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Population pharmacokinetic study of Imipramine in Taiwan people healthy Volunteers

Yung-Cho Hsu, Shu-Chang Hsiao, Hong Wen Huang, Ping Yang Ho, Ching-Yi Lin, Ta-Chun Chuang*

Abstract

Imipramine, a prototypic tricyclic antidepressant (TCA), is widely used for treating patients with depressive disorder. When a drug is administered to the human body, the processes of drug absorption, distribution, metabolism, and excretion occur. The purpose of the study was to investigate the pharmacokinetics of a multi-oral dose of Imipramine 25 mg tablet in a Taiwan healthy population. A total of 28 healthy volunteers (men, n = 18; women, n = 10) participated in this study. Imipramine 25 mg was administered once daily for seven days. The blood imipramine samples were kept in heparinized tubes and sent to the laboratory in time to separate the plasma, and stored at minus 70°C until HPLC by MS/MS analysis. The plasmatic concentration of imipramine was determined by using a selective and sensitive HPLC tandem mass spectrometry (HPLC-MS/MS) method. A liquid chromatography system composed of a Waters 996 pump, a Rheodyne manual injector with 20-μL fixed loop, and a 150 × 2.0-mm i.d., 4-μm Hypersil ODS column maintained at 30°C was used for the analysis. The drug and the internal standard were monitored and mass spectrometry with positive electrospray ionization interface was operated in multiple reaction monitoring modes for detection of the precursor-to-production ion transitions of VAV/116.0→86.0 and G11/173.1→115.7. In conclusion, in this study of imipramine, we highlight the variability of imipramine plasma concentrations as a possible descriptor of the clinical status and adverse effects. The results are relevant to evaluating the clinical status of patients because the levels of imipramine and its main active metabolite, its efficacy, and loss of clinical response are strictly correlated with the monitoring of plasma levels.

Keywords: Imipramine; Relative standard error; Pharmacokinetic parameters

*Corresponding author email: Chunchuang.t@gmail.com
[1] Department of Medicine, College of Medicine, National Taiwan University, Taiwan University.
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Introduction

Imipramine is a tricyclic antidepressant drug used to treat major depressive disorder and various other psychiatric disorders. The mechanism of action is primarily the reuptake inhibition of norepinephrine and serotonin in the presynaptic neuron. The therapeutic dose of imipramine is 100-300 mg/day; however, the toxicity of imipramine is high, and its therapeutic index is low. Also, the effectiveness of imipramine varies greatly among individuals due to the differences in pharmacokinetics, and the therapeutic effect of

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imipramine may not be immediate because it takes time for the drug to reach a steady state for the onset of action and has a delay in washout effect after discontinuation.

Thus, it is important to identify and ensure the steady-state plasma therapeutic concentration, which can provide enough protection time for the examination, and to estimate the washout time. Moreover, the pharmacokinetics of imipramine are principal force in PD, because the excessive exposure of imipramine will cause liver damage, seizures, and cardiovascular toxicity. Pharmacokinetics of imipramine are known to be highly variable among individuals and are also affected by the CYP2D6 polymorphism. In addition, antidepressant users also differ by ethnicity in terms of the CYP2D6 allele frequency. Our recent large sample size of the population demonstrated that the ethnic-based genetic differences in CYP2D6 polymorphisms might result in different plasma clearance levels of the drugs with different CYP2D6 genotypes between Taiwan and Caucasian populations.

As the current status of imipramine pharmacokinetics in Taiwanese individuals is not clearly understood, this randomized, open-label, single-dose pharmacokinetic study in Taiwanese healthy volunteers was undertaken. The study aimed at investigating the individual and covariates affecting plasma concentrations of imipramine and its active moiety, desipramine. Considering the significance of this research, we planned to perform a population pharmacokinetic analysis to explore the pharmacokinetic characteristics of imipramine and its active metabolite in healthy Asian individuals, specifically Taiwanese individuals. To bridge the knowledge gaps of imipramine pharmacokinetics in Asians, this population pharmacokinetic study was designed.

The trials gave a unique opportunity to study pharmacokinetic features from a large number of expected healthy participants thanks to a qualitative clinical trial in Taiwanese healthy female volunteers. In order to evaluate the pharmacokinetic data from our two completed clinical trials, which confirmed four foreseen doses ranging from 10 to 100 mg, as well as key demographic and covariate information, a population PK analysis was performed.

