CHAPTER-II

INTRODUCTION

Application of modern technology, sound public health measures, synthesis and successful clinical use of potent antibacterial and antiprotozoal agents has been so effective that over the past three or four decades diseases such as leprosy, malaria and tuberculosis have nearly disappeared from western countries. Unfortunately such is not the situation in several of the tropical and subtropical countries.

Tuberculosis is a public health problem of major importance in almost all developing countries. The number of infectious cases of tuberculosis in the world today is 5-20 million. This infectious pool is maintained by the occurence of 1-2 million new cases and 1-2 million deaths in the world. In India also prevalence of tuberculosis is estimated to be 4/1000 implying that there are about 30,00000 patients. This would explain the gravity of the problem to be tackled in our country. For this reason, National Tuberculosis Control Programme has been started. It also occupies a high priority in the 20-point programme of Government of India.

Successful and toxicity-free use of chemotherapeutic agents requires detailed knowledge of how frequently, in what dosages and in what combinations these agents must be administered to a large population. Equally important is

the knowledge of what effects, if any, disease state, age, sex, ethnicity, diet, nutritional status, drug metabolites, gastrointestinal flora and other environmental factors will have on in vivo behaviour, effectiveness and toxicities of chemotherapeutic agents when they are being used in clinical practice.

Reasonable amount of information and data are available on these factors as they pertain to the population in western countries. This information, although very useful, cannot be applied as such to the population from the Indian subcontinent. To bridge this gap and to generate appropriate data applicable to the population from the Indian subcontinent, it is desirable to study the pharmacokinetic behaviour of drugs in patients who are generally undernourished.

One of the important environmental factors altering pharmacokinetics of a drug is undernutrition (Krishnaswamy, 1978), a complex problem with its multiple inter-relationship involving a host of other factors.

Undernutrition can have two important influences -

(A) Pathophysiological changes: Pathophysiological changes brought about by undernutrition are likely to alter drug kinetics and metabolism as enumerated below. Changes unrelated to pharmacokinetics and metabolism are cell functions such as phagocytosis.

i) Gastrointestinal changes,

ii) Changes in body composition, body fluids, electrolytes and minerals,

iii) Plasma and tissue proteins,

iv) Hepatic changes,

v) Renal changes,

vi) Cardiac changes,

vii) Hormonal changes,

viii) Metabolic changes,

ix) Immunological changes

x) Psychopharmacological changes.

(B) Pharmacokinetic processes: Pharmacokinetic processes likely to be altered by undernutrition are as documented below -

i) Absorption and gastrointestinal metabolism of drugs,

ii) Distribution,

iii) Plasma protein binding,

iv) Uptake and localization within tissues,

v) Biotransformation processes,

vi) Excretion - biliary and renal,

vii) Drug interaction.

There is now increasing awareness of the interplay between nutrition and drug metabolism. Studies are available showing that in undernourished subjects there is

decrease in metabolism , half-life and apparent volume of distribution of tetracycline (Shastri and Krishnaswamy, 1976), metabolism of chloroquine (Wharton and McChesney, 1970), conjugation of chloramphenicol (Mehta et al., 1975) and clearance of antipyrine (Krishnaswamy and Naidu, 1977). On the other hand, there is increased acetylation of sulfadiazine (Shastri and Krishnaswamy, 1978) and no change in the pharmacokinetics of streptomycin (Prasad and Krishnaswamy, 1977). However, most of the studies in this area are still confined to experimental stage and there are very limited data on human population. Also, there is little information about how undernutrition modifies drug elimination, plasma level and therapeutic responses to drugs (Jaffery, 1976). Since undernutrition has several therapeutic implications, the need for additional studies to investigate the same has been felt, particularly in a developing country like India, where it is widespread. Though it is often observed that undernutrition forms a vicious cycle with tuberculosis, exact cause-effect relationship is not well established. It is likely that the interaction between the drugs on the one hand and co-existing disease and undernutrition on the other, are not well explored. These interactions and their consequences in terms of toxicity and/or course of disease may assume a significant importance in India.

This study was therefore undertaken to investigate the pharmacokinetic parameters of rifampicin, a widely used antitubercular drug with special reference to its use in undernourished patients, so as to help in formulating a regimen which may culminate into a better cure with minimal toxicity.

In particular, in a tropical environment a number of factors such as malnutrition, tropical disease, parasitic infestations, naturally occuring toxins and contaminants and food habits may profoundly influence the disposition of drugs by individuals. Rational use of antitubercular drugs based on pharmacokinetic and pharmacodynamic studies on this population would be very useful. This study was undertaken to conduct carefully designed kinetic study in the local population and to obtain optimal dosing regimen. The effect of factors such as dose size, route of administration, age and co-administered drugs on the kinetics of rifampicin were investigated. Information gained from this study could then be used in designing rational dosing-regimen of this drug in undernourished tuberculous patients. As the goal of every therapeutic drug treatment is to achieve optimal response, the knowledge gained from the study will be useful in establishing safe and effective drug therapy.

The work was focussed on the relationship between undernutrition and pharmacokinetic behaviour of rifampicin.

The specific aims of the study were -

1. (a) To carry out studies on the pharmacokinetic behaviour of rifampicin in better and poorly nourished patients suffering from pulmonary tuberculosis with study of various parameters like rate and extent of absorption of rifampicin from the gut, distribution in various tissues and body fluids, metabolism, plasma protein binding and excretion in urine together with its metabolites.

   (b) Simultaneously to generate information in healthy human volunteers, both well nourished and undernourished with intention to determine the influence of undernutrition alone on the pharmacokinetics of rifampicin eliminating the role played by tuberculosis.

2. To check how interaction between the drugs is affected in the presence of undernutrition.

3. To carry out similar studies in tailor-made model of human undernutrition in rats to derive information which otherwise cannot be obtained from human studies,

e.g. enteral absorption of rifampicin using an *in vitro* model, in normal and undernourished rats, distribution of rifampicin in various body tissues and effect on microsomal enzyme system.

4. To suggest modification in the doses of rifampicin and/or frequency of administration of rifampicin in undernourished patients with a view to achieve better and smoother cure. Hopefully this would culminate into better patient compliance in the long term treatment.