

INCIDENCE OF RAPID AND SLOW ISONIAZID INACTIVATORS WITH SPECIAL REFERENCE TO CLINICAL RESPONSE AND TOXICITY OF THE DRUG AMONGST SPUTUM POSITIVE PULMONARY TUBERCULOSIS CASES

S. AJMAL HUSAIN, K.C. MATHUR AND J.P. JHAMARIA

(Sardar Patel Medical College and Associated Group of Hospitals, Bikaner).

Introduction

The individual capacity to inactivate isoniazid varies from person to person (Mandel et al, 1959 and Peters, 1960), but in a given individual it is relatively constant (Gangadharan et al, 1961). The status of isoniazid inactivation (by process of acetylation) is determined genetically (Sunahara, 1962; Titinen et al, and Evans 1968). The individuals are categorised into rapid and slow inactivators of isoniazid by their serum levels of isoniazid, determined at an arbitrary time interval after a test dose of the drug. Rapid inactivators have lower serum level of active isoniazid and vice versa. Such isoniazid acetylation dependent variations in serum levels might have significant effect on therapeutic efficacy of the drug (Dufour et al, 1964 and Evans, 1965), that is sputum conversion rate (Mitchell and Bell, 1957 and Gangadharan et al, 1961), drug toxicity (Gangadharan and Selkon, 1962) and development of drug resistance (Selkon et al, 1964). In rapid inactivators, low serum levels caused loss of therapeutic efficacy, thereby necessitating increase in dosage which in turn is associated with increase in toxicity or addition of drugs which block isoniazid acetylation i.e. PAS (Krekniel et al, 1966 and Mitcheson, 1970) Mitchell and Bell (1957) opined that it was of therapeutic importance to find isoniazid inactivation status of a patient in order to administer individualized doses of isoniazid with maximum therapeutic efficacy and minimum side effects.

Incidence of rapid inactivators of isoniazid in different racial groups and different countries vary significantly. Highest incidence of 95 per cent is recorded among Eskimos (Armstrong and Peart, 1960), 88 per cent Japanese (Sunahara et al, 1961), 39 per cent among Finns (Tiitonen et al, 1968) and lowest 32 per cent Swedish (Hanngren et al, 1970). In India rate of inactivation of isoniazid has been studied only in South Indian population (Gangadharan et al, 1961 and Gangadharan and Selkon, 1962) which revealed that 39 per cent were rapid inactivators. But India being a vast country with possibility of ethnic variations it was thought desirable to study isoniazid inactivation rate among North Indian population with special reference to

therapeutic efficacy and toxicity of the drug isoniazid.

Material and Method

All the patients admitted in T.B. Hospital, Bikaner, during June and July, 1970 were studied, 118 patients were selected according to the criteria of Gangadharan et al, (1961). It comprises of :—

- (1) Patients having positive sputum by direct smear or concentration method.
- (2) Patients who had no treatment or had less than 15 days treatment with anti-tubercular drugs.
- (3) Patients who were not acutely ill.
- (4) Patients above the age of 12 years.

Relevant clinical, radiological and bacteriological examinations were carried out initially, at monthly intervals and finally at the end of the study period of three months.

Serum INH estimations were done 48 hours after a test dose of INH (3 mg per kg per body weight) by the chemical method of Kelly and Poet (1952).

Serum INH levels at 0.6 /ug/ml or less were designated as rapid inactivators, levels above 0.6/ug per cc were labelled as slow inactivators (Gangadharan used 0.58/ug/ml as the dividing levels). All patients were put on anti-tubercular treatment with triple drug therapy namely Regimen 'A' (consisting of SM 1 Gm+INH 300 mg and Thiacetazone 150mg) or Regimen 'B' (consisting of PAS 10 Gm+INH 300 mg+Thiacetazone 150 mg) depending upon the amount of toxemia present. Final analysis could be done in 109 cases only as 9 patients left hospital before the completion of the study. Toxic effects were graded according to the criteria laid down by Pamra (1971).

Mild

When they were minor and did not call for withdrawal of drug.

Moderate

When toxic effects disappeared on temporary withdrawal of drug and did not reappear after reinstatement of therapy.

disease respectively. These tables reveal that there was no significant difference between the patients of these two groups, hence they were comparable.

Severe

When toxic effects were such as to effect a permanent withdrawal of drug or serious side effects like Stevens Johnson syndrome.

There was no statistically significant difference between the clinical improvement (92.9% and 93.8%); radiological clearing (82.2% and 91.3%) and bacteriological conversion of sputum (78.6% and 85.2%) among rapid and slow activators of INH.

Observations

Rapid inactivators were 32(27.1 %) and remaining 86 (72.9%) were slow inactivators showing preponderance of slow inactivators in North Indian population (Table I).

According to Table V rate of sputum conversion was almost the same with Regimen 'A' (68.7% and 87.5%) as with Regimen 'B*' (91.7% and 81.8%) amongst rapid as well as slow inactivators of INH. The difference in rate of sputum conversion among patients of various groups was not statistically significant.

