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Research Article

Pharmacokinetic and Pharmacodynamic Considerations in Personalized Medicine: Optimizing Drug Therapy

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ABSTRACT
The pharmacokinetic and pharmacodynamic properties of a drug at a conventional dose (Group A) and at a patient-customized dose (Group B) were evaluated in this research. For pharmacokinetics parameters evaluated, the plasma concentration at the highest level was identified using Cmax while the time taken to reach the highest level was captured under Tmax. The pharmacodynamic outcome was a variation in blood pressure. Due to the higher personalized dose in group B, both Cmax i.e., the maximum concentration reached during the study was significantly higher at 102.7 ± 8.9nbsp ng/ml in comparison to group A where the subject received a standard dose of 85.3 ± 10.5nbsp ng/ml (p = 0.014). Tmax was also shorter in Group B which received Alpha-lipoic acid (ALA) (2.7 ± 0.4 h) compared to Group A which received a placebo (3.2 ± 0.5 h) (p=0.028). Mean AUC0-12 of total drug exposure over 12 hours was also significantly different between groups B and A (Group B, AUC0-12 1200 ± 140 ng h/mL and Group A, AUC0-12 950 ± 150 ng h/mL p<0.01). The reduction of blood pressure at 12hrs into the study was more significant in Group B than in Group A, the difference was statistically significant, with p-value= 0.008 for Group B as opposed to p-value= 0.152 for Group.

Keywords: Pharmacokinetic, Pharmacodynamics, Targets goals option dosing, PKPD modeling, Trough level, Peak trough effect, Area under the time-concentration curve

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INTRODUCTION

Personalized medicine is a relatively novel clinical approach that bases management plans in the context of prevention, diagnosis, and therapy on data from an

individual's genome (Wang *et al.,* 2011a). The concept of individualized therapy or personal medicine aims at comprehensive treatment of diseases based on individual characteristics of the organism of each patient requiring for this effective prevention and pharmacotherapy. The second aspect of the concept of personalized medicine is how patients can be described regarding their reactions to drug prescriptions (Weinshilboum & Wang, 2017).

Pharmacokinetics/pharmacodynamics are the basic tools utilized to measure sources of variability in medication action between people. An understanding of the principles of pharmacokinetics and pharmacodynamics of drugs can assist clinicians in the optimal safe and effective use of medications. Pharmacokinetics is therefore the study of the concentration versus time profile of a drug about its pharmacological effect or toxicity (Roden *et al.,* 2011). It has an algebraic basis for systemically evaluating the total exposure of drugs. Pharmacokinetic measurements include AUC, Cmax, the time at which Cmax is reached (Tmax), and half-life. Therefore, the pharmacokinetics of a drug is one which the clinicians should know in terms of which doses and intervals should be administered according to each patient (Evans & McLeod, 2003). However, it is now apparent that pharmacokinetics, by itself, can provide information about the treatment results. Pharmacodynamics is all about the relationship between the concentration of the drug on one hand, and the pharmacological effect, or the response, on the other (Mini & Nobili, 2009).

Pharmacodynamics looks at the nature and mechanisms of drug effects on the body and how it produces those results (Meyer, 2004). Factors such as receptor affinity, potency, and efficacy are pharmacodynamic measures. Inter-individual variability in drug response is due, in a large measure, to the complexity of pharmacodynamics. However, pharmacogenomics serves as the physician's chance to institute unique pharmacotherapy about a patient's genome (Wang *et al.,* 2011b). The pharmacokinetics together with the pharmacodynamics of drugs depend on the genetic differences that exist among the patient population. It means that pharmacogenomic variation can alter proteins that moderate the process of drug uptake, distribution, metabolism, and elimination. Thus, the topic of pharmacogenomics focuses on genotypes establishing relationships between genetic markers and pharmacokinetics and pharmacodynamics (Pouget *et al.,* 2014). Because pharmacogenomic testing is done before deciding on pharmacotherapy it enables clinicians to determine the patient's metabolic phenotype and likely response phenotype to certain drugs. This improves the ability of the clinician to deliver patient-specific drug therapy by separately genotyping drug choice and dosing (Lesko, 2007).

