

# SERUM CONCENTRATION AND URINARY EXCRETION OF ETHAMBUTOL ADMINISTERED ALONE AND IN COMBINATION WITH ISONIAZID IN PATIENTS OF PULMONARY TUBERCULOSIS

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**Summary :** Ethambutol (20 mg/kg) was administered orally to 10 patients of pulmonary tuberculosis for seven consecutive days at 8 a.m. after over night fast. On 7th day serum levels were measured at 2, 4, 6, 8 and 24 hr intervals and urinary excretion was estimated at 2, 4, 6 and 24 hr following ethambutol administration. Simultaneous administration of isoniazid (300 mg, orally) for next seven days to the same patients significantly raised the serum levels of ethambutol at 4, 6 and 8 hr and the cumulative per cent dose excreted was decreased significantly at 4, 6 and 24 hr. The serum levels and urinary elimination was not significantly different at 2 hr.

**Key words :** ethambutol

isoniazid

serum level

pulmonary tuberculosis

urinary elimination

## INTRODUCTION

Serum levels of para-amino salicylic acid remain unaltered if isoniazid is co-administered during treatment of tuberculosis (6). Half life values and urinary excretion of rifampicin are not influenced significantly by isoniazid administered simultaneously (1). However, serum levels of rifampicin tend to decrease in healthy subjects and increase in patients with chronic liver diseases when administered together with isoniazid for seven consecutive days (1). On the other hand pyrazinamide administration has been shown to be associated with reduced serum levels of acetyl-isoniazid, specially in slow isoniazid acetylators (11). In combination therapy with cycloserine, isoniazid has been shown to cause higher incidence of central nervous system toxicity. This has, however, been attributed to combined toxic effect of two drugs than to any pharmacokinetic interaction (8). No report of pharmacokinetic interaction of isoniazid with ethambutol is available. The present investigation was designed to study the effect of isoniazid on the serum levels and urinary elimination of ethambutol.

## MATERIAL AND METHODS

A total of 10 patients suffering from pulmonary tuberculosis were selected from Tuberculosis and Chest Outpatients, Department of J.N. Medical College, A.M.U., Aligarh. These included 7 males and 3 females with a mean age of 32.44 years (20-50 years) and a mean weight of 42.4 kg (30-50 kg). Their liver and renal function tests were within normal limits. The patients were not given any drug for seven days before the study.

*First step* : After overnight fast patients were administered ethambutol (20 mg/kg) on empty stomach at 8 a.m. for 7 consecutive days with 200 ml of water. On 7th day venous blood samples (3 ml) were collected at 2,4,6,8 and 24 hr following ethambutol ingestion and total urine passed upto 2,4,6 and 24 hr was collected separately. For upto 2 hr following ethambutol administration patients were allowed nothing by mouth. To ensure sufficient urine volume, in addition to breakfast patients were administered 200 ml of water at 2, 4, 6 hr and liberally thereafter. The quantity of urine passed at different time intervals was measured and 5 ml of urine from each sample was stored in glass stoppered bottle at 5°C. Serum was separated from blood samples and stored as above till ethambutol was estimated.

*Second step* : For the next 7 days same patients were administered a combination of ethambutol (20 mg/kg) and isoniazid (300 mg) after overnight fast on empty stomach with 200 ml of water at 8 a.m. No other drug was given to patients during this period. On 14th day samples of venous blood and urine were collected and stored as described above.

Ethambutol was estimated in serum and urine samples by a spectrophotometric method (3)

## RESULTS

Observations on the effect of isoniazid on the serum levels urinary excretion of ethambutol are shown in Fig. 1. Significantly higher levels of ethambutol in serum were obtained at 4, 6 and 8 hr when combination of ethambutol and isoniazid was administered.

The urinary elimination of ethambutol during fractional time period of 2 hr was not different when ethambutol was administered combination with isoniazid. However, simultaneous administration of isoniazid significantly decreased the urinary elimination of ethambutol at 4, 6 and 24 hr.