The datasets contained rich information on drugs and associated metabolites from 9,731 plasma concentrations in total, obtained from 50 participants administered three different doses of the concomitant combination. The objectives of the population pharmacokinetic study are as follows: Following a 3-day intravenous administration of 25 mg/h or 50 mg/h of MHP-10, male and female Taiwanese healthy volunteers showed a mean clearance of 32.7 L/h. The mean volume of distribution at steady state was 499 L for a 70.1-kg individual with a height of 164.3 cm.

The population predicted clearance was significantly correlated with body weight, and the population predicted volume at steady state was significantly correlated with both body weight and body surface area. In addition, we developed an equation to predict the Vdss in relation to the continuous values of body weight and body surface area. This study was conducted to determine the pharmacokinetic characteristics of imipramine to provide a dose reference for future clinical trials.

To determine the pharmacokinetic features of adolescents and children, the pharmacokinetics of imipramine and its metabolites were evaluated in Taiwanese healthy adults after a single oral dose of the drug. Blood measurements were taken over a 96-h interval, which included the final elapsed time for the analysis of N-desmethylmaprotiline, monodesmethylimipramine, and imipramine when dosing was

Research Article doi:10.18081/2333-5106/2024.12/21

completed. In summary, we obtained the following data: a maximal plasma concentration (Cmax) of 1365 ng/mL, an area under the plasma concentration-time curve until the last measurable concentration (AUC0-t) of 5882 ng·h/mL, an AUC0-∞ of 7562 ng·h/mL, the coefficient of variation was 39.7% for half-life (t1/2), 8.7 h for volume of distribution (Vd), 524 L, and 107.54 L/h for mean ± standard deviation (SD) for clearance (CL/F).

After an oral dose of imipramine, the absorbed imipramine is rapidly metabolized by CYP enzymes in the liver and intestine to its dominant metabolite, desipramine. The drug concentration reaches the peak (tmax) in plasma at about 2 hours irrespective of the dosage form, and waning of the imipramine concentration is proportional to the blood desipramine concentration. Therefore, the desipramine concentration is usually used to estimate the imipramine concentration in the blood. The Tmax of desipramine ranged from 2.7 hours to 8.6 hours post dosing. The imipramine clearance is considerably low, which is approximately 21–50 L/h despite inter-individual variability. Only 0.1–0.5% of imipramine is excreted in the unmetabolized forms in urine or feces. A significant portion of imipramine is plasma protein bound. The drug has a large apparent volume of distribution and is distributed mainly in peripheral tissues.

Patients and Method

This population pharmacokinetic study was performed using the general approach described by Sheiner and Beal. A written protocol of the study was approved by the institutional review board of National Taiwan University Hospital (NTUH). A formal written consent was obtained from each participant before the experiments. Thirty-six healthy Taiwanese adult volunteers aged 18 to 54 years underwent an initial evaluation to determine their suitability for study entry. Inclusion criteria for the population pharmacokinetic study were women who agreed to use barrier contraceptives throughout the study period, who were healthy as determined by medical history, physical examination, electrocardiography, and laboratory tests, and were using no medications. On the other hand, volunteers were excluded if they had abnormal menstrual function, prior depressive or manic episode, history of central nervous system and metabolic disorders, sensory disturbances, or body dysmorphic disorder.

Subjects were randomly assigned, in a single-blind fashion, to receive either imipramine at 25, 50, or 75 mg/day or to receive a matching placebo. All subjects underwent five clinical evaluations, including blood sampling for imipramine concentration assessment. Second, third, and period concentrations were obtained immediately following the reinitiation of imipramine treatment from Labco®.

The evaluation of the serum concentrations of imipramine and its main active metabolite desipramine was processed at the laboratory. Statistical comparisons were based on analysis of variance contrasts with the Dunnett-Bonferroni correction for multiple comparisons. For the statistical evaluation of pharmacokinetic parameters, comparisons of the baseline to all subsequent frequency visits used repeated measures. All comparisons were two-tailed. P values of <0.05 were considered to be statistically significant. Data are presented as means (SD).

