

Incidence of Rapid and Slow Acetylators of Isoniazid in NWFP

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Summary

In order to determine the phenotype frequencies of rapid and slow acetylators of Isoniazid in N.W.F.P., fifty four tuberculous patient volunteers, who had not had anti-tubercular treatment before, were studied. The concentration of free and total INH, plasma half life and serum transaminase levels were measured. The rapid acetylators constituted 48.1% in this population. All patients, especially the rapid acetylators receiving INH, should be carefully evaluated for symptoms of hepatitis and serum transaminase levels measured at monthly intervals, so that patients with elevated transaminase levels be taken off the hepatotoxic drugs and alternative drugs administered to them.

Introduction

The importance of genetic factors as determinant of drug metabolism in man has become recognized.¹ This phenomenon is manifest in the genetic heterogeneity with regard to the rate of acetylation of isoniazid (INH).^{6,12,15} Therefore population can be divided into two phenotypes of rapid and slow acetylators.^{2,6}

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The slow acetylators will have higher plasma concentration of the parent drug and lower concentration of the acetylated metabolites: therefore slow acetylators will be at a greater risk from over-dose toxic reactions such as INH peripheral neuropathy due to the parent compound.⁴ Whereas rapid acetylators will be at greater risk from adverse reactions such as INH hepatitis due to the acetylated metabolites.¹³

The aim of the present study was to determine the phenotype frequencies of rapid and slow acetylators of isoniazid in NWFP in an attempt to evaluate the toxic potentials of INH with other antitubercular drugs in rapid and slow acetylators during treatment in this population.

Material and Methods

Patient volunteers, who were diagnosed as tuberculous for the first time and did not have isoniazid treatment before, were selected for the trial. Patients with this criteria were difficult to find because they were not frequent. However during last two years only 54 patients (28 males and 26 females, mean age 23.7 years, range 16–65 years) were motivated to participate in the trial. They all gave informed consent.

In all these patient volunteers, the concentration of INH (free and total), plasma half life, SGOT and SGPT levels were measured.

Drug and its Determination in Plasma

INH was given orally in a dose of 10 mg/Kg body weight using the commercial dividable tablets containing 100 mg of INH (Pfizer Lab. Pak. Ltd.).

4 ml. EDTA plasma was collected before and 2, 4, and 6 hours after administration of the drug by mouth. All the plasma samples were stored at -20°C until INH was determined. The concentration of free and total INH in blood plasma was measured by spectro-photometric method described by Maher.¹¹ SGOT and SGPT levels were measured by Rietman and Frankle method.¹⁴ All samples from one patient were measured simultaneously.

The plasma half life of INH was determined graphically from a semilogarithm. (Log plasma concentration against time).¹¹

Results

The plasma half lives range from 40 min. to 400 min. in the 54 patient volunteers studied.

Their plasma half lives are plotted in Fig. I.

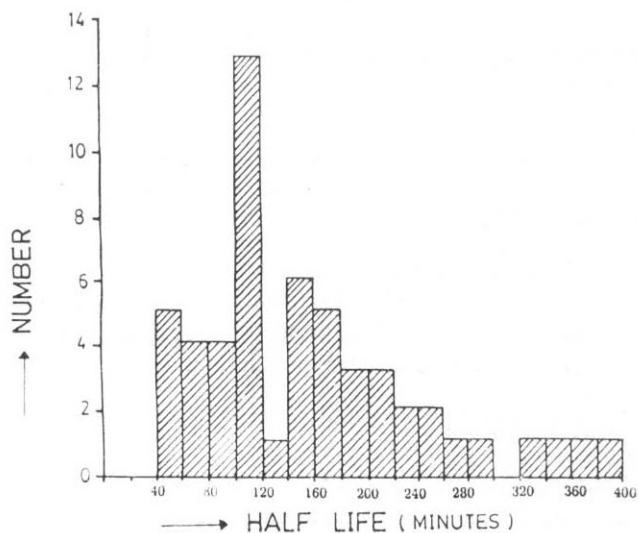


Fig. 1 - Frequency distribution of plasma half lives.