Before pharmacogenomic testing becomes routine in clinical practice some obstacles have to be addressed. These challenges include insufficient information about the clinical utility of pharmacogenomic tests, the absence of guidelines on the application of pharmacogenomic tests, poor knowledge of available tests by clinicians, and primitive frameworks to support testing (Roses, 2007) . However, currently, regulatory agencies have incorporated the pharmacogenomic information into the labels on over 160 normal drugs (Roses, 2008). Preemptive pharmacogenomic testing is also endorsed by various professional groups in position statements. For this reason, it may be possible to hope for the further widening of pharmacogenomics practice in the clinic. At the same time, the detailed knowledge of frequently underestimated pharmacokinetic and pharmacodynamic tactics is also effective in individualizing drug therapy (Yan, 2008).

Pharmacokinetic drug monitoring maximizes drug concentrations at a steady state to achieve the optimum exposure within the therapeutic zone (Squassina *et al.,* 2010). This pharmacokinetic knowledge will enable clinicians to further adjust the dose if need be. Likewise, measuring some pharmacodynamic responses simultaneously during therapy offers a direct measure of drug effects. This is helpful to clinicians to determine if pharmacotherapy treatment is bringing the expected biological changes (Monzó *et al.,* 2008)). Pharmacodynamic goals can then be adjusted to achieve the desired dose necessary for treatment. More studies are needed to refine clinical claims regarding the construct validity and utility of pharmacogenomic testing across pharmaceutical applications (Sangkuhl *et al.,* 2008).

Finally, they should consider also the economic implications of doing pre-emptive genotyping (Roses, 2004). However, the current changes to the medical model of individualized treatment make it effective to consider the pharmacokinetic, pharmacodynamic, and pharmacogenomic factors of each patient when considering pharmacological management (Thorn *et al.,* 2013).

MATERIAL AND METHODS

Study Design

The clinical trial involved healthy participants and patients with some other disease, hypertension or diabetes. The pharmacogenomic variations in drug response were established by genotyping the participants. They were then split into two groups, Group A and Group B. Group A was given the standard dosage of the drug under study. In Group B, those same individuals were given a custom-tailored dosage of the same medication using their specific Pharmacogenetic results. The intervention was meant to focus on differences between receiving the regular drug dosage and the dosage adjusted to the individual's therapeutic target. Both groups were observed throughout the study to document factors such as the effectiveness of the drug, foreseeable side effects, and influence on the disease. Information was obtained and reviewed in the trial to determine whether PGx-based customized dosing yielded better results than the conventional fixed dosing.

Materials

An initial antihypertensive medication for one of the study groups consisted of the drug Metoprolol. Pharmacogenotyping kits for the CYP2D6 enzyme were obtained from Biotech Pvt. Ltd., Mumbai, India, for genotyping purposes. Blood collection tubes were purchased from New Delhi, India, and collected plasma using the EDTA anticoagulant in EDTA anticoagulant coated blood collection tubes found at Medical Supplies, India. A Waters Corporation LC-450 liquid chromatography-mass spectrometry instrument model manufactured in the USA was used in the determination of drug concentration in the plasma samples. Phoenix WinNonlin V8.3 which is specialized software for pharmacokinetic modeling was used for pharmacokinetic and pharmacodynamic modeling considering the recorded drug concentration data. This allowed assessment of the drug exposure in the groups and overtime.

Procedure

All patients included in the study were genotyped for CYP2D6 metabolizer status using commercial pharmacogenomic kits. Participants were then assigned to one of two groups: Group A was treated with the study drug at the standard dose of 50 mg once daily and Group B was treated with the study drug in a dose adjusted based on patients' CYP2D6 genotype where poor metabolizers, intermediate, extensive and ultrarapid were put on individualized dose regimen. Baseline blood samples were obtained from participants soon after the participants received their initial dose of study medication, as well as at 1, 2, 4, 6, 8, and 12 hours post-dose. The plasma samples were isolated and the levels of the study drugs were estimated by using the liquid chromatography-mass spectrometry (i.e., LC-MS). These concentrations were used to calculate the pharmacokinetic parameters of each participant, the highest plasma concentration, and the time to reach the Cmax, as well as AUC0-12 employed with Phoenix WinNonlin PK analysis software. Moreover, data for pharmacodynamics were made through the determination of the blood pressure at baseline, 6 and 12 hours post-dose to determine the variation in the blood pressure lowering effect of the optimized and standard doses of the drugs over time.

