tuberculosis. It has been postulated that peak plasma O concentrations should be  $3.14 \pm 0.53$  µg/ml with a single oral dose of 400 mg for good therapeutic response (Yuk *et al.*, 1991). Evidence preserved in this report suggests when O is administered together with all the other three anti-tuberculosis drugs viz., R, H and Z respectively, the results of our study show that the pharmacokinetic parameters

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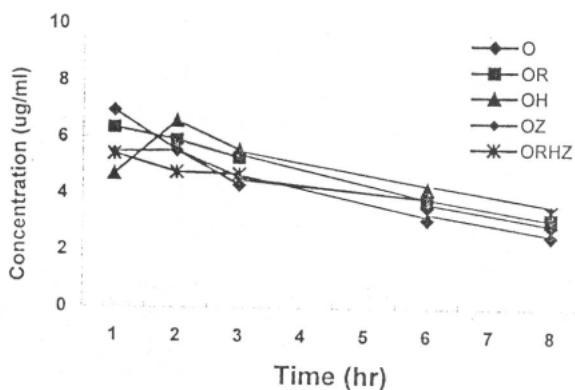


Fig.1: Mean plasma concentration - time profiles of ofloxacin when given alone and in combinations

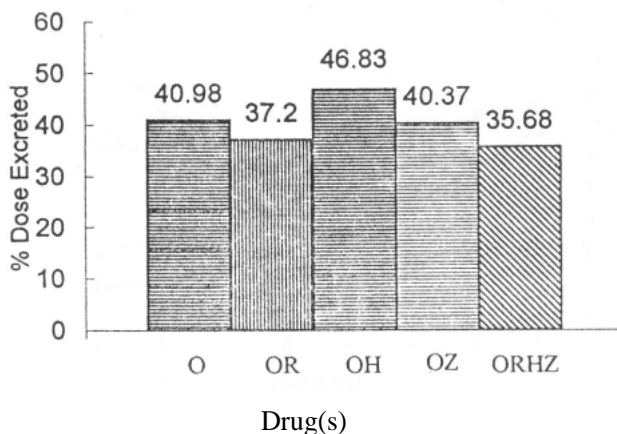


Fig.2: Urinary excretion of ofloxacin

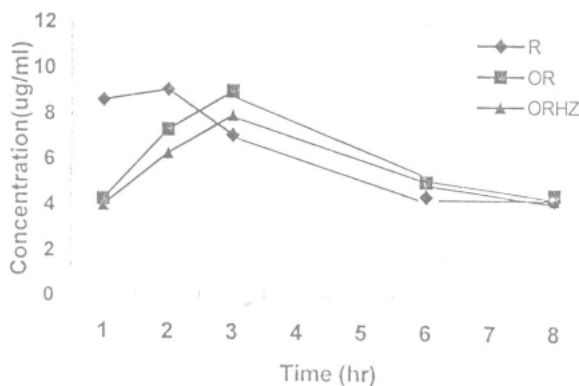


Fig.3: Mean plasma concentration - time profiles of rifampicin when given alone and in combinations

