Clinical Prediction of Acetylator Phenotype in Tuberculosis Patients on Medicare using Blood Group

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Abstract
Individual acetylation phenotype detected by metabolic phenotyping tests using a number of surrogate drugs, such as isoniazid is time consuming. The aim of this work was to determine the clinical prediction of acetylator phenotype in tuberculosis patients on medicare using blood group. 150 Tuberculosis patients (102 males and 48 females) on medicare were examined using urinalysis technique for acetylator status and tile method for blood group analysis. The result of the acetylator phenotypes revealed that 46.7% were fast acetylators while 53.3% were slow acetylators. The highest frequency of fast acetylators were subjects with blood groups O+ve and A+ve. Similarly, the highest frequency of slow acetylators were observed in blood groups B+ve and O+ve. Blood groups AB-ve and B-ve formed the lowest frequency of fast acetylators while A-ve and AB-ve formed the lowest percentage of slow acetylators respectively. Analysis of the blood groups and the acetylator phenotype using Pearson's correlation showed a

significant ($p < 0.01$) relationship with a coefficient of 0.852; between the blood groups of M. Tb patients and the fast and slow acetylators ($p < 0.05$, with a coefficient of 0.76) respectively. We imply that for standard TB treatment, more treatment time be considered for subjects with blood groups that are predominantly fast acetylators (e.g., O+ve) and close monitoring through the treatment period for predominantly slow acetylators (e.g B+ve). Further study on the serum concentration of each blood group for the drugs and molecular analysis of the blood phenotypes is advocated.

Key words: Acetylator, Phenotype, ABO, regimen, tuberculosis

Introduction

Mycobacterium Tuberculosis (M.Tb) is a deadly infectious disease which affects about One Third of the World population with about 10 million cases recorded in the M.Tb account
(Barberis et al., 2017, WHO, 2018). According to World Health Organization (WHO) 2020 report, tuberculosis (Tb) is the leading cause of death worldwide ranking above HIV/AIDS. In 2020, there were an estimated 1.3 million TB deaths among HIV-negative people with 10.4 million infected people (WHO, 2020). This disease remains a matter of grave concern as the graph of Tb. infection continues to incline in spite of highly efficacious treatment available for decades (Khan et al., 2022).

The acceptable first line therapy (Directly Observed Treatment Short Course) for drug susceptible Tb comprises of multiple antibiotics such as Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol administered over a lengthy period (Tousif et al., 2015, WHO, 2020). Though the first line Tb regimen provides optimal efficacy, it has been observed to be potentially

hepatotoxic (Saukkonen et al., 2006). The drug response varies from individual-to-individual suffering from the same disease and on the same treatment plan, as some experience adverse drug reactions (ADR). The variations among individuals may be due to several factors including different allele frequency distributions of single nucleotide polymorphisms (SNPs) that have a functional impact on genes associated with drug response (Bachtiar et al., 2019).

Studies on Isoniazid (INH) mono-therapy for instance, have reported about 0.5% hepatoxicity in patients and even higher percentage in combination therapies (Kinzig-Schippers et al., 2005). Similarly, study on the polymorphism of INH acetylation profile has reported variability in acetylation status among individuals, races, ethnicity, and geographical locations (Mairiga et al., 2021). This knowledge has been found useful in tailoring individual dosing of treatment regimen to minimize side effects and maximize clinical outcome (Patin et al., 2006., Richardson, 2019).
Earlier, reports on individual acetylation capacity were detected by metabolic phenotyping tests performed using a number of surrogate drugs, such as isoniazid and sulphadimidine (Kumar et al., 2018; Dwi et al., 2018; Tostmann et al., 2008; Mairiga and Odeigah, 2009). However, the process of determining this individuals acetylator status is observed to be rigorous and time consuming. These and several other potential limitations associated with phenotyping test have necessitated the development of alternative methodologies (Selinski et al., 2011). Whereas much work has been reported on individual acetylator status all over the World (Mukanyangezi et al., 2015), there is paucity of information on the use of blood group as a technique for detecting individual acetylator status in human population. The need for an alternative approach that is generic, fast, consistent and specific in predicting individuals' acetylator status by physicians during prescription or prior to the administration of drugs is therefore necessary.

The knowledge of individual acetylator status is a useful indicator for genetically controlled phenotype, which confirms a given population's classification as fast or slow and could help in therapeutic application for maximized impact towards ensuring the safety and effectiveness of drugs used in the treatment process. The aim of this work therefore was to examine the use of blood group for clinical prediction of acetylator phenotype in tuberculosis patients on medicare.

Materials and Methods

Study design

One Hundred and Fifty in-patients infected with Tuberculosis were recruited for the study. The sampled population was made of 102 males and 48 females. The sample size was determined according to (Lwanga, and Lemeshow, 1991).

