ISONIAZID ACETYLATION AND POLYMORPHISM IN HUMANS

Pages with reference to book, From 284 To 286

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Abstract

Phenotypes of slow and fast acetylators of isoniazid (INH) were determined in 157 subjects (80 normals and 77 patients with tuberculosis) from the twin cities of Rawalpindi and Islamabad. Plasma INH concentrations were determined chemically six hours after the drug ingestion. The findings indicate that 31.8% subjects were fast acetylators of the drug (JPMA 39: 285, 1989).

INTRODUCTION

Studies have shown that a number of drugs including INH are acetylated and inactivated in the liver by the acetyl- transferase enzymes[1]. The rate of inactivation of INH varies in different individuals and in different races and is found to be genetically controlled[2]. It is well established that in the treatment of tuberculosis slow acety-lators of INTL are more prone to the untoward effects of the thug. The frequency of hepatic disorders on the other hand is connected with the fast acetylation of INTL. The greater hepatotoxicityby fast acetylators appears to result from the synthesis of acetylisoniazid which is further metabolized to acetyihydrazide which is extremely hepatotoxic[3]. Thberculosis is not a rare disease among Pakistanis and a considerable number of patients are taking INK. For all the above reasons, the present study was undertaken to determine the extent of fast and slow acetylators of INH.

PATIENTS AND METHODS

Subjects included 80 apparently healthy males from the National Institute of Health, Islamabad, weighing 50-70 Kgs, whose ages ranged from 20-60 years and 77 male tubercular patients from the Thberculosis Centre, Rawalpindi weighing 40-50 Kgs whose ages ranged from 17-60 years. The patients had proven infection with tubercle bacillus. After taking informed consent, the medications of the patients were stopped for 48 hours prior to the entry into the trial. The subjects were given INH orally in a single dose of 10 mg/Kg body weight (Isonex containing 100 mg INH, Pfizer Lab. Pak. Ltd.). Blood sample was collected in a stoppered tube containing EDTA six hours after the ingestion of the drug. The plasma was separated immediately and stored at -20°C until INH was determined. INH was determined spectrophotometrically by the method of Braun et al[4] using ammonium vandatc, measurement of absorbance followed immediately at a wavelength of 430 nm. Calibration graphs were made on INH and used to determine IN}I concentration in the plasma. Back ground absorbance of plasma and recovery of INTL was also determined, so as to check the reliability of estimation.

RESULTS

The distribution of INH concentrations in 157 subject is shown in Figure 1.

