Genetic Polymorphism of N-Acetylation of Isoniazid with Non-insulin-dependent Diabetes Mellitus Patients in Japanese

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1. Determination of isoniazid acetylation phenotype was carried out in 213 Japanese patients with pulmonary tuberculosis (control group) and 52 Japanese patients with both non-insulin-dependent diabetes mellitus and pulmonary tuberculosis (NIDDM group).
2. Distribution of the log (INH/AcINH) ratio of the Japanese population was observed in the two groups. 3. Assuming an antimode of 0.6, the proportion of slow acetylators was found to be 10.0% in Japanese pulmonary tuberculosis patients, and 3.6% in Japanese NIDDM patients with pulmonary tuberculosis. These differences were not significant statistically.

Key words: isoniazid, phenotype, genetic polymorphism, non-insulin-dependent diabetes mellitus

It is well established that there are genetically determined differences in the N-acetylation of a number of arylamine and hydrazine xenobiotics. These include clinical useful drugs such as isoniazid, hydralazine, phenceline, procainamide, dapsone, aminoglutethimide, sulfamethazine, sulfasalazine, nitrazepam, clonazepam, acebutold and caffeine as well as some putative carcinogenic arylamines such as β-naphthylamine, benzidine, and 2-aminofluorene. On the family studies with isoniazid, slow acetylation is an autosomal homozygous recessive trait, whereas rapid acetylation is either a heterozygous or a homozygous dominant trait. There are considerable interethnic differences in the frequency distribution of slow and rapid acetylators. For example, populations of Caucasians and Negroes appear to show an approximately equal percentage of slow and rapid acetylators. In contrast, in Japanese and Eskimo populations, the number of slow acetylators is nearly 10%. There are implications for rational drug treatment in different racial groups. Polymeric N-acetylation has been linked to variations in drug response and susceptibility to an adverse effect of drugs; thus, knowledge of acetylator phenotype is important in assessment of the risk of some drug-related toxic and therapeutic responses.
On the other hand, polymorphic N-acetylation has recently been studied to detect relationships between an acetylator phenotype and the incidence of spontaneous disorders\(^\text{19}\). A predominance of slow acetylators has been shown in Gilbert’s disease\(^\text{20}\) and in bladder cancer\(^\text{21}\); slow acetylation also appears to be more common in patients with gastric cancer\(^\text{22}\), rheumatoid arthritis\(^\text{23}\), and Sjögren’s syndrome\(^\text{24}\). Conversely, rapid acetylator status has been reported to be predominant in patients with breast carcinoma\(^\text{25}\) and colorectal carcinoma\(^\text{26}\). An increased prevalence of rapid acetylators has also been described in patients of European origin with diabetes, both of the insulin-dependent (IDDM) and NIDDM types\(^\text{27}\). In Saudi Arabian patients, an association was found between the slow acetylator phenotype and IDDM. But, in other studies, phenotype frequencies in diabetic patients have not been significantly different from those in the normal population\(^\text{28}\). It is not known relationship between the acetylator phenotype and the incidence of diabetes mellitus in Japanese population groups.

The object of this investigation was to compare the distribution modes in Japanese for N-acetylation on NIDDM patients with pulmonary tuberculosis (TB) and pulmonary TB patients.

**Method**

Fifty-two Japanese NIDDM patients with pulmonary TB (NIDDM group; 10 females and 42 males, 35 to 73 years old) volunteered for the study from National Tokyo Chest Hospital. Two hundred and thirteen Japanese pulmonary TB patients (control group; 71 females and 142 males, 16 to 80 years old) participated in the study from National Tokyo Chest Hospital.

The subjects were instructed (in Japanese language) of the objective of the study and their rights, as set down in the Helsinki Declaration. Interviews and physical examinations were performed and informed consent forms obtained.

All patients were randomly allocated to 6 or 9 months daily treatment with isoniazid (INH; 10 mg/kg) plus rifampicin 450 mg, ethambutol (15-25 mg/kg) and pyrazinamide (3.0 g) according to their age or body weight.