Study Area

This study was carried out on tuberculosis infected individuals assessing treatment in Evangelical Reformed Church of Christ (ERCC) Alushi Medical Centre, Akwanga, Nasarawa State, Nigeria, located on latitude 8.9067 oN and longitude 8.4075 oE (Akwa et al., 2007).

Ethical approval

Ethical approval was obtained from the ethics committee of the ERCC Hospital while individuals who met the inclusion criteria provided written consent to participate in the study.

Sample collection/analysis

Test for Sugar

Each urine specimen was first subjected to sugar test as described briefly; 5cm3 of Benedict's solution was put into a test tube followed by the addition of 8 drops of the urine sample. The mixture was heated under a spirit lamp for about five minutes. Samples that changed to red yellow colour

indicated the presence of sugar and were discarded because the urine of diabetics will give false reactions with isoniazid (Mason & Russel, 1971).

Phenotyping Method

The phenotype analysis was determined by spectrophotometric method, a modification of Eidus et al., (1973) and Mukanyangezi et al.,(2015). After a test dose of isoniazid, free isoniazid (INH) and its acetyl derivative (AcINH) were estimated in urine. The classification into slow acetylator (SA) and fast acetylator (FA) was based on the ratio of the metabolite acetyl isoniazid to the total hydrazine excreted (%AcINH). Acetylator status was obtained as percentage acetylation, where values below 70% were considered as slow acetylators while above 70% were considered fast acetylators.

Blood Grouping

The ABO blood group antigens test was performed using the tile method. The ABO blood grouping was based on the agglutination of red blood cells by antibody (Raman et al., 2008). It was performed using commercially prepared monoclonal anti-A and anti-B according to the manufacturer's instructions.

Statistical Analysis

The data obtained were subjected to descriptive analysis using SPSS version 23.0. software to express the parameters in percentages. Pearson's correlation analysis was used to compare the relationship between the blood group and acetylator status. Where it was required, data were given as mean ± standard deviation. One-way ANOVA was used to compare the mean where applicable. The value $p<0.01$ was considered significant for blood group, and acetylators status.

Results

Distribution of the population based on Gender

Figure 1: shows the frequency distribution of the population based on Gender. Of the 150 subjects 102 (68 %) were males and 48 (32 %) were females respectively.

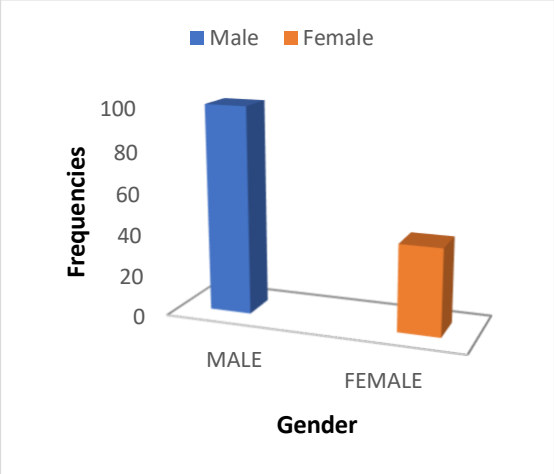


Figure 1: Frequency distribution of the population sampled based on gender

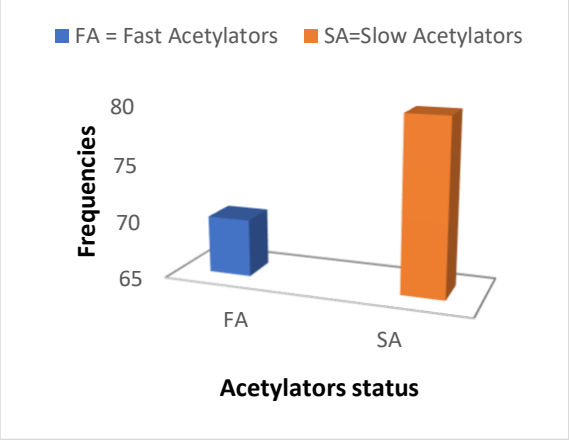


Figure 2: The frequency of acetylator status of patients

Frequency distribution of patients based on their Acetylator Status

Figure 2: shows the frequency of acetylator status of patients. The result shows that the frequency distribution of fast acetylators were 70 (47.0 %) while the slow acetylators were 80 (53 %)Distribution of the Blood Group types

Figure 3: shows the outcome of the frequencies of the various blood groups

analyzed. Which comprises of 16 (10.7 %) A+, 5 (3.3 %) A-, 39 (26 %)B+, 5 (3.3%) B-, 66 (44 %) O+, 8 (5.3 %) O-, 10 (6.7 %) AB+ and 1 (0.7 %) AB- blood groups respectively.