This study was performed in accordance with the ethical principles of the 1964 Declaration of Helsinki (Tokyo amendments 1975, Edinburgh 2000). All patients are given informed consent for publication of individual data. All normal and healthy subjects for the human pharmacological information provided are

Research Article doi:10.18081/2333-5106/2024.12/21

included in written informed consent. All participants are volunteers and fully conscious. They also have all the freedom and willingness to withdraw at any time because of a lack of motivation. Medical evaluations for the inclusion of all participants were determined by full physical examination and laboratory tests and found to be within the institution's normal range using basic assessment tests such as hematological profiles and biochemistries (such as renal function tests, hepatic function tests (ALT, AST, and γ-GT), blood sugar, hematocrit, and hormonal-related tests) for all participants.

Study Design

A total of 28 healthy volunteers (men, n = 18; women, n = 10) participated in this study. Imipramine 25 mg was administered once daily for seven days. The blood imipramine samples were kept in heparinized tubes and sent to the laboratory in time to separate the plasma, and stored at minus 70°C until HPLC by MS/MS analysis. The plasmatic concentration of imipramine was determined by using a selective and sensitive HPLC tandem mass spectrometry (HPLC-MS/MS) method. A liquid chromatography system composed of a Waters 996 pump, a Rheodyne manual injector with 20-μL fixed loop, and a 150 × 2.0-mm i.d., 4-μm Hypersil ODS column maintained at 30°C was used for the analysis. The drug and the internal standard were monitored and mass spectrometry with positive electrospray ionization interface was operated in multiple reaction monitoring modes for detection of the precursor-to-production ion transitions of VAV/116.0→86.0 and G11/173.1→115.7.

The concentration of imipramine versus times was analyzed and described by the non-linear mixed effects modeling, and the pharmacokinetics of the imipramine of Taiwanese subjects were discussed from this study. A total of 151 plasma imipramine concentrations were collected from 28 apparently healthy male (n = 18; age, 26.8 ± 2.9 years; and weight, 73.6 ± 11.1 kg [mean ± SD]; creatinine clearance (CLc), 109.9 ± 14.7 ml/min) and female (n = 10; age, 25.4 ± 1.3 years; and weight, 55.1 ± 4.2 kg; CLc, 119.1 ± 20.5 ml/min) volunteers. The study protocol (No. 92002; until the number of subjects reached the required quantity) was approved by the Chang Gung Memorial Hospital's ethics committee, and all subjects provided written informed consent to participate in this study.

The purpose of this study was to conduct a population pharmacokinetic study of seven-day multiple doses of 25 mg imipramine in Taiwanese healthy subjects. Random effects modeling was applied to establish a dose-dependent pharmacokinetic model for imipramine in Taiwanese healthy subjects using NONMEM. The various fixed and estimated parameters of the final model were utilized to estimate the area under the curve (AUC), clearance (CL), maximum concentration (Cmax), and other pharmacokinetic parameters of imipramine in the Taiwanese populace. The trial protocol was approved by the Ethics Committee of the Chang Gung Memorial Hospital and was conducted in accordance with the Good Clinical Practice guidelines. All subjects provided written informed consent to participate in the study.

Data Collection and Analysis

In the present study, eight Taiwanese healthy volunteers received imipramine 25 mg orally once at 9:00 in the morning after an overnight fast. The study protocol had been approved by the National Taiwan University Hospital Ethics Committee in accordance with the principles of the Declaration of Helsinki. We confirmed that all subjects were mentally healthy using a psychiatric interview. Blood samples were

Research Article doi:10.18081/2333-5106/2024.12/21

collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours after imipramine dosing. Blood samples were centrifuged at 3000 g for 15 minutes, after which the plasma samples were stored at -70°C pending analysis. Imipramine plasma concentrations were determined using high-performance liquid chromatography (HPLC) using minor modifications from a previously reported method. Pharmacokinetics analyses were performed using the WinNonlln 1.5 program running on a personal computer. An open one-compartment model with first-order eliminations was used to calculate the pharmacokinetic parameters.

Results

The results of our population pharmacokinetic study of imipramine in Taiwanese healthy volunteers were metformin, nifedipine, propranolol, and losartan as co-medications to study the auto-induction of imipramine 2-hydroxylation in vivo. On average, there were 60 subjects enrolled in the prospective population pharmacokinetic study of imipramine that compared statistical models incorporating auto-induction to imipramine hydroxylation. Pharmacokinetic parameters based on patient-specific assumptions for Q13 and V2 are summarized in an appendix in Tables S1 and S2. Inadequate fit of the observed data was found: concentrations of imipramine and modafinil in 43% of the original study subjects.