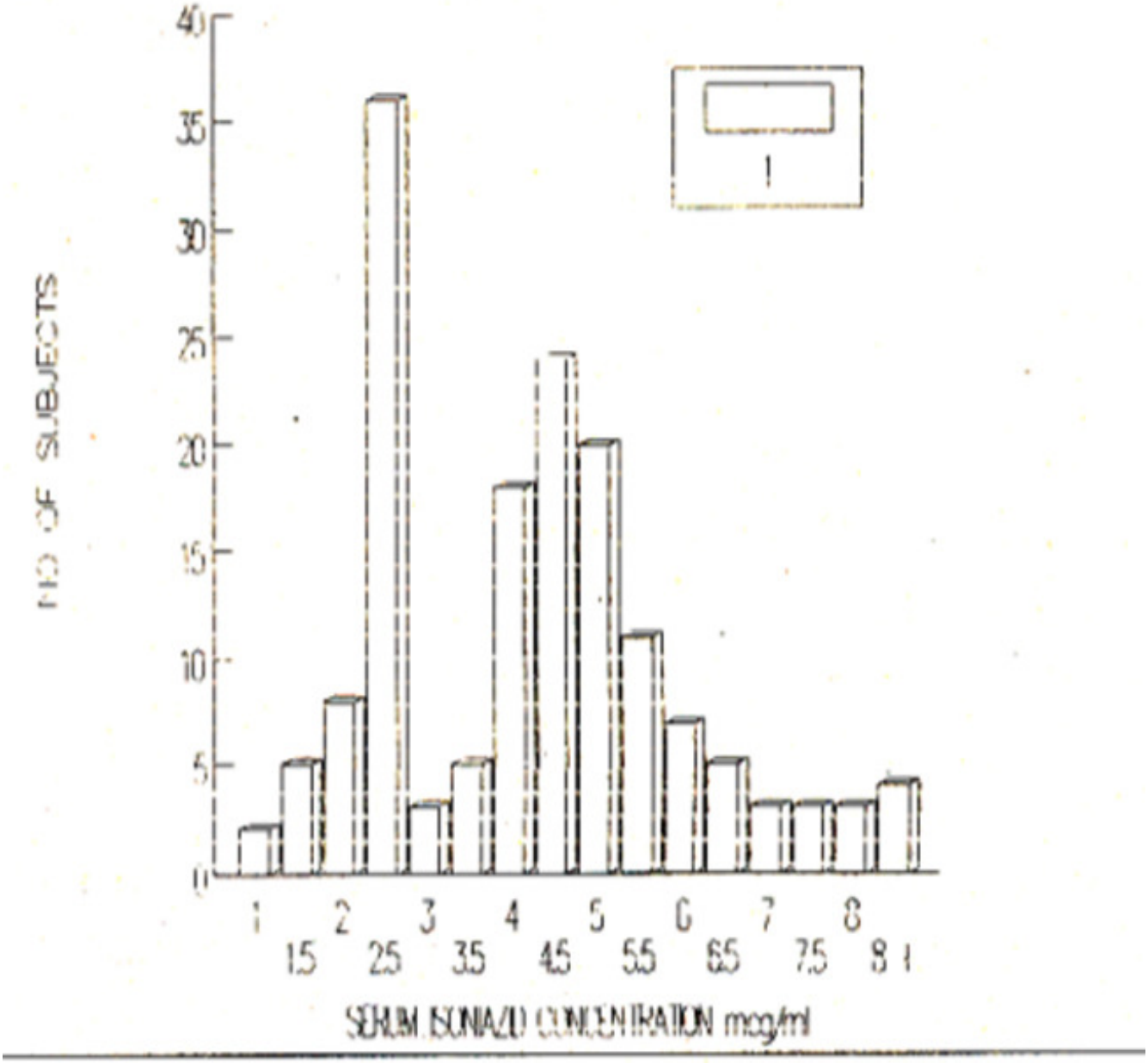

Figure 1. Serum Isoniazid concentration in 157 subjects. (6 hours after oral dose of 10mg/kg).

This distribution is bimodal. Very low back-grounds were observed in this method, When Applied to freshly drawan drug free plasma. The absorbance are therefore, uncorrected for the dilution factor (Table 1).

TABLE I. Absorbance of Drug Free Plasma.

*Subject Number	Absorbance (430 mu)
1.	0.003
2.	0.007
3.	0.005
4.	0.005
5.	0.003
6.	0.006
7.	0.003
8.	0.003
9.	0.004
10.	0.007
	**0.0046 ± 0.0014

* Normal healthy donors.

** Represents mean ± standard deviation.

The results of the recovery of INH added to plasma was found to be 95% (Table 11).

TABLE II. Recovery Data of Isoniazid.

Sample Number	INH (ug/ml) * Acutal	Recovered	% Recovery
1.	5.48	4.66	85.03
	5.48	5.21	95.07
2.	5.48	4.93	89.96
	5.48	4.93	89.96
3.	5.48	5.48	100.00
	5.48	5.75	104.92
4.	5.48	6.03	110.03
	5.48	4.93	89.96
5.	5.48	5.48	100.00
6.	5.48	4.93	89.96
	Mean	5.23 (n = 10)	95.43±8.2 (Mean ± SD)

*Added to the plasma of normal, non-tuberculosis donors.

The distribution of INN slow and fast acetylators is shown in Table III.

TABLE III. Number and distribution of fast and slow Acetylators (Polymorphs) among normal subjects and Tuberculosis Patients.

Types of Subjects	No. of Subjects	Acetylators Fast (No: %)	Slow (No: %)
Normal	80	24: 30.0	56: 70.0
Tuberculosis patients	77	26: 33.8	51: 66..2
Total:	157	50: 31.8	107: 68.2

There is very little difference between the percentage of fast and slow acetylators among normal subjects and tuberculosis patients.

DISCUSSION

The drug free background of human plasma in the method used is sufficiently low to cause any appreciable interference. Ninety five percent recovery of INH, when the drug was added to drug free plasma, further confirms the reliability of the method employed. The present data demonstrates that 31.8% subjects are fast acetylators. There was no significant difference in normal population and subjects suffering from tuberculosis. Similar results have been reported by Sharma et al who reported 39% subjects as fast acetylators of INH[5]. The highest percentage of fast acetylators (91%) is found in Japanese population[6], while of Thai population are fast acetylators[7]. The distribution of fast acetylators in Negro and Caucasian population is about 50 percent[6]. The speed of inactivation of isoniazid has no practical effect on the response, if the drug is used dailyor2to 3 times a week, it has a marked influence on the frequency of neurotoxicity, i.e. peripheral neuropathy is lower in fast inactivators. It may be desirable to determine whether a patient is fast or slow acetylator if once a week regimen is contemplated.

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