Tables I, II and III deal with distribution of rapid and slow activators of INH on basis of their age, sex and radiological extent of the

Table VI reveals that speed of sputum conversion was almost the same with Regimen

TABLE I

Age wise distribution of rapid and slow inactivators of INH

Age in years	Rate of inactivation of isoniazid					
	Rapid		Stow		Total	
	NO.	%	No.	%	No.	%
Upto 19	6	37.5	10	62.5	16	100
20-29	8	29.6	19	70.4	27	100
30—39	6	15.8	32	84.2	38	100
40-49	7	31.8	15	68.2	22	100
50 and above	5	33.3	10	66.7	15	100
All	32	27.1	86	72.9	118	100

TABLE II

Sex wise distribution of rapid and slow inactivators of INH

of inactivations of Isoniazid	Male		Female		Total Rate	
	No.	%	No.	%	No.	%
Rapid	29	29.9	3	14.2	32	—
Slow	68	70.1	18	85.8	86	—
All	97	100	21	100	118	—

TABLE III
Radiological extent of disease in terms of lung zones involved and cavity status among pulmonary tuberculosis (rapid and slow inactivators of INH)

Lung zones	Rate of inactivation of isoniazid					
	Rapid		Slow		Total	
	No.	%	No.	%	No.	%
1—2	8	25.0	36	41.8	44	—
3-4	15	46.8	43	50.0	58	—
5—6	9	23.2	7	8.2	16	—
<i>Cavity status</i>						
Non-cavitary cases	12	37.5	31	36.0	43	—
Cavitary cases	20	62.5	55	64.0	75	—

TABLE IV
Clinical, radiological and bacteriological response to three months treatment in relation to rate of inactivation of isoniazid among bacillary positive pulmonary tuberculosis patients

Response	Rapid		Slow		Total	
	No.	%	No.	%	No.	%
<i>Clinical status</i>						
Improved	26	92.9	76	93.8	102	
Not improved	2	7.1	5	6.2	7	
All	28	100	81	100	91	
<i>Radiological status</i>						
Improved	23	82.2	74	91.3	97	
Not Improved	5	17.8	7	8.7	12	
All	28	100	81	100	109	
<i>Bacteriological status</i>						
Converted	22	78.6	69	85.2	91	
Not converted	6	21.4	12	14.8	18	
All	28	100	81	100	109	

TABLE V
Bacteriological conversion response with triple drug regimens given for three months in relation to rate of inactivation of isoniazid

Bacteriological status	Rapid						Slow					
	Reg. 'A'		Reg. 'B'		Total		Reg. 'A'		Reg. 'B'		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Converted	11	68.7	11	91.7	22	78.6	42	87.5	27	81.8	69	85.2
Not converted	5	31.3	1	8.3	6	21.4	6	12.5	6	18.2	12	14.8
All	16	100	12	100	28	100	48	100	33	100	81	100

TABLE VI

Response to two triple drugs combination inform of speed of sputum conversion in relation to isoniazid inactivation stains

Rate of inactivation of	Drug combination (Regimen) isoniazid	No. of patients		Progressive speed of sputum conversion at the end of							
				1 Month		2nd Month		3rd Month		Not converted	
		No.	%	No.	%	No.	%	No.	%	No.	%
<i>Rapid</i>	SM+INH+TH (A)	16	100	7	43.7	9	56.2	11	68.7	5	31.3
	PAS+INH+TH (B)	12	100	8	66.6	11	91.7	11	91.7	1	8.3
	Total	28	100	15	53.5	20	71.4	22	78.6	6	21.4
<i>Slow</i>	SM+INH+TH (A)	48	100	29	60.4	37	77.0	42	87.5	6	12.5
	PAS+INH+TH (B)	33	100	16	48.4	25	75.7	27	81.8	6	18.2
<i>All</i>	Total	81	100	45	55.5	62	76.5	69	85.2	12	14.8
		109	100	60	55.0	82	75.2	91	83.4	18	16.6

'A' and 'B' amongst rapid as well as slow inactivators of INH.

There was no toxicity attributable to isoniazid. Incidence of toxicity attributable to SM and thiacetazone was almost the same amongst rapid and slow inactivators of INH.

Discussion

The present study deals with the determination of isoniazid inactivation status, its effect on the drug toxicity and response to the treatment among 118 sputum positive pulmonary tuberculosis cases admitted to Tuberculosis Hospital, Bikaner (North India) during the study period of June—July, 1970. The rate of inactivation of isoniazid has been determined in terms of amount of isoniazid in serum by chemical method of Kelly and Poet (1952).

The rate of inactivations of isoniazid has been shown to be determined genetically (Harris et al, 1958 ; Evans, 1959 ; Peters 1960 ; Sunabara, 1962; Harris 1964 and Evans, 1968).

Studies carried out by various workers resulted in the classification of individuals as 'rapid' and 'slow' inactivators of isoniazid.

Marked racial differences in the incidence of rapid and slow inactivators of isoniazid has been observed by various investigators, ranging from 95% of rapid inactivators amongst Eskimos (Armstone and Peart, 1960) to 32% among Swedish (Hanngren et al, 1970).