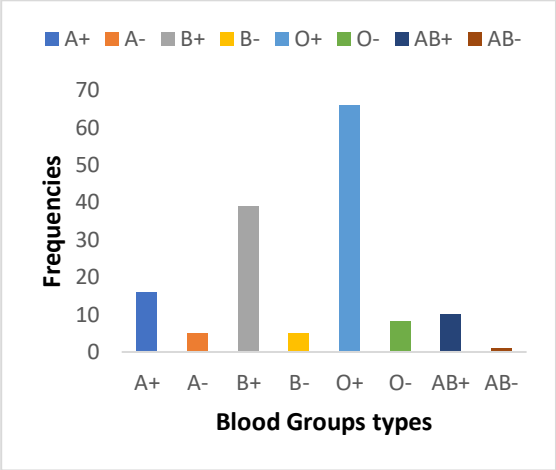


Figure 3: Frequency distribution of the blood Groups types

Blood groups and the Acetylator Status

Table 1 shows that 16 subjects had blood group A+ with 11 (7.30%) as fast acetylators and 5 (3.30%) as slow acetylators. Blood group A- recorded 5 subjects, 4 (2.70%) were fast acetylators and 1 (0.70%) slow acetylator. Blood group B+ had 3 (2.00%), fast acetylators and 36 (24.00%) slow acetylators, while blood group B- had 1 (0.70%) fast acetylator with 4 (2.70%) slow acetylators. A total of 66 blood group O+ subjects were tested for acetylator status, 43 (28.70%) were fast acetylators, while 23 (15.30%) were slow acetylators. Subjects with blood group O- had 2 (1.30%) fast acetylators and 6 (4.00%) slow acetylators. A total of ten subjects had AB+ blood group, 6 (4.00%) were fast acetylators and 4 (2.70%) slow acetylators. The AB- blood group showed 1 (0.70%) slow acetylator status with no fast acetylator for the blood group.

Analysis of the Blood group and the acetylator phenotype using Pearson's correlation showed a significant ($p < 0.01$) correlation (with a coefficient of 0.852); between the blood group of TB patients and the fast and slow acetylators ($p < 0.05$, with a coefficient of 0.76) respectively.

Table 1: Blood Group and the Acetylator Status of the studied population.

Blood Groups	**No of Samples**	**Frequency of Fast Acetylators**	**Frequency of Slow acetylators**	**Correlation coefficients of each blood group**		**Correlation coefficients of blood**	
				Fast Acetylators	Slow Acetylators	Fast Acetylators	Slow Acetylators
A^+	16 (10.70%)	11 (7.3%)	5 (3.30%)	-0.500	-0.500	0.852^{**}	0.767^{*}
A^-	5 (3.30%)	4 (2.70%)	1 (0.70%)	-1.00**	-1.00**		
B^+	39 (26.0%)	3 (2.00%)	36 (24.0%)	-1.00**	-1.00**		
B^-	5 (3.30%)	1 (0.70%)	4 (2.70%)	-1.00**	-1.00**		
O^+	66 (44%)	43 (28.70%)	23 (15.30%)	-1.00**	-1.00**		
O^-	8 (5.30%)	2 (1.30%)	6 (4.00%)	-1.00**	-1.00**		
AB^+	10 (6.70%)	6 (4.00%)	4 (2.70%)	-1.00**	-1.00**		
AB^-	1(0 .70%)	0 (0.00%)	1 (0.70%)	-	-1.00**		

Discussion

Our findings on the frequency of fast acetylator phenotype in the studied population agrees with the report of Sahiratmadja et al., (2021), even though their classification incorporated the intermediate acetylator phenotype. The highest percentage of fast acetylators in our study were observed in subjects with blood group O+ve followed by blood group A+ve. While the least percentage of fast acetylators were observed in subjects with blood group AB-ve and blood group B-ve respectively. Similarly, the highest frequency of slow acetylators were observed in blood group B+ve and blood group O+ve in this order. The lowest percentage of slow acetylators were observed in blood groups A-ve and AB-ve respectively. The analysis between acetylator status and blood group using Pearson's correlation, showed a significant ($p < 0.01$) relationship between the blood group of patients with fast, and slow acetylators phenotypes ($p < 0.05$) respectively.

Previous acetylation studies have established that the frequency of occurrence of the rapid (R) and slow (S) alleles differs substantially between populations and has therefore accounted for the observed variation in the overall acetylation process (Mairiga and Odeigah, 2009; Lakkakula et al., 2014). This factor, along with the increasing global TB-HIV pandemic affecting some countries more than others, have necessitated a renewed interest in the study of the effects of acetylation on the epidemiology of TB (Ramachandran and Swaminathan, 2012).

