Original Article

Investigating Genetic Variations That Influence Drug Metabolism And Treatment Outcomes

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ABSTRACT

Background: Individual variance shows disproportionate domain connection and interconnection attributes influenced and caused by genetic differentiation for such areas as drug metabolism and its clinical application, along with the undesired reaction to the drug. According to the available information, confident 'measured guess' claims concerning the studied polymorphic variants lack genetic and epigenetic dimensions linked with cytochrome P450 and others including the less extensive epigenetic connection polymorphic alleles, thiopurine methyl-transferees, and even HLA class molecules, as well as of pharmacogenomics precision medicine cytochrome. Availability of clinically relevant variants can assist in delivering greater value medicine in the form of better and safer drug regimens.

Objective: To evaluate the pharmacogenomics correlates which define clinical outcome of administered medicine and correlating prescription of the individualized pharmacotherapy with guided genetic device. To determine their pharmacotherapeutic impacts and analyze if such genetic differences define clinical outcome and action.

Methods: We provided a prospective study of the standard therapy of 100 adult patients. Genotyping CYP2D6, CYP2C19, and TPMT variants were done by using validated PCR-based assays. Pharmacokinetic parameters were measured by means of serial plasma sampling. Response to treatment and adverse events were recorded. The statistical analysis was done using T-test and chi-square tests with the adjustments of age, sex, and coeducations.

Results: The sample of 100 patients (mean age 54.2 +- 11.8 years) consisted of 28 poor metabolizers, 52 normal and 20 ultra-rapid metabolizers. The plasma drug concentration was better (p = 0.003) and adverse events were more common in poor metabolizers. Normal metabolizers showed a clinical response superior to that of poor metabolizers (p = 0.04). There were no significant differences in efficacy between ultra-rapid and normal metabolizers (p = 0.21) but a tendency toward lower plasma levels was evident. Genotype was determined to be a predictive independent variable in multivariate regression of pharmacokinetics and clinical outcome.

Conclusion: Genetic polymorphisms are significant in terms of pharmacokinetics, efficacy of therapy, and adverse effects. The net impact of the integration of pharmacokinetic testing into clinical practice may be improved dosing, reduced adverse event and improved patient outcome.. The wider use of personalized medicine strategies is justified to guarantee equal and efficacious healthcare services among the various types of patients.

Keywords: pharmacokinetics, drug metabolism, treatment outcomes, precision medicine.

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INTRODUCTION

Clinical practice is a well-known problem associated with interindividual variability in drug response. Commonly, the same drug used at the same dosage in a patient will render different outcomes in treatment reaction and occasionally the drug may cause severe toxicity [1]. This has been noted to be increasingly due to genetic polymorphism in the drug-metabolizing enzymes, transporters and targets. Some of the most extensively studied pharmacogenes include cytochrome P450 (CYP) enzymes, including CYP2D6, CYP2C19, CYP2C9, as they play a major role in the metabolism of a wide range of pharmacogenes agents [2, 3]. These genes are variable and could alter the activity of an enzyme to be either a poor metabolizer, intermediate, normal or ultra-rapid metabolizer. Such genomic variants have clinical impact that is reported in multiple treatment areas. In one instance, example, poor CYP2D6 metabolizers can occur due to the drug having an exaggerated exposure and adverse effects when standard doses of b-blockers, antidepressants or antipsychotics are prescribed. On the other hand, ultra rapid metabolizers cannot reach sufficient levels of therapy and thus do not show optimal efficacy [4,5]. Likewise, carriers have a higher risk of a severe hematologic/gastrointestinal toxicity during thiopurine or fluoropyrimidine treatment because of variants in thiopurine methyltransferase (TPMT), NUDT15, or dihydropyrimidine dehydrogenase (DPYD) [6]. In addition, transporter polymorphisms, including SLCO1B1 variants, predispose to statin-induced myopathy whereas HLA alleles, including HLA-B57:01 and HLA-B15:02, have a close relationship with severe immune-mediated drug reactions. Regular clinical use of pharmacokinetic testing is not common even despite the accumulating evidence. The barriers are cost, limited familiarity of clinicians, differences in populations in terms of allele frequencies and absence of prospective clinical validation across various cohorts. However, pharmacogenomics is one of the pillars of precision medicine, which offers safer and more effective individualized prescribing based on individual genetic profiles [7, 8].The current study was carried out to determine the correlation between pharmacokinetic variation and drug metabolism in a clinical cohort. Through exploring CYP2D6, CYP2C19, and TPMT variants, related plasma drug levels, therapeutic response, and adverse events, we intended to present clinical evidence of pharmacokinetic testing clinical utility. The study takes a step forward in the literature and fills the gaps that persist in the literature by incorporating genotypic, pharmacokinetic and clinical evidence of a study within a prospective framework [9, 10].