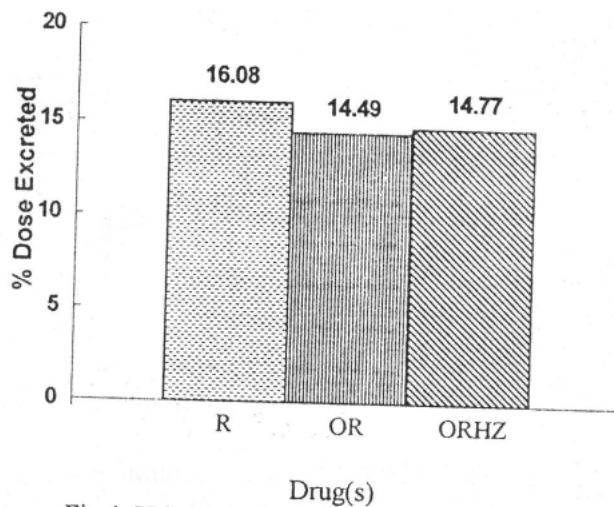


Fig.4: Urinary excretion of rifampicin

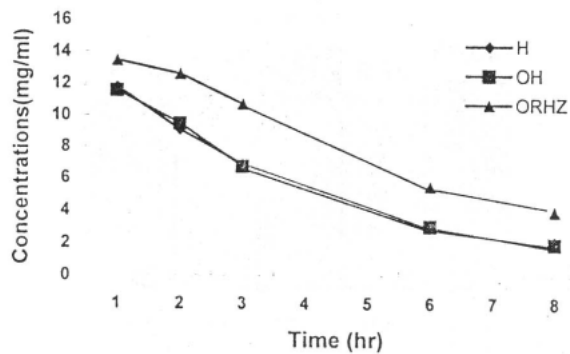


Fig.5: Mean plasma concentration – time profiles of isoniazid when given alone and in combinations

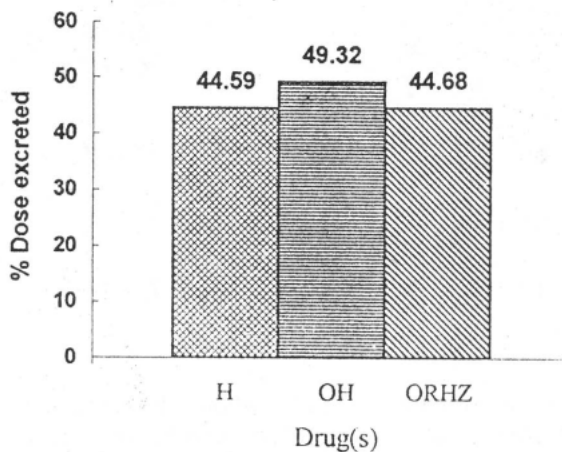


Fig.6: Urinary excretion of Total INA



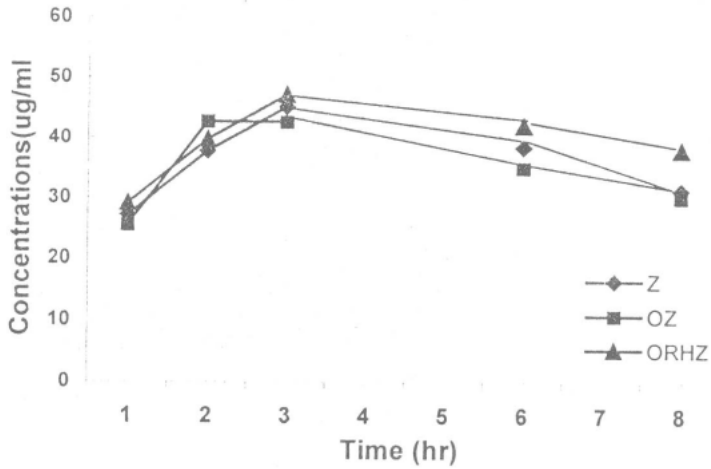


Fig.7: Mean plasma concentration - time profiles of pyrazinamide when given alone and in combinations

