

CHAPTER-VI

S U M M A R Y

1. Undernutrition and tuberculosis are common contemporary problems in a developing country like India. For the treatment of tuberculosis various drug regimens are available; however, they suffer from a serious handicap, in that the nutritional status of the patient is not taken into consideration in suitably modifying the drug regimen. Scarce data are available on the influence of undernutrition on pharmacokinetics of rifampicin, a very widely used, effective antitubercular drug. In most regimens, doses are used based on information generated in well developed western countries, which may not be directly relevant to tropical situations. This work was undertaken to study the changes in pharmacokinetic profile of rifampicin brought about by undernutrition if any, and to suggest suitable modification of antitubercular regimen involving use of rifampicin.
2. The pharmacokinetic investigations were carried out in newly diagnosed 63 undernourished patients suffering from tuberculosis and also on healthy human volunteers both undernourished and well nourished. It was observed that in patients, with decreasing nutritional score, there was increase in T_{max} and decrease in C_{max} ,

- indicating some correlation between the nutritional status and serum rifampicin level. Since it was difficult to obtain enough number of normally nourished patients of tuberculosis, the available patients were studied under two subgroups, (a) with nutritional score between 0.140 and 0.180 and (b) with nutritional score below 0.140. The mean body weights were significantly different in the two subgroups.
3. To study detailed pharmacokinetics of rifampicin, tailor-made rat model of undernutrition was examined, in particular to check tissue distribution of rifampicin, to focus on changes in hepatic microsomal enzyme system and to observe in vitro absorption pattern of rifampicin in intestinal loops.
 4. There was significant difference in the mean body weights of rats in NP and LP groups (of rats) at the end of eighth week of dietary treatment. Undernutrition failed to modify lung and kidney weights; however, liver weight was significantly decreased. Drug treatment from 9th to 15th week of dietary treatment did not modify the above picture.
 5. The peak serum rifampicin concentration obtained was lower in undernourished patients, volunteers or rats,

after acute or chronic treatment, alone or along with other antitubercular drugs. The lowered serum rifampicin concentrations in undernourished group may be because of decreased absorption, some change in plasma protein binding, tissue uptake and/or metabolism and excretion,

6. Results of in vitro absorption study clearly indicate that absorption of rifampicin is significantly impaired because of undernutrition.
7. The absorbed rifampicin was distributed well amongst the organs studied. After chronic treatment, concentrations were generally observed higher in all the tissues studied. In the lung rifampicin attained concentrations which on the whole, were roughly on par with those measured in the serum at all time points. Also comparatively higher concentrations were seen in the liver and the kidney, the main organs dealing with handling of rifampicin.
8. The urinary excretion of rifampicin expressed as percentage of dose administered was higher in LP group of rats, although, ug/ml/kg excretion of rifampicin was lower in LP group than in NP group.

In undernourished human volunteers also mg/day excretion of rifampicin was significantly less than that in well nourished subjects. More passage of rifampicin towards kidney may be a result of lower plasma protein binding.

9. In vitro plasma protein binding of rifampicin in undernourished patients of tuberculosis at the 24th hour of incubation was 20% to albumin, 79% to α_2 globulin and 3 to 18% to fibrinogen, much less than that for healthy subjects reported by Boman and Reinberger. In our study, this data was not worked out in comparatively healthy volunteers.
10. Higher urinary excretion and comparatively lower plasma protein binding support the contention that in undernourished group, rapid clearance of rifampicin is responsible for decreased $t_{1/2}$.
11. The amount of desacetylated rifampicin eliminated in the urine decreased after chronic treatment in both the NP and LP groups, a finding which can possibly be explained by the fact that desacetylation gradually becomes largely superseded by glucuronidation; this change may be further promoted by enzyme induction.

12. An increase in cytochrome P-450 and cytochrome b₅ was observed following 6 weeks chronic treatment with rifampicin + INH in both control and undernourished rats, but it was statistically insignificant. Undernourished group had significantly lower levels of cytochromes.
13. Concurrent administration of other antitubercular drugs like INH and streptomycin or ethambutol or pyrazinamide with rifampicin failed to produce any significant change in pharmacokinetics of rifampicin.
14. In conclusion, data of the present study, both from human and rat experiments, suggest that undernutrition affects the pharmacokinetic behaviour of rifampicin with special reference to its absorption, biological half-life and rate of elimination from kidney. Our results on cytochrome from rat liver can, at best be judged as preliminary on the mixed effects of INH and rifampicin warranting a further extension of the work.

The levels of rifampicin noted in our study in relatively well nourished and undernourished patients are well above the minimal inhibitory concentration and also above the minimal bactericidal concentration for mycobacterium tuberculosis.

Since, the MIC and MBC concentrations are achieved, the current dosage schedule of rifampicin for the tuberculous treatment need not be changed. It should be worthwhile studying whether the large concentrations in liver and kidney in undernourished would entail greater toxicity requiring reduction in dose, but enough to keep concentration of rifampicin well above MIC and MBC and yet have lesser incidences of liver and kidney adverse effects. However, it is too early to recommend any change in the dosage and/or frequency of rifampicin administration at this juncture.

Many areas need to be explored, these are -

- (a) Metabolism of rifampicin in undernourished human patients, along with kinetics of rifampicin metabolites,
- (b) the possible deviation in plasma proteins and the binding of rifampicin to them in undernourished patients compared to that in healthy subjects, and
- (c) in human volunteers and patients, change in pharmacokinetic profile of rifampicin after chronic treatment.