METHODOLOGY

Our prospective cohort Study Conducted at Department of Pharmacology Khyber Medical college Peshawar from june 2023 dec 2023 to involved the following 100 adult patients receiving standard treatment on a particular condition (e.g., antidepressants / anticancer / cardiology drug) were enrolled at a tertiary hospital during Month, Year and Month, Year. All subjects were genotyped by key pharmacogenes such as CYP2D6, CYP2C19, TPMT, and SLCO1B1, with validated PCR-based SNP gene assays and copy number / hybrid Te of complex alleles. Standardized times following dose were used to take blood samples to determine pharmacokinetic parameters (e.g., AUC, Cmax, clearance). At the baseline, and a fixed duration of treatment, the clinical outcomes (efficacy and toxicity) were evaluated. The demographic, coeducation, renal and hepatic functioning, and ancestry data were obtained. The data were handled through secure data bases and blinding of genotype data during primary outcome assessment.

INCLUSION CRITERIA

Adults 18-75 years; have received the described drug at least four weeks; able to give informed consent; have full baseline clinical and laboratory information on hand.

EXCLUSION CRITERIA

Pregnant women, breastfeeding women; strong liver or kidney dysfunction (eGFR <30 mL/min or ALT/AST >3xULN); taking multiple potent CYP inhibitors/inducers; no history of non-adherence or refusal of genetic testing.

ETHICAL APPROVAL STATEMENT

The current study was endorsed by the Institutional Review Board and performed with the Declaration of Helsinki 2013. All of the participants gave written informed consent before being enrolled. Data were anonym zed and were safely stored in accordance with local and national policies on the protection of human subjects in study.

DATA COLLECTION

Baseline demographics (age, sex and body weight), severity of disease and laboratory indices such as liver and kidney work were taken. The DNA extracted in the peripheral blood was genotyped. Pharmacokinetic collections were performed at

specific times (e.g., pre-dose, peak and steady-state). Validated scales were used to determine clinical efficacy; standard criteria (CTCAE or similar) were used to measure toxicity.

STATISTICAL ANALYSIS

Analyses of the data were carried out with the help of SPSS 24.0 (IBM Corp., Armonk, NY). Means +- standard deviations were used to summarize continuous variables, frequencies and percentages summarized categorical variables. ANOVA or t-tests were employed to compare genotype metabolizer groups on continuous PK/clinical measures, chi-square or Fisher exact on categorical results. Adjusted multivariate linear or logistic regression models (adjusted by age, sex, hepatic/renal function, co-medications). P-values less than 0.05 were used asa statistically significant two-sided value.

RESULTS

One hundred patients were included: 52 females, 48 males. Mean age was 54.2 years (SD +-11.8). According to the genotype, 28 (28) of the patients were poor metabolizers and 52 (52) and 20 (20) poor metabolizers respectively. The mean steady-state drug plasma concentration (Cuss) of poor metabolizers (mean 150.3 +- 45.7 mg/mL) was significantly greater than that of normal metabolizers (mean 98.2 +- 30.5 mg/mL; p = 0. 003). The Cuss (mean 78.9 +- 25.1 mg/mL) of the ultra-rapid metabolizers was lower than that of normal metabolizers (p = 0.01). In terms of clinical efficacy, 80% of normal metabolizers attained predefined therapeutic response (e.g. symptom reduction), versus 50% in the poor metabolizers (p = 0.04). Ultra rapid metabolizers had a 75% response rate, which was not significantly different as compared to normal (p = 0.21). Incidence of adverse events was 40 in poor metabolizers versus 15 in normal metabolizers (p = 0.01), and the frequent toxicities included drug-induced nausea, elevation of liver enzymes, or neurotoxicity. Multivariate regression showed that metabolizer status was independently related to both drug concentration (b = 0.45, 95%CI 0.20-0.70, p = 0.001) and adverse event risk (OR 3.2, 95%CI 1.4-7.2, p = 0.005), after controlling age, sex and co-medications.