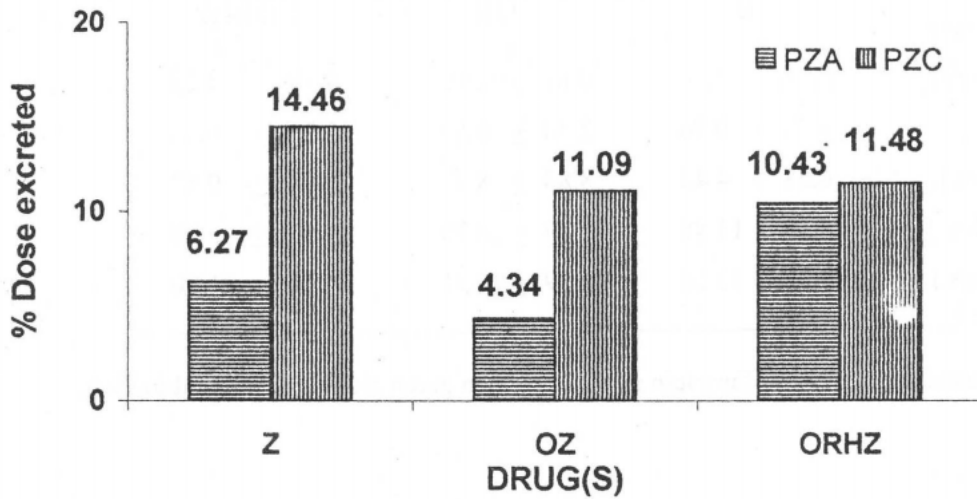


Fig. 8: Urinary excretion of PZA and PZC

Parameter	O n=12	OR n=6	OH n=5	OZ n=9	ORHZ n=4
C-max ( $\mu\text{g/ml}$ )	7.14 $\pm$ 1.44	6.98 $\pm$ 1.57	7.19 $\pm$ 2.17	6.06 $\pm$ 0.93	6.38 $\pm$ 1.45
T-max (hrs.)	1.25 $\pm$ 0.45	1.67 $\pm$ 0.82	1.80 $\pm$ 0.84	1.67 $\pm$ 0.71	1.50 $\pm$ 1.00
Half life (hrs.)	5.21 $\pm$ 1.69	6.02 $\pm$ 1.20	6.08 $\pm$ 2.22	6.51 $\pm$ 1.81	10.00 $\pm$ 5.23
Coverage (hrs.)	20.27 $\pm$ 6.09	23.51 $\pm$ 5.79	24.45 $\pm$ 8.01	24.37 $\pm$ 7.06	34.46 $\pm$ 16.29
AUC (0-8 hrs.) ( $\mu\text{g/ml.hrs}$ )	27.49 $\pm$ 5.74	31.5 $\pm$ 12.74	32.08 $\pm$ 7.89	27.86 $\pm$ 6.05	27.98 $\pm$ 13.22

**Table 1:** Pharmacokinetics of ofloxacin in plasma when given alone and in combinations

Parameter	R n=7	OR n=5	ORHZ n=4
C-max ( $\mu\text{g/ml}$ )	11.71 + 4.76	9.61 $\pm$ 2.92	9.18 $\pm$ 4.25
T-max (hrs.)	1.71 + 0.76	2.40 $\pm$ 0.89	2.25 $\pm$ 0.96
Half life (hrs.)	6.53 + 4.42	8.88 $\pm$ 8.40	5.58 $\pm$ 0.82
Coverage (hrs.)	27.29 + 13.88	36.79 $\pm$ 28.75	24.80 $\pm$ 3.98
AUC (0-8 hrs.) ( $\mu\text{g/ml.hrs}$ )	43.51 + 13.18	43.09 $\pm$ 10.91	9.74 $\pm$ 21.00

**Table 2:** Pharmacokinetics of rifampicin in plasma when given alone and in combinations

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Parameter	<b>H</b> n=8	<b>OH</b> n=5	<b>ORHZ</b> n=4
C-max ( $\mu\text{g/ml}$ )	11.80 $\pm$ 3.08	11.57 $\pm$ 2.51	13.77 $\pm$ 1.71
T-max (hrs.)	1.00 $\pm$ 0.00	1.00 $\pm$ 0.00	1.33 $\pm$ 0.58
Half life (hrs.)	2.85 $\pm$ 0.88	2.80 $\pm$ 1.08	3.71 $\pm$ 0.61
Coverage (hrs.)	17.63 $\pm$ 5.23	17.27 $\pm$ 5.93	24.00 $\pm$ 2.93
AUC (0-8 hrs.) ( $\mu\text{g/ml.hrs.}$ )	43.20 $\pm$ 12.08	42.73 $\pm$ 12.36	63.90 $\pm$ 4.84