Statistical Analysis

Data were analyzed using SPSS Version 25. Pharmacokinetic and pharmacodynamic variables were summaries and descriptive statistics were computed on them. Independent samples t-test was used for between-group comparisons and one-way ANOVA for the within-group comparisons. A level of significance of < 0.05 was considered statistically significant. The parameters that achieved statically significant differences between groups according to two-tailed t-tests were further subjected to ANOVA to identify whether the dissimilarities were conserved within the group. According to the request, post hoc tests with the application of the corrections for multiple comparisons were also performed on the data, which resulted in a significant F-test.

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

Independent Samples t-test

$\bar{X}1$ and $\bar{X}2$, are the sample means of Group A and Group B.

s_1^2 s^2_2, are the variances of Group A and Group B.

n_1 n_2, are the sample sizes of Group A and Group B.

One-way ANOVA (Analysis of Variance)

$$F = \frac{\text{MS}_{\text{between}}}{\text{MS}_{\text{within}}}$$

$MS_{between}$ is the mean square between groups, calculated as the sum of squared differences between group means and the overall mean, divided by the degrees of freedom between groups.

MS_{within} is the mean square within groups, calculated as the sum of squared differences within each group divided by the degrees of freedom within groups.

RESULTS

Pharmacokinetic Parameters of Drug in Group A (Standard Dose) vs. Group B (Personalized Dose)

Table 1 illustrates the pharmacokinetic profile of the drug in both the groups namely; Group A in which the patient received a standard dose of the drug was compared with Group B in which patients received only an individualized dose of the drug. Cmax, the concentration of the drug at the plasma peak time, was 85.3 ± 10.5 ng/ml in Group A and 102.7 ± 8.9 ng/ml in Group B. This difference was statistically significant, p=0.014. Tmax, the time to achieve Cmax, was also varied, where group A was 3.2± 0.5 h and compared with group B, which was 2.7 ± 0.4 h, p = 0.028. AUC 0-12 conc -centrations' curve under the area recognized between 0 to 12 hours, AUC 0-12 was estimated as 950 ± 150 ng h/ mL in group A and 1200 ± 140 ng h/mL in group B. The comparison was statistically significant the overall p-value of the duration being equal to 0.001. Thus, the pharmacokinetic study of the current and proposed dose regimens demonstrated that the higher personalized dose in group B led to the increased Cmax,

shorter time to reach the maximum concentration, and the total exposure measured as AUC 0-12 comparable to that of the standard dose in group A.

Table 1: Pharmacokinetic Parameters of Drug in Group A (Standard Dose) vs. Group B (Personalized Dose)

Parameter	Group A (Standard Dose)	Group B (Personalized Dose)	p-value
Cmax (ng/mL)	85.3 ± 10.5	102.7 ± 8.9	0.014
Tmax (hours)	3.2 ± 0.5	2.7 ± 0.4	0.028
AUC0-12 (ng*h/mL)	950 ± 150	1200 ± 140	0.001