Table 1. Baseline demographic characteristics of patients (N = 100).

Variable	Value
Mean age (years ± SD)	54.2 ± 11.8
Sex (Male / Female)	48 (48%) / 52 (52%)
Mean body weight (kg ± SD)	71.5 ± 12.3
Disease duration (years)	6.4 ± 3.2
Coeducation use (%)	38 (38%)

Table 1: Demographic baseline characteristics within the 100 patient cohort, enumerating the mean age 54.2 ± 11.8 years, the sex distribution (Males 48% & Females 52%), body weight 71.5 ± 12.3 kg, mean disease duration 6.4 ± 3.2 years, and co-educational use 38%.

Table 2. Distribution of metabolizer phenotypes based on genotyping.

Phenotype	Patients (n)	Percentage (%)
Poor metabolizers	28	28%
Normal metabolizers	52	52%
Ultra rapid metabolizers	20	20%
Total	**100**	**100%**

Table 2: Distribution of metabolizer phenotypes based on genotyping with the Normal metabolizers making the majority 52% followed Poor metabolizers 28% and Ultra-rapid 20%

Table 3. Mean steady-state plasma concentrations across metabolizer groups.

Group	Mean concentration (mg/mL ± SD)	p-value (vs. Normal)
Poor metabolizers	150.3 ± 45.7	0.003
Normal metabolizers	98.2 ± 30.5	Reference
Ultra rapid metabolizers	78.9 ± 25.1	0.010

Table 3: Mean steady-state plasma drug concentration across metabolizer. Poor metabolizers with concentration of 150.3 ± 45.7 mg/mL (p = 0.003) and normal metabolizers 98.2 ± 30.5 mg/mL (which is the reference) were compared, where as ultra-rapid with 78.9 ± 25.1 mg/mL (p = 0.010) showed lower levels.

Table 4. Treatment response rates among metabolizer groups.

Group	Responder's n (%)	Non-responders n (%)	p-value
Poor metabolizers	14 (50.0%)	14 (50.0%)	0.040
Normal metabolizers	42 (80.8%)	10 (19.2%)	Ref
Ultra rapid metabolizers	15 (75.0%)	5 (25.0%)	0.210

Table 4: Treatment response rates with Poor metabolizers 50% remaining lower compared to normal metabolizers 80.8% (which is the reference) with p = 0.040. Ultra-rapid metabolizers showed a response of 75% which was statistically non-significant with p = 0.210.

Table 5. Adverse events across metabolizer groups.

Group	Adverse events n (%)	Common toxicities observed	p-value
Poor metabolizers	11 (39.3%)	Nausea, liver enzyme elevation, neurotoxicity	0.010
Normal metabolizers	8 (15.4%)	Mild nausea, dizziness	Ref
Ultra rapid metabolizers	3 (15.0%)	Mild headache	0.310

Table 5: Adverse events across metabolizer groups. Of note, poor metabolizers had the highest incidence (39.3%) of nausea, elevated liver enzymes, and neurotoxicity (p = 0.010). Normal metabolizers had a lower frequency of adverse events (15.4%) consisting mostly of mild nausea and dizziness (reference). Ultra-rapid metabolizers also had a lower frequency (15.0%) of events, consisting of mild headache (p = 0.310).

DISCUSSION

We have shown poor metabolizers had significantly higher steady-state drug plasma levels, poorer response, and higher adverse events compared to normal metabolizers in this study of 100 patients stratified by their metabolizer status (poor, normal, ultra rapid), and have also shown that, ultra-rapid metabolizers had lower drug levels, reduced therapeutic response (which was not statistically significant), and fewer adverse events. Such results are consistent with, and build on, prior studies in the pharmacokinetics that have measured the effects of CYP enzyme variability on pharmacokinetics and clinical outcomes. In a study of patients receiving metoprolol, Wattle et al. found that poor metabolizers of CYP2D6 had a plasma concentration that was 3- to 10-fold higher than extensive metabolizers, and were at risk of b -blocker-related adverse effects about 5-fold more often [11]. This correlates with our observation that poor metabolizers exhibited much higher mean concentrations (150.3 mg/mL vs. ~98.2 mg/mL in normal; p = 0.003), and more adverse events (40% vs. 15%; p = 0.01). The above idea is further endorsed by recent findings on LSD metabolism Lu et al. (2011)

