Original Article

Effect of Smoking on Isoniazid

A Non-Randomized Clinical Trial: Effect of Smoking on Isoniazid Metabolism by N-Acetyltransferase in Tuberculosis Patients

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ABSTRACT

Objectives: To find out effect of smoking on isoniazid metabolism in tuberculosis patients.
Study Design: Non-Randomized Clinical Trial study.
Place and Duration of Study: This study was conducted at the Gulab Devi Chest Hospital, Lahorefrom September to December 2016.
Materials and Methods:40 volunteers were included in this study, who were equally divided in four groups as healthy smokers,healthy non smokers, tuberculosis smokers and tuberculosis non smokers. Collection of blood samples was done after three hours of isoniazid dose (300mg) after overnight fasting to avoid food interactions. Concentration of isoniazid and its metabolites were determined using gas chromatography mass spectrometry test.
Results: No statistically significant difference in isoniazid metabolites/isoniazid ratio was established(p value<0.05). This shows that the metabolism of isoniazid by N-acetyltransferase-2 enzyme in healthy and tuberculosis patients remains same in smokers and non smokers
Conclusions: This trial proved that metabolism of isoniazid by N-acetyltransferase-2 enzyme is independent of smoking. Isoniazid use should be encouraged and adherence should be made imperative in tuberculosis smoker patients for better outcome of tuberculosis treatment.
Key Words: Descriptive Tuberculosis, Smoking, Isoniazid, N-acetyltransferase-2.

Citation of article:Sattar S, Ansar A, Daud S, Kazmi T, Iftikhar S, MirWA. A Non-Randomized Clinical Trial: Effect of Smoking on Isoniazid Metabolism by N-Acetyltransferase in Tuberculosis Patients.Med Forum 2017;28(5):102-105.

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INTRODUCTION

Tuberculosis stands to be the commonest infection by incidence and mortality according to WHO global report 2014[1]. TB is a disease that can be cured with ease. Worldwide 10.4 million new patients suffering from tuberculosis are reported annually[2] Burden of tuberculosis is majorly shared by developing countries with high prevalence in Asia, Pakistan ranking fifth in number[3]. This global disease has emerged as largest public health issue in our country as 350 people per 1 million population are having TB in Pakistan[4]. Smoking is becoming dilemma of present era affecting healthy and diseased. About one-fifth of the patients with TB, are smokers[5]. Smoking is more commonly seen in countries where tuberculosis prevalence is high[6] and it is an independent risk factor for TB[7].

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Received: March 12, 2017; Accepted: April 19, 2017

Smoking has an adverse affect on TB treatment and can lead to the recurrence of TB infection[8].
DOTS is recommended for tuberculosis treatment worldwide with Isoniazid as first line most widely used anti-tuberculosis drug[9]. According to the treatment guidelines available, duration of treatment for active disease is 6 months and for latent disease is 12 months[10]. Isoniazid , rifampicin , pyrazinamide and ethambutol constitute initial phase of treatment ,with isoniazid and rifampicin, being the two main drugs ,used in continuation phase[11]. Isoniazid is degraded by N Acetyltransferase-2 enzyme[12].Likewise caffeine and aryl amines in tobacco smoke are also metabolized by NAT-2 enzyme[13]. Many drugs like antipsychotics, anti-platelets, oral contraceptive pills, beta-blockers and benzodiazepines are having effect on their metabolism by the chemicals in smoke through various pharmacokinetic and pharmacodynamic drug interactions[14 15].
Pakistan has increasing burden of tuberculosis patients, with smoking trends increasing day by day. Many patients spotted with tuberculosis fail to quit smoking ,although getting anti-tuberculosis drug treatment including isoniazid. Since number of drug interactions are reported with smoke chemicals and also isoniazid and caffeine along with aryl amines in tobacco smoke are metabolised by same NAT 2 enzyme ,we conducted

our study to find out the impact of smoking on isoniazid metabolism.

MATERIALS AND METHODS

A cross sectional survey was carried out to identify the prescription pattern of isoniazid amongst tuberculosis patients and detailed history about their smoking habits was taken, to proceed for a clinical trial to find out the effect of smoking on isoniazid metabolism for duration of three months(Sept to Dec 2016) in Gulab Devi Hospital Lahore. Approval for this study was granted by Ethical Review Committee. Sample size of 40 individuals included the volunteers who agreed to undergo this clinical trial at that point in time. Four groups labelled as A,B,C and D were formulated, each containing 10 volunteers. Group A consisted of healthy male non smokers and group B consisted of healthy smokers. Non smoker 10 male tuberculosis patients were the part of group C while 10 male smoker tuberculosis patients were the part of group D. Ethnically all volunteers were from Punjab District of Pakistan. Consent from all volunteers was taken on consent forms. Volunteers with overnight fast were administered with 300 mg oral dose of isoniazid, ensuring next three hours of fasting to avoid occurrence of food interactions. Cubital vein of forearm was selected as a site to collect 4ml heparinized blood using aseptic techniques three hours after drug administration. Analysis of the concentrations of INH, N-acetyl hydrazine and diacetylhydrazine was done in the blood samples withdrawn from the volunteers using Gas chromatography mass spectrometry technique. The ratios of acetylhydrazine and diacetylhydrazine to isoniazid were detected in all four groups. Collected data was then entered and analysed using SPSS version 17. Descriptive statistics(mean) were used to present the results and independent sample t-test applied to compare them.