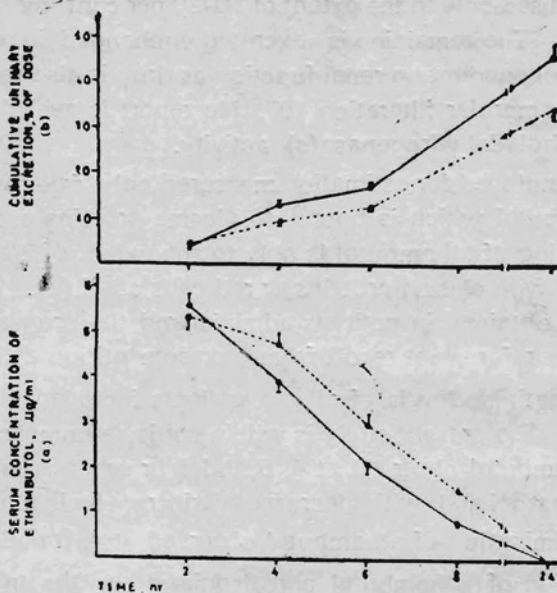


Fig. 1 : Serum concentration (in a) and cumulative urinary excretion (in b) of ethambutol in patients of tuberculosis (n = 10) given the drug alone (20 mg/kg 0—0) or in combination with isoniazid (300 mg, 0—0) at various times (hr) after the administration. All values are mean ( $\pm$  S. E. M., vertical bars).

### DISCUSSION

The study reported here was designed as 'within subjects' comparison of serum levels and urinary elimination of ethambutol given alone and in combination with isoniazid in patients of pulmonary tuberculosis. In previous studies peak serum ethambutol concentration varied significantly at the same dose levels (2,4,10). The time at which peak occurred has been reported to range from 2-4 hr (10). In the present study following administration of ethambutol alone or in combination with isoniazid peak serum concentration was obtained at 2 hr. The higher serum levels of ethambutol when administered simultaneously with isoniazid may result from increased absorption, decreased metabolism, increase transfer to binding site or decrease in elimination.

Both ethambutol and isoniazid are rapidly absorbed from gastrointestinal tract. It is unlikely that higher levels of ethambutol in combination chemotherapy results from increased absorption of ethambutol, since this should have reflected in ethambutol levels estimated in even first sample collected after 2 hr following drug administration. Levels of ethambutol administered alone or in combination with isoniazid were not different at the end of 2 hr.

For isoniazid a process of acetylation is regarded as an essential step in the metabolic fate probably mediated by a non-microsomal enzyme system present in liver (5).

Ethambutol is metabolised only to the extent of 10-20 per cent by an alcoholic dehydrogenase(s) in liver (9). The remaining is excreted unchanged in urine. The serum levels, therefore, are closely dependent on renal function as drug is also excreted by tubular secretion in addition to glomerular filtration (9). No report is available to suggest the effect of isoniazid on alcohol dehydrogenase(s) activity.

The method employed for estimation measured only free form of ethambutol. The proportion of ethambutol which is bound to plasma proteins and red blood cells is not estimated. The binding of ethambutol is only to the extent of 20-30 per cent and isoniazid does not combine with plasma proteins or red cells at all (7). The differential levels of ethambutol in serum obtained in patients administered the drug alone or in combination with isoniazid can, therefore, not result from any competition at binding site.

The serum creatinine levels of all the patients included in the present study were within normal limits. The present study is within subjects comparison. The higher serum concentration of ethambutol observed at 4, 6 and 8 hr when administered in combination with isoniazid was associated with decreased urinary elimination. This is reflected in cumulative urinary elimination of ethambutol observed at 4, 6 and 24 hr.

The combination of ethambutol and isoniazid in the treatment of tuberculosis appears to influence the kinetics of ethambutol favourably. It can not, however, be said that difference of this magnitude in concentration of ethambutol would prove to be of a significant clinical advantage, especially under conditions of chronic drug administration.

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