Reports on the various associations between particular ABO blood phenotypes and increased susceptibility to disease have also been documented (Huston et al., 2002). And researchers have shown considerable attempts in determining the significance of particular ABO blood phenotype to genetic variability and disease susceptibility (Richmond et al., 2016). Though, the incidences of ABO groups are essential indices for various studies, they are said to vary markedly among different races, ethnic and socioeconomic groups in different parts of the world (Barua, 2002; Shikha et al., 2015). These inconsistencies and variations in outcome may have the tendencies of marring prognosis and diagnosis in clinical practice.

Though there are limited or non-existing literatures on blood group types and acetylator phenotypes of infected patients, this study attempts to proffer that individual blood groups associated with rapid acetylator phenotypes should have their treatment plan longer than those with slow

acetylator phenotypes since studies have proven that low serum INH concentrations were observed in individuals with rapid acetylator phenotypes (Fukino et al., 2008; Alsutan and Peloquin, 2014; Dwi et al., 2018). This was supported by the findings that the mean blood INH concentration 2 hours after INH administration in individuals with slow acetylator phenotypes was two times higher than those with rapid acetylator phenotypes (Schaaf et al., 2005). Other studies also reported an association between INH acetylators status with outcome of TB treatment on once-weekly INH and rifapentine regimen (Weiner et al., 2003., Yuliwulandari et al., 2008).

Adjudging from our findings and based on the frequency of each blood type, a significant proportion of blood group O+ve subjects were fast acetylators even though a considerable fraction were also slow acetylators. This study may not have provided a clear perspective that will lead to the adoption of a particular blood group for clinical prediction of acetylator phenotype of individuals on treatment, there is however a clue as to the relationship between blood groups and acetylator status hypothetically. Secondly, the knowledge of the acetylator status of the sampled population as obtained is adequate to direct prognosis, prescription and monitoring of subjects' responses to treatment as well as cases of adverse drug reactions using ABO blood group system.

The implication of our findings is that the treatment plan for the sampled population should be guided. The duration for treatment schedule especially for subjects with blood groups B+ve. who are predominantly slow acetylators should be within the intensive period of administration. However, improved dosage should be required for those with blood groups O+ ve who are mostly fast acetylators, even though the sampled population had a mixed proportion of slow acetylators in blood group O+ve. Our assumption is that since many subjects with blood group B+ve are slow acetylators, close monitoring should be observed where standard medication of the first line treatment regime is administered. Similarly, more treatment time be considered for subjects with blood group O+ve who are predominantly fast acetylators in the sampled population.

This is with a view to balancing the level of serum concentration of drugs acetylated in patients, being that fast acetylators are less susceptible to INH toxicity. As reported by Pasipanodya. et al., (2012) in a meta-analysis, that rapid acetylators contribute to microbiological failure, acquired drug resistance, and TB relapse, by exhibiting lower INH levels in bloodstream. This is could be as a result of rapid acetylation of INH molecules, thus decreasing INH exposure to M.Tb in the affected tissues (Unissa et al., 2016, Rens et al., 2020, Sahiratmadja et al., 2021).

As a result, determining individual acetylator status prior to the administration of treatment regime would be an effective strategy towards curbing with incidences of hepatotoxicity and adverse side effects experienced by Tb patients undergoing treatment in various centers. Incidentally, every patient in the population is still being treated in a similar manner without pathology-based evidence as if they are all of the same acetylator status (Nwose et al. 2016). As clearly put by some authors, acetylation phenotype is yet to be on the post-treatment or pre-treatment laboratory testing list (add-on- test); probably because there is still controversy over the necessity of acetylation monitoring including the role of genetics (Azuma et al., 2013, Hayashi et al., 2015, Jung et al., 2015). Though, numerous studies have reported how individual genetic profile may be relevant in adjusting drug dosages and selecting medications (Bachtiar et al., 2019), adopting this knowledge will be useful in

tailoring individual dosing to minimize side effects and maximize clinical outcomes (Patin et al., 2006, Nwose et al. 2016, Richardson et al., 2019).

Conclusion

Blood groups have been widely studied as Mendalian traits across populations, however, the predictive clinical use of blood group as a possible alternative technique for determining acetylators phenotypes in Tb patients may not be feasible in the interim. This is because, blood group phenotype lacks the consistency to be adopted as a marker for determining acetylator status in infected subjects prior to treatment. This study is however of interest because it has pointed to the fact that some blood groups are prone to treatment outcome or susceptible to toxicity (slow acetylator) and the need for physicians to take precautionary measures at the point of prescription. Exploring the serum concentration of each blood group for the drugs and molecular analysis of the blood phenotypes is hereby recommended for further acetylator studies.

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Conflict of interest

There is no conflict of interest

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