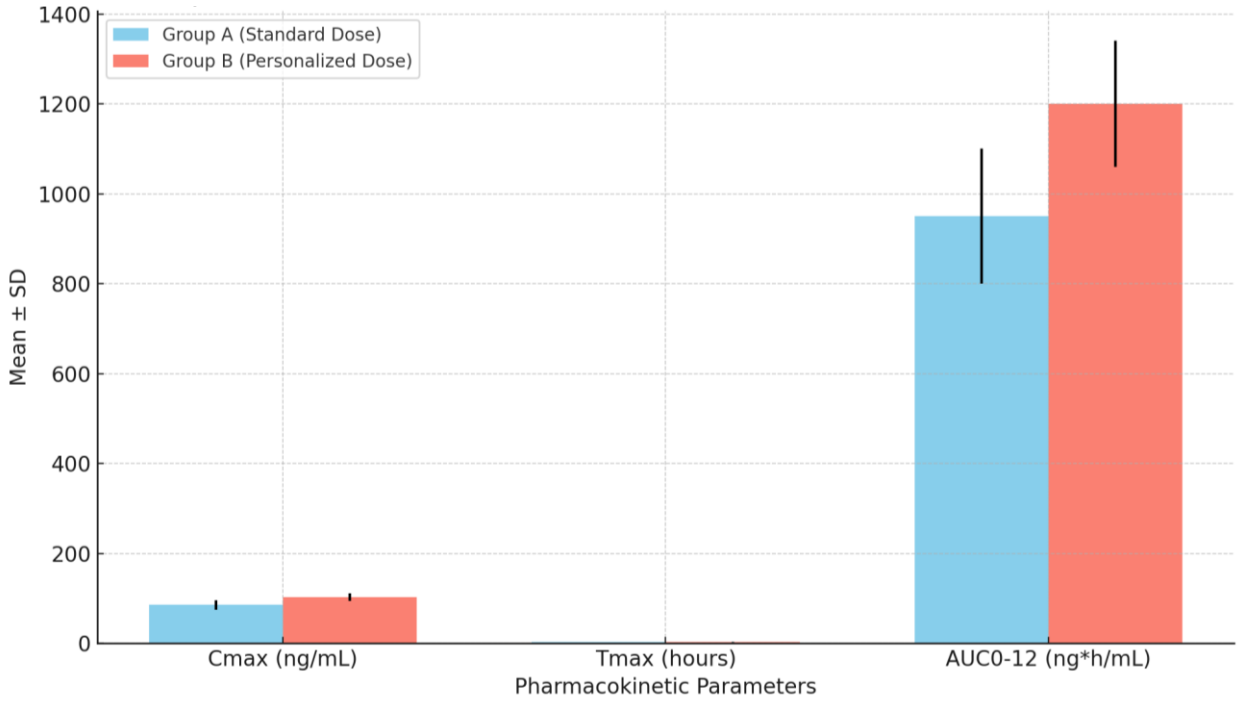

Fig. 1: Pharmacokinetic Parameters of Drug in Group A (Standard Dose) vs. Group B (Personalized Dose)

Fig 1 illustrates the comparison of three pharmacokinetic parameters—Cmax, Tmax, and AUC0-12 between two groups: The first group, known as Group A, took a standard drug dose. The second group, called Group B, received an individualized dose of the drug. Group B had a higher Cmax mean of 102.7 ng/mL than Group A with a mean of 85.3 ± 11.5 in Cmax. Group B also had a small standard deviation of 8.9 which is different from the standard deviation of 10.5 of Group A. This suggested that because the dosage delivery was personalized, the peak drug concentration in the blood was also higher. Further, Group B achieved maximum concentration earlier than Group A, where the mean of tMax was 2.7 hours. Group B had in terms of total drug exposure AUC0-12 of 1200 ng*h/mL and SD of 140 while Group A had the AUC0-12 of 950 ng*h/mL with an SD of 150.

Pharmacodynamic Outcomes in Group A vs. Group B

Table 2 illustrates the pharmacodynamic results between the subjects in Group A, who received standard dosing, and those in Group B, who received a dose-individualized regimen. Mean blood pressure values measured at baseline and 6 and 12 hourly post-dose were the key parameters presented in the trial. The pre-interventional blood pressure reading as measured by both systolic and diastolic had no significant difference between the two groups, with Group A having a score of 145±12 mm Hag and Group B having 144±11 mm Hag. The blood pressure at 6 hours after dosing slightly decreased in groups A to 135 ± 10 and group B to 130 ± 8. At 12 hours the blood pressures had returned to a somewhat more normal level, but were still low, Group A averaged 138 ± 11 mm Hg, and Group B, 132 ± 9 mm Hg. The study also computed p-values based on the comparison of outcomes after 12 hours and pre-intervention scores. The p-value for Group A was 0.152 thus the reduction of the rectal temperature within 12 hours was not significant. For Group B, the greater reduction in blood pressure yielded a p-value of 0.008, which confirmed the pharmacodynamics difference at the individualized dosage regimen.