The plasma $T_{1/2}$ are distributed in two modes with an antimode between 120–140 min. Those which fall before 120 min. are rapid acetylators and those after 140 min. are slow acetylators.

The rapid acetylators (26) constitute 48.1% and the slow acetylators (28) constitute 51.9% of the population studied.

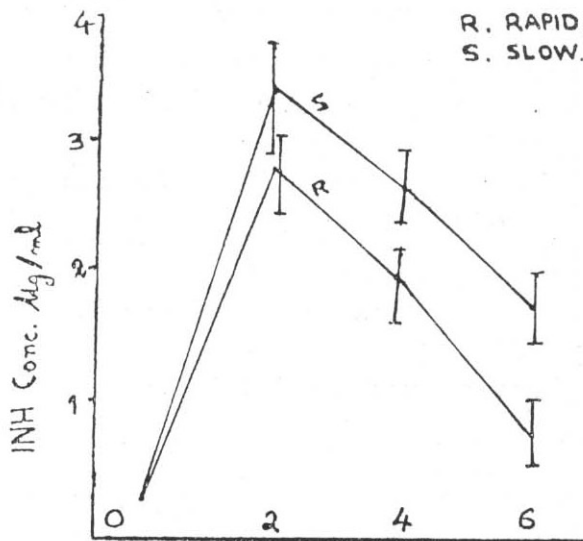


Fig. 2 - Mean free isoniazid concentration with SEM. (rapid and slow acetylators)

The mean plasma levels with SEM of free and total INH of rapid acetylators at 2, 4 and 6 hours are lower than those of the slow acetylators respectively. (Fig. 2).

The plasma concentration of free INH at the end of 6 hours is less than 0.8 $\mu\text{g/ml}$ in the rapid acetylators and more than 1.4 $\mu\text{g/ml}$ in the slow acetylators. (Table I).

TABLE I.

Mean free INH concentration with SEM of rapid & slow acetylators at 0, 2, 4 and 6 hours

| Time Period | Rapid Acetylators $\mu\text{g/ml}$ | Slow Acetylators $\mu\text{g/ml}$ |
|-------------|------------------------------------|-----------------------------------|
| 0—Hours | 0.048 \pm 0.028 | 0.05 \pm 0.03 |
| 2—Hours | 2.54 \pm 0.251 | 3.15 \pm 0.46 |
| 4—Hours | 1.68 \pm 0.372 | 2.37 \pm 0.22 |
| 6—Hours | 0.523 \pm 0.182 | 1.49 \pm 0.20 |

The concentrations of free and total INH fall off in straight lines parallel to each other at 2, 4 and 6 hours after drug administration. The release of the bound drug is therefore uniform and proportionate to the decrease in concentration of free INH. (Fig. 3).

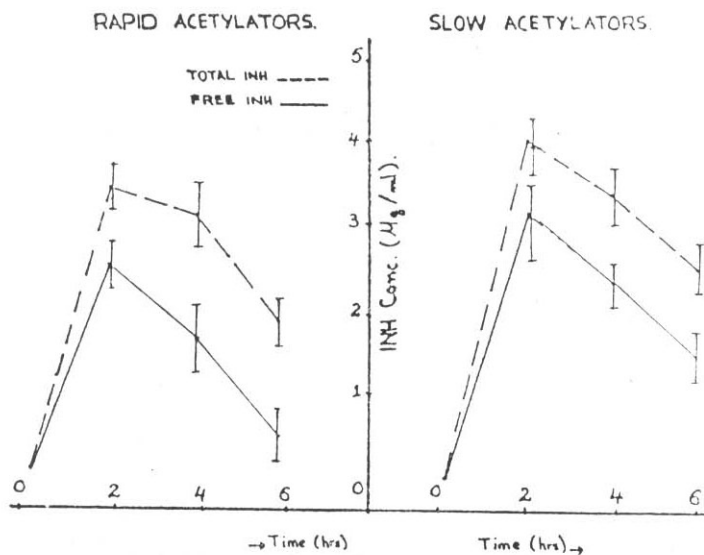


Fig. 3 - Mean plasma concentration with SEM of free and total INH in rapid (n - 26) and slow acetylators (n - 28).