**Table 3** : Pharmacokinetics of isoniazid in plasma when given alone and in combinations

Parameter	<b>Z</b> n=10	<b>OZ</b> n=7	<b>ORHZ</b> n=4
Cmax ( $\mu\text{g/ml}$ )	47.62 $\pm$ 10.62	51.97 $\pm$ 16.82	49.58 $\pm$ 3.81
T-max (hrs.)	3.20 $\pm$ 1.62	2.43 $\pm$ 0.53	3.50 $\pm$ 1.73
Half life (hrs.)	8.86 $\pm$ 4.30	9.96 $\pm$ 5.57	16.02 $\pm$ 8.64
Coverage (hrs.)	22.28 $\pm$ 9.19	24.69 $\pm$ 14.33	41.09 $\pm$ 22.76
AUC (0-8 hrs.) ( $\mu\text{g/ml.hrs.}$ )	202.94 $\pm$ 67.28	191.51 $\pm$ 113.84	226.39 $\pm$ 54.24

**Table 4** : Pharmacokinetics of pyrazinamide in plasma when given alone and in combinations.

like coverage and half-life are significantly increased, thereby rendering the bioavailability of O to the system for a longer period. This may at times lead to drug toxicity and may require adjustment of drug dosage when given in combinations.

In the ORHZ group, the pharmacokinetic parameters calculated based on the plasma estimates were with lots of individual variations, although the differences in the peak concentrations and AUC are not statistically significantly when O alone is compared with ORHZ. This is rather surprising that for any bioavailability studies, peak and AUC are important determinants for assessing proper absorption and metabolism of the drugs. Nevertheless, these differences in both coverage and half-life cannot be ignored. This could mainly be due to the differences among volunteers in terms of absorption and metabolism. Sample size i.e. the number of volunteers tested is very small. Due to the reasons indicated above, these results could well be interpreted if larger volunteers are included in the ORHZ group.

Similarly our reports have also shown that the bioavailability of other anti-tuberculosis drugs viz., R, H and Z do not get affected or altered when administered with O.

The results demonstrate that the absorption of O, R, H and Z in healthy volunteers is not modified when given in combination. It is well known that the therapeutic value of any drug depends on proper absorption, metabolism and excretion.

The proportions of the doses excreted in urine over 8 hour period are compared with the plasma kinetics and it was found that there are no significant differences between the blood kinetics and renal clearance of all the four drugs. It can, therefore, be concluded that for bioavailability studies involving these drugs, invasive blood collection can be replaced by simple non-invasive urine collections. Ofloxacin undergoes a limited degree of

biotransformation. In individuals with normal renal function, less than 5% of O is excreted in the urine as metabolites (Lode *et al.*, 1987). Three metabolites have been identified, Ofloxacin glucuronide, Desmethyl-Ofloxacin glucuronide, Desmethyl-Ofloxacin and Ofloxacin-N-Oxide (Borner *et al.*, 1986a). Such a low concentration of the metabolites is present even in renal failure and it is of negligible clinical importance (White *et al.*, 1988). Our results strengthen the previous reports (Abdallah *et al.*, 1995) that the addition of O to regular tuberculosis treatment regimen would reduce the therapeutic period.

Ofloxacin may be used as a second-line drug in the treatment of tuberculosis-resistant organisms. But, several studies have proved that O can be combined with first-line anti-tuberculosis drugs in the treatment of primary cases of pulmonary tuberculosis patients. Our findings also support that O may be used along with other first-line anti-tuberculosis drugs in the treatment of pulmonary tuberculosis. Usually the problem encountered in combination therapy would be drug interactions. Our data show that when O is combined with R, H and Z, the bioavailability of either O or other anti-tuberculosis drugs does not get altered or affected, thereby facilitating effective treatment. Since there are no drug interactions, the use of O in the treatment of pulmonary tuberculosis is justified.

Ofloxacin is completely absorbed and has a long half-life, an apparent high volume of distribution, predominant renal elimination and only limited biotransformation. The addition of O to regular tuberculosis treatment regimen would reduce the therapeutic period and render the patient productive. Patients treated with O in the multiple regimens are cured with minimal or no side effects.

However, further studies, in patients, in a larger population, by administering multiple

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doses or with different dosages, are required to provide a better definition of the efficacy of O in the treatment of mycobacterial infections. However, multiple doses of administration of O do not appear to result in significant accumulation (Farinotti *et al.*, 1988).

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