RESULTS

No statistical significant difference is found in the ratios of acetylhydrazine to isonazid in healthy smokers and non-smokers(p value 0.50) (Table 1). Similarly no difference is present in the ratios of diacetylhydrazine to isoniazid in healthy smoker and non smoker patients, as evident from p-value of 0.64(Table2).Comparison of means of acetylhydrazine/INH ratios in tuberculosis smoker and non-smoker patients was also non significant,with p- value of 0.52(Table 3).Means of diacetylhydrazine/INH ratios when compared ,showed no difference with p-value of 0.51(Table 4).

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Table No.1:Difference between means of acetylhydrazine/INH ratioinhealthy smokers and non smokers (n=20)

		Independent sample t-test								
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% CI (keeping 5% margin of error) Lower	Upper
NS	With equal variances supposed	5.4	.032	0.68	18	0.50	0.0	0.13	-0.19	0.37
	Without Equal variances supposed			0.68	16.3	0.50	0.09	0.13	-0.19	0.37

Table No.2:Comparison of means of diacetylhydrazine/INH ratios in healthy smokers and non-smokers (n=20) Independent Samples Test

		Independent sample student t-test for Means								
		F	Sig.	T	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Confidence Interval of the Difference at 5% margin of error Lower	Upper
Sample	With Equal variances supposed	.005	0.94	0.48	18	0.64	.06	0.14	-0.23	0.36
	Without Equal variances supposed			0.48	17.9	0.64	.07	0.14	-0.23	0.36

Table No.3: Comparison of means of acetylhydrazine/INH ratios in tuberculosis smoker and non smoker (n=20)

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									Confidence Interval of the Difference at 5% margin of error	
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sample	With Equal variances supposed	.509	0.49	-0.7	18	0.52	-0.08	0.13	-0.35	0.18
	Without Equal variances supposed			-0.7	17.8	0.52	-0.08	0.13	-0.35	0.18

Table No.4: Comparison of means of diacetylhydrazine/INH ratios in tuberculous smokers and non smoker (n=20) **Independent Samples Test**

		Independent sample test for Means								
									Confidence Interval of the Difference at 5% margin of error	
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Sample	With Equal variances supposed	0.15	0.71	-0.7	18	0.51	-0.11	0.17	-0.5	0.24
	Without Equal variances supposed			-0.67	17.9	0.51	-0.11	0.17	-0.5	0.24

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DISCUSSION

Our findings suggest that statistically smoking has no remarkable effect on metabolism of isoniazid by NAT-2 enzyme. This study was a clinical trial to find out the effect of smoking on metabolism of isoniazid among smokers and non-smokers tuberculosis patients. Isoniazid though being the main stay of treatment in initial and continuation phase of anti-tuberculosis treatment, was not studied earlier for the effect of smoking on its metabolism. In this study ,we identified the ratios of isoniazid metabolites (acetylhydrazine and diacetylhydrazine) to Isoniazid in smoker and non-smoker healthy and tuberculosis patients and compared them using independent sample t test, to assess the effect of smoking on isoniazid metabolism. On analysis it was found with statistical significance that isoniazid metabolism remains independent of smoking in healthy and tuberculosis patients.

Many studies show clinically significant interactions with various drugs like caffeine clopidogrel, clozapine and theophylline with smoking inducing CYP1A2 enzyme [16]. Murphy et al studied effect of smoking on caffeine which showed noteworthy effect on caffeine pharmacokinetics[17]. In 2010,Jae Kean Ryu study showed increase in clopidogrel efficacy because of cigarette smoking[18]. Previous studies are available , presenting relationship between isoniazid metabolism and NAT2[19]enzyme and NAT 2 genotypes with smoking[20], but to best of our knowledge ,no study is available which aims to establish the relation of smoking with isoniazid metabolism by NAT 2. These studies support the point that smoking interferes with drug metabolism ,but our study proposed that metabolism of isoniazid is independent of smoking.

Many organizations including The International Union Against Tuberculosis and Lung Disease and The European Respiratory Society along with WHO, are putting their efforts to address the increasing burden of tuberculosis with reference to smoking and to help TB patients quit smoking[21.] . Despite the relentless efforts, both by health education and pharmacological interventions, no effective outcome is witnessed in decreasing the magnitude of smoking in general population as well as in tuberculosis patients. Even those who try to quit ,need longer durations and remakrable conditioning, which is practically not easy because long term behavioral change and interventions are required. So smoking tends to remain achilles heel in tuberculosis patients. This study is in strong favour of isoniazid use in both smoker and non-smoker tuberculosis patients. Other studies have concluded

,thatsmoking is linked with tuberculosis treatment failure[22]. In this trial, we tried to study one of the mechanisms, which might be responsible for poor response of isoniazid in tuberculosis smokers during treatment, which proved no difference in metabolism of isoniazid by NAT-2 enzyme in both healthy and diseased smokers and non-smokers. This study suggests, more probing is required to recognize the responsible mechanisms for treatment failures in smokers.

Limitations to our study is small sample size, which could not be increased because of less number of people, both healthy and diseased ,volunteering to be the part of the study.

CONCLUSION

Adherence to isoniazid, as the main stay of anti-tuberculosis treatment, should be encouraged in all tuberculosis patients irrespective of their smoking habits. More probing is required to identify other potential mechanisms for the interaction of smoking with anti-tuberculosis drugs to improve the treatment outcomes.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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