SGOT levels ranged from 40 to as high as 76 I.U. in 17 patients on the first visit before starting the drug.

SGPT levels ranged from 40 to as high as 50 I.U. in 8 patients on the first visit before starting the drug.

Discussion

The frequency of rapid acetylators ranges from 32% to 95% as reported by various investigators all over the world.¹ The distribution does not follow any pattern with regard to latitude or longitude. (Fig. 4).



Fig. 4 - Distribution of rapid acetylators in the world.

As far as the authors know, the present study of 54 patient volunteers was carried out for the first time in Pakistan. 48.1% of the population studied were rapid acetylators with the plasma half life of less than 120 min. (mean 91.46 min.) and 51.9% slow acetylators with the plasma half life of more than 140 min. (mean 225.75 min.) is in agreement with Evans.^{5,7}

N-acetyl transferase, mainly present in liver and also in gastro-intestinal mucosa and some in other tissues, has been shown to acetylate a number of aromatic amines including isoniazid, sulphapyridine, dapsone, hydralazine and procainamide.¹⁰ This N-acetyl transferase shows genetic variation in activity and therefore population can be divided into two phenotypes of rapid and slow acetylators. This genetic polymorphism of INH inactivation^{2,6} is inherited as an

autosomal dominant trait for rapid acetylators and has been shown to depend on the individual capacity to acetylate INH.⁸ The frequency of the rate of acetylation of INH is dependant upon race but is not influenced by sex or age.¹² Rapid acetylators are at a great risk from adverse reaction such as INH hepatitis due to phase II activation of INH to a hepatotoxic metabolite (Monoacetylhydrazine) which may play a crucial role in INH induced hepatitis.¹³ (Fig. 5).

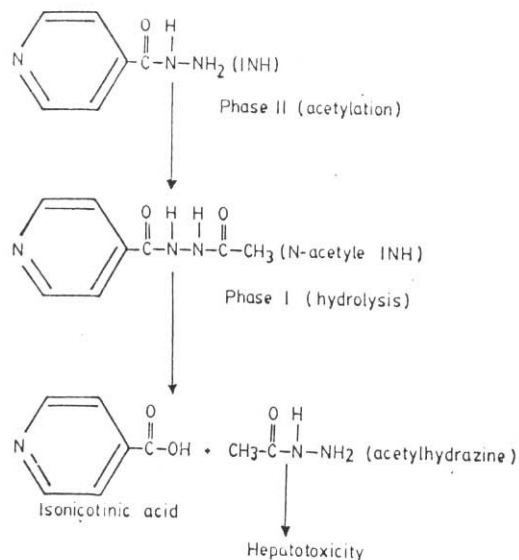


Fig. 5 — Phase II acetylation of isoniazid to a hepatotoxic metabolite.

Isoniazid has been used in the developed countries as a single drug in the prophylaxis of tuberculosis. In developing countries like Pakistan, the problem is greater because active tuberculosis has to be treated by at least triple drug therapy in patients whose liver may already be affected by mal-nourishment in addition to the disease itself. As such, combination with other anti-T-B drugs, which are also hepatotoxic, may aggravate the toxicity.

Recommendations

Phenotyping of rapid and slow acetylators may be attempted in newly diagnosed tuberculous patients where facilities exist and all patients, specially the rapid acetylators receiving INH, should be carefully evaluated for symptoms of hepatitis and determination of serum transaminase done at monthly intervals. Those patients with elevated transaminase levels should therefore be taken off the hepatotoxic drugs till serum transaminase comes back to normal; and less toxic alternative drugs administered to them.

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