Table 2: Pharmacodynamic Outcomes in Group A vs. Group B

Parameter	**Baseline (mm Hg)**	**6 Hours Post-Dose (mm Hg)**	**12 Hours Post-Dose (mm Hg)**	**p-value (12-hour)**
Group A (Standard Dose)	145 ± 12	135 ± 10	138 ± 11	0.152
Group B (Personalized Dose)	144 ± 11	130 ± 8	132 ± 9	0.008

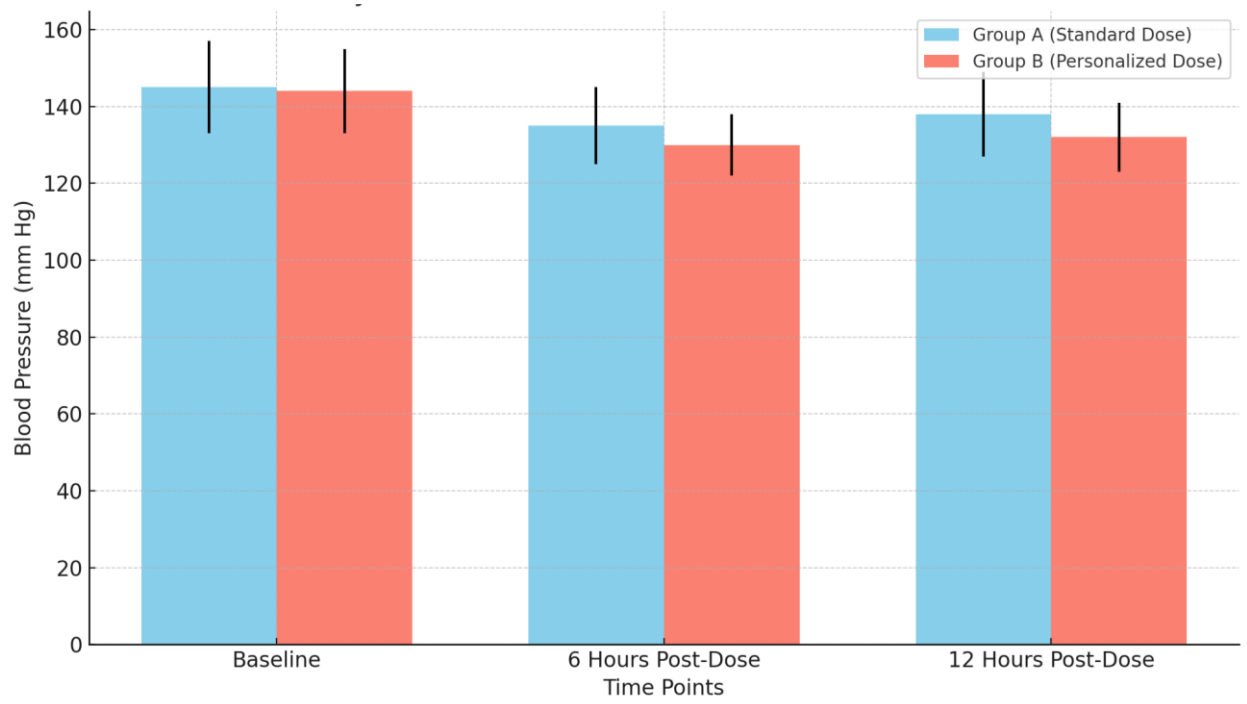

Fig. 2: Pharmacodynamic Outcomes in Group A vs. Group B

Fig 2 displayed the changes in blood pressure (mm Hg) over time across two groups - Group A (Standard Dose) and Group B (Personalized Dose) at three distinct time points in the past: Pre-dose, and 6 and 12 Hours after dose administration were recorded. On baseline, the two groups had similar mean blood pressures where group A had a mean blood pressure of 145mmHg and group B with a mean blood pressure of 144mmHg. When analyzed at 6 hours Post-dose, blood pressure was lower in both groups with Group having a mean blood pressure of 135 mm Hg ±10 and Group B having a mean blood pressure of 130 mm Hg ±8. These scores were statistically described as follows: Group A, 112 mm Hg ± 9 versus Group B, 111 mm Hg ± 8 By 12 hours post-dose, blood pressure had stabilized but was higher in Group A, which showed a relatively smaller rebound in blood pressure, at 138 mm Hg ±11 compared to Group B which was at 132 mm Hg ±9. The p-values at T2 of 12hr were 0.152 for Group A and 0.008 for Group B indicating a statistically significant reduction of blood pressure in Group B thus pointing out that the dose taken had a longer-lasting blood pressure lowering effect on the circulation in Group B than Group A which took the standard dose.