All patients ingested INH (10 mg/kg body weight) in the form of tablets (iscotin, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) without antidiabetic (glibenclamide) at before and test day. After an overnight-fast, each patient emptied his bladder and was then given a single oral dose of INH at dose of 10 mg/kg body weight. Urine samples were collected during the period 0 to 8 hr post-dose. Aliquots were frozen at \(-20^\circ\text{C}\) until analysis.

INH and acetylisoniazid (AcINH) in urine were assayed by the HPLC method\(^\text{29}\). Among the several terms employed to express the activity of polymorphic hepatic N-acetyltransferase, the expression of phenotyping used the “molar acetylation ratio” \(\log (\text{INH}/\text{AcINH})\).

**Data Analysis**

Frequency histograms and probit plots (cumulative frequency distribution) were constructed with data obtained from each calculation. Statistical significance was determined by the U-test of Mann-Whitney.

**Results**

The frequency histograms and probit plots of \(\log (\text{INH}/\text{AcINH})\) in Japanese control group and NIDDM group are shown in Fig. 1 and 2. In the histogram of control group (A of Fig. 1), “the molar acetylation ratio” allowed a much wider range from 0.01 to 2.33, a 233-fold variation. In the histogram of NIDDM group (B of Fig. 1), “the molar acetylation ratio” allowed a wider range from 0.02 to 1.72, a 86-fold variation.

There were no significant difference between U-test of Mann-Whitney. Using 0.6 as the
antimode for the two distributions (Fig. 2), the percentage of slow acetytators (SA) was 10.0\% in the Japnese pulmonary TB patients, and 3.6\% in the Japanese NIDDM patients with pulmonary TB, respectively (Tab. 1). The percentage of SA phenotypes was significantly different amongst the two populations as a whole or between the Japanese pulmonary TB patients and the Japanese NIDDM patients with pulmonary TB. However, population of the Japanese NIDDM patients with pulmonary TB was very small.

**Discussion**

There is ample evidence that the human acetylator phenotypes are associated with drug-induced phenomena. It is likely that the slow acetylators exhibit toxic side-effects because of their relative inability to detoxify the parent drugs. In rare instances, however, the rapid acetylators also exhibit toxic side-effects.

Mattila and Tiitinen\(^2\)\(^7\) pointed out that in a series of 28 Finnish diabetic patients there was an unexpectedly high frequency of rapid acetylators. It was subsequently proposed that there was a genetic linkage between diabetes, some of its complications and acetylator status. Several studies\(^3\)\(^0\)–\(^3\)\(^3\) have appeared in which the elimination
of sulfadimidine was examined in diabetic and nondiabetic populations. Evans has recently analyzed the results of these and other studies and has concluded that, in Type I and II diabetes, there is an association with the rapid acetylator phenotype. Recently, in a study on the metabolic fate of caffeine in diabetic and non-diabetic individuals, it was found that acetylation was decreased in the former\textsuperscript{34}. Furthermore, as the blood glucose control improved, acetylation together with other metabolic routes approached the values seen in the controls. Our results indicate that the Japanese NIDDM group is not different from the control group in the incidence of acetylation phenotype. In the early study of the acetylation polymorphism it was observed with regard to phenotype distribution that American Negroes did not differ much from American Caucasians. And Japanese were much different from Caucasians in that nearly 10% of Japanese were slow acetylators. Using 0.6 as the antimode for the two distributions, the percentage of SA was 10.0% in the Japanese pulmonary TB patients, and 3.6% in the Japanese NIDDM patients with pulmonary TB. The percentage of SA phenotypes was significantly different in the two populations as a whole or between the Japanese pulmonary TB patients and the Japanese NIDDM patients with pulmonary TB. However, population of the Japanese NIDDM patients with pulmonary TB was very small.

Although our data do not show a preponderance of acetylator status in NIDDM despite applying various phenotyping methods previously reported, further studies on NIDDM would be required to explore a risk in relation to acetylator phenotype. This observation cannot yet be interpreted and further investigation will be needed.

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References