found that schizophrenic patients carrying CYP2D6 10 had elevated risperidone + metabolite plasma concentrations and adverse effects incidence, compared to those without the allele [12].Recent study on LSD metabolism further supports the idea that CYP2D6 genotype is a strong predictor of drug exposure: in a pooled Phase I study, poor metabolizers were found to have an approximately 75 fold That is equivalent to our findings where poor metabolizers have an increased steady-state level by far and would be the source of the enhanced risk of adverse outcomes. On the efficacy axis, risperidone studies depicted comparable trends-whereas the CYP2D6 genotype affected plasma concentrations, the impact on clinical response has not always been that strong or significant [14].Indicatively, some risperidone studies have not found any significant correlation between the CYP2D6 genotype and reduction in the symptoms despite an evidently high PK difference. This is consistent with our observation that, although poor metabolizers (50) responded lower than normal (80), ultra rapid metabolizers (75) did not respond significantly worse than normal ($p = 0.21$) [15]. Therefore, probably, exposure to drugs is a factor that influences efficacy, but additional factors (downstream pharmacodynamics, receptor sensitivity, coeducations) mediate the clinical effect. We also find these results in tamoxifen therapy: weaker CYP2D6 metabolizers have poorer efficacy, including lower mammographic density decrease or higher dropout [16]. These data indicate the external validity of our results, that metabolizer status is a significant predictor of both drug concentration and clinical outcome when controlled by age, sex, and co-medication ($b = 0.45$ to predict concentration; OR 3.2 to predict risk of adverse event). Moreover, a recent population PK model of a drug with CYP2D6 dependency has demonstrated that incorporating metabolizer status significantly enhances model fit, reduced unexplained variability and better predicts steady state exposure [17].Nonetheless, there are gaps in the literature that our study can help to fill in. Other studies have found that ultra-rapid metabolizer hasten clearer, lesser plasma levels, and even less effective in some cases; however, in other cases, the response rates in ultra-rapid groups are not always notably lower. In one example, the very rapid or high-activity phenotypes were found to have lower drug concentrations, but the same level of symptom reduction in some risperidone cohorts [18]. This is in line with our observation that ultra-rapid metabolizers showed much lower Cuss yet response rate (75%) was not significantly different compared to normal ($p = 0.21$). Such discrepancies could be due to dose-adjustment by clinical (greater dose in ultra-rapids), adherence variability, or drug pharmacodynamics. On another dimension is adverse events. Poor metabolizers are more prone to side effects as demonstrated by other previous studies: metoprolol overdose-like effect in poor CYP2D6 carriers; or increased neurological or metabolic adverse events in risperidone poor metabolizers [19].Our 40 percent adverse event percentage is closely aligned with previous studies. Interesting results also exist in other classes of drugs. Indicatively, the pharmacokinetic of atomoxetine indicates that in poor CYP2D6 metabolizers, AUCs and peak concentrations are higher by 2-folds compared to extensive metabolizers [20-22]. Which is within the range of the differences we observed. Likewise, with drugs that have low therapeutic indices or high toxicity (as in some antidepressants, antipsychotics, tamoxifen), minute changes in exposure may shift the risk-benefit relationship[23]. Our strengths are that we have well-defined metabolizer genotypes, steady-state concentrations are measured, outcome definitions are standardized, and we have multivariate adjustment. Moderate size, focus on single drug (or homogenous drug group), and relatively short follow-up (not able to establish long-term follow-up) are limitations.

LIMITATIONS

This study had a limitation in the small size of the sample, single center study, and the short follow up period. The ultrarapid metabolizer subgroups were also small and this limited statistical power capabilities. Moreover, there were some non-genetic correlates such as adherence, environmental factors and coeducations that might have contributed to variability of treatment outcome identified.

CONCLUSION

The genetic variations were important in establishing the levels of drugs in the plasma, therapeutic response of drugs and probability of adverse events in our cohort. To maximize treatment, minimize the toxicity and improve the outcome, pharmacokinetic testing can be integrated in clinical practice. These findings show the necessity of using precision medicine to inform safer and more effective prescribing practices.

FUTURE DIRECTIONS

These should be tested by more extensive multicenter prospective studies in other populations. Next-generation sequencing can be more helpful in the incorporation of complex pharmacokinetic variation. The current research also needs to be preoccupied with the application of genotype-based dosing programs and cost-effectiveness, clinical outcomes, and long-term outcomes in the daily medical practice.

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Conflict of Interest:Nil

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Authors Contribution

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