Frequency of rapid inactivators of isoniazid was 89% among Koreans, 88% among Japanese (Sunahara, 1962), 62 % among Burmese (Smith and Kyi, 1968) and 36% among Finns (Mattila et al, 1967). These variations in the incidence have been due to ethnic difference. In India so far only one study of this type was carried out among South Indian population by Gangadharan et al, (1961) which revealed that incidence of rapid inactivators of isoniazid was 39%. The present study which was carried out amongst North Indian population revealed that such incidence was 27.1%. The difference in the two figures is statistically significant by method of two proportions ($T=2.5$ and $P < 0.05$). This difference may possibly be attributable to ethnic differences between the study material.

Both the groups namely rapid and slow inactivators of INH were almost similar as far as age, sex and radiological extent of disease in the lungs were concerned, hence both the groups were comparable. Bell et al, 1957 ; Mitchell and Bell, 1957 and Evans 1960 denied any correlation between rate inactivation of INH and age or sex while Gangadharan (1961) found females in greater proportion than males among slow inactivators.

Available literature denies the relationship of extent of disease and rate of inactivation of INH (Bell et al, 1957, Mitchell et al, 1957 and Evans et al, 1960). Similarly the present study has also not revealed such relationship.

Studying the influence of rate of inactivation of INH on the response to treatment

TABLE VII

Incidence of individuals drug toxic manifestation in relation to rate of in activation of isoniazid

Drug used	Rapid inactivators			Slow inactivators		
	Total pts.	Incidence of toxicity		Total pts.	Incidence of toxicity	
		No.	%		No.	%
Streptomycin	16	3	18.7	48	15	31.3
Isoniazid	28	—	—	81	—	—
Thiacetazone	28	7	25.0	81	15	18.5

(Table IV) with two triple drug regimen 'A' (SM/INH/TH) and regimen 'B' (PAS/INH/TH) there was little difference in clinical improvement, radiological clearing and bacteriological conversion of sputum of the patients belonging to the main two groups namely rapid and slow inactivators of isoniazid. Similarly speed of sputum conversion was also almost the same amongst rapid and slow inactivators of isoniazid (Table VI). Thus the rate of inactivation of INH has not influenced the result of treatment with triple drug therapy.

Mitchell and Bell (1957) has provided suggestive evidence that rate of inactivation of INH influences the speed with which sputum conversion occurs. Selkon et al, (1961) suggested that slow inactivators responded to treatment slightly more favourably than the rapid inactivators of INH. But a few observers have failed to demonstrate the relationship (Bell, 1957; Schmiedal, 1958; Barclay, 1959; Sunhara, 1962, Schmidt, 1962, Tiitinen, 1969) similarly the present study also failed to show influence.

In the present study, response to PAS containing regimen ('B') was almost the same as that of SM containing regimen ('A') amongst rapid as well as slow inactivators of INH (Table V). It was claimed by some workers (Johnson, 1954; Carlson et al, 1956; Johnson and Corte, 1956; Morse et al, 1956; Mandel, 1956; Morse et al, 1958; Launer and Faves, 1958; Krenknet, et al, 1966; Tiitinen, 1969) that the addition of PAS raised the level of INH in serum and delays the emergence of INH resistance thus lengthens the activity of isoniazid among rapid inactivators and not much in slow inactivators of INH. Consequently, more favourable response to PAS containing regimen was expected amongst

rapid inactivators compared to slow inactivators of INH, but no such evidence was available in the present study. Sunahara (1962) and Menon (1970) also could not establish this advantageous response of PAS, amongst rapid inactivators of PAS.

As regards effect of rate of INH acetylation on INH toxicity specially polyneuritis, there was no case of such toxicity in our dosages and hence it can be presumed that such doses (300 mg daily in two equal doses) with companion drugs there is very little chance of neurotoxicity of INH (Dingley and Sehgal, 1967 and Pamra et al, 1971) though in higher dosage (16 mg per kg without pyridoxine significant incidence of peripheral neurotoxicity has been reported especially such incidence is more with slow than rapid inactivators 23% and 3% respectively (Gangadharan and Selkon, 1962; Evans et al, 1960; and Devdutta et al, 1960). Incidence of toxicity attributable to streptomycin and thiacetazone remained uninfluenced by the rate of inactivation of INH. One case each from slow and rapid inactivators manifested Stevens Johnson syndrome probably attributable to thiacetazone toxicity.

Thus the present study failed to provide any evidence of the influence of rate of inactivation of INH on therapeutic efficacy and toxicity of treatment given in form of triple drug therapy including isoniazid.

Summary and Conclusions

1. Incidence of rapid and slow inactivator of INH among the study material as a representative of North India were 27.1% and 72.9% respectively.

2. Response to treatment was almost the same amongst rapid and slow inactivators of isoniazid.
3. Response to treatment with PAS containing regimen was almost similar to that with SM containing regimen amongst rapid as well as slow inactivators of isoniazid.
4. No INH toxicity was observed in the present study. From toxicity point of view differentiation into rapid and slow inactivators of INH is not helpful if INH is given in routine dose of 300 mg daily.

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