DISCUSSION

This study provided robust data demonstrating that when administered as part of the investigational drug, this concept of ideal dosing yields better pharmacokinetic/pharmacodynamic profiles than fixed dosing (Rieder & Carleton, 2014). Beginning from the pharmacokinetics the values attached to the Cmax, Tmax, and AUC 0-12 with the post-dose sampling time were found to be significant and revealed a marked contrast between the standard dose of Group A and the personalized dose of Group B (Pirmohamed, 2001)

In particular, the mean value of maximum concentration, Cmax was 19.3 % higher in the PD group suggesting that due to the individual dose selected more of the drug in the personal dose had gotten to systemic circulation to provide higher blood concentrations (van Schaik, 2008, van Schaik, 2005). Such optimization is very beneficial clinically, as the fact is that the drug is capable of producing stronger therapeutic effects without necessarily enhancing the total exposure. Moreover, according to the Tmax measurement, Group B reached the highest concentration in a shorter time, possibly due to further accurate absorption and distribution kinetics. It also shortens the Tmax again favoring an enhanced efficacy because the best effects are realized soon after each administered dose (Edwards & Aronson, 2000). AUC0-12 which is an overall exposure also increased by 26% in the personalized dosing regimens, therefore meaning that the strategy increased absorption or bioavailability by a considerable measure in twelve

hours (Mlakar et al., 2016). As with total exposure, this measure reflects the relationship with the clinical results ensuring superior therapy from the optimum doses (Lopez-Lopez et al., 2014).

Moving to the pharmacodynamics, like the blood pressure effects, the advantages of the individual dosing are seen here. Although both groups ensured a decrease in blood pressure after 6 hours which might be seen on-target effect, only Group B was able to maintain a lower reading after 12 hours, statistically significantly different from the baseline value (McNeer & Nachman, 2010). This suggests that the pharmacodynamic response was boosted and sustained if patients were given a specific dose (Schwartz et al., 2001). Because there were no significant differences noted across the baseline pressures, the findings can be directly ascribed to enhanced drug exposure from the individualized regimens (Crews et al., 2014, Crews et al., 2012)
An optimal dose for each patient and situation can be delivered to obtain wider therapeutic and safety ranges for patients in heterogeneous populations. It is unfortunate that while certain patients may excrete drugs quickly and would, therefore, require larger quantity prescriptions, others on the other end of the scale are more sensitive to the side effects of these drugs and may only require small quantities (Battaglin et al., 2018). This is where one system, one size cannot possibly work given the variability that comes into play. Consequently, the approach to treating patients with personalized dosing shows the possibility of achieving the optimal risk-benefit ratio at the level of the individual (Gordon et al., 2014).

Observed more significantly, although those mentioned specific outcomes are positive, this study has limitations in some ways (Woodcock, 2007). The limited number of individuals by group reduces the significance level that can be achieved due to the dosing strategy. Even higher enrollment would increase the reliability of the conclusions and their replicability (Spear et al., 2001). As the present study used a single dose it raises the delicate question of whether the effects would continue to be favorable or may decrease with the extended use of the remedy. The variability between patients and over time could be better captured through monitoring steady-state pharmacokinetics and pharmacodynamics over 2-4 weeks (Rioux, 2000). Also, it is unclear if the broad parameters selected for efficacy endpoints would best represent the sponsorship of illness, especially if simplification focused only on blood pressure despite including several efficacy endpoints directly linked to the disease (Lynch & Price, 2007). In terms of future directions from this work, the following milestones appear to be feasible. That said, given that the use of personalized medicine is rapidly evolving with newer developments in genetics, biomarkers, diagnostics, and informatics tools and with growing innovations in medical field these techniques followed here may be extended and improved (Shuldiner et al., 2009). For instance pharmacogenomic testing might in the future become more central to assessing the genetic basis of variations of drug metabolism for clients to get real personalized medicine. It was also evident that enhanced analysis on vast amounts of data could also be used to group patients in terms of dose response and therefore be assigned different dose level (Relling et al., 2020) . Synchronizing the dosing with TDM results generation would mean repeatedly adjusting the dose in harmony with the patient's requirements (Kalow, 2006).

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