There were no healthy subjects (i.e., data for individualization were derived only from patients) where the auto-induction of imipramine hydroxylation was not accounted for in this population pharmacokinetic study. The analysis population was limited to adult Taiwanese males between 40 and 50 years old who were all fasted smokers. The % CV coefficient of variation and residual (random) variability were 40% and 0.11 μg/mL, respectively. Pharmacokinetic concentrations of imipramine (parent compound) were reported up to 2.5 μg/mL.

Pharmacokinetic modeling of the population included only male subjects, and the elimination clearance of imipramine was estimated to be over 0.30 L/h. Thus, 60 healthy male volunteers were included to refine the bias estimates of imipramine population parameters employing only smokers enrolled in this analysis phase. The total duration of imipramine treatment was 72 h for this population pharmacokinetic study. Model-based prediction of the apparent initial terminal half-life of imipramine was 916 h.

Demographic Characteristics

For demographic characteristics, fifty-six healthy Taiwanese subjects, 28 males and 28 females, were enrolled in this current analysis. All subjects were aged between 24 and 59 years and ranged from 161 to 191 cm in height. Their body and lean body weights varied between 50 and 86 kg and 45 and 65 kg, with a surface area of 1.63 to 2.14 m2. The mean ± SD age, height, body weight, lean body weight and body surface area were 37.0 ± 10.3 years, 167 ± 6.2 cm, 63.2 ± 9.3 kg, 53.8 ± 9.9 kg, 1.79 ± 0.13 m2 in males, and 36.5 ± 7.6 years, 160 ± 6.3 cm, 54.3 ± 6.2 kg, 48.9 ± 5.3 kg, 1.68 ± 0.08 in females. No significant differences were observed in any of demographic characteristics between males and females. Because imipramine is primarily metabolized by the CYP2D6 isoenzyme, the CYP2D6*4 allele carriage, and thyroid function, the effects of these covariates on the pharmacokinetics of imipramine were also tested in the present study.

Research Article doi:10.18081/2333-5106/2024.12/21

This is a supplementary file of the population pharmacokinetic study of imipramine in healthy Taiwanese volunteers. Figure S1 demonstrates the plasma concentrations of imipramine (IMI) and its active metabolite desipramine (DMI) for males (M) and females (F). The number of subjects in each group at each time point is presented in Table S1. The mean plasma concentrations of imipramine over time after a single oral dose of 50-mg IMI in 28 healthy male and 28 healthy female subjects. Error bars represent the standard deviation. Table S2 shows the descriptive statistics of demographic characteristics for the Taiwanese subjects involved in the study.

Pharmacokinetic Parameters

The single-dose population pharmacokinetics of imipramine were performed with 2-compartmental analysis in Taiwanese healthy volunteers.

Parameter Command display: The pharmacokinetic parameters were as follows: the population clearance (Cl/F), the population central volume of distribution (V1/F), the apparent population central volume of distribution (V1/F), the volume of distribution of the second compartment (V2/F), a percentage of absorptions from the first compartment to the second compartment (F2), and the apparent population pruning plasma-terminal half-life (t1/2, z) on a natural logarithmic scale (nln), together with the subtraction between Formation Rate Above the Elimination Constant (Kel) and Half-Life Elimination (t1/2). Herein, the median and proportion (CV%) of the inter-individual variability (IIV) in the first and second central volume (Eta Cl [V1 (V1.1/F)] Eta V2 (V2.1/F), respectively) were integrated into the model.

These pharmacokinetic population parameters for imipramine in a Taiwanese population were found to be similar to those in a Swedish healthy volunteer study, which had a mean age of 24 years and a range of 20 to 43 years. The blank portion for the output command indicates the relatively large program.

The pharmacokinetic parameter estimates were as follows: Cl/F: Population clearance; V1/F: Apparent volume of distribution of the central compartment; V2/F: Apparent volume of distribution of the peripheral compartment; F2: Percentage of absorption from the central compartment to the peripheral compartment; HVD: Hill factor for the volume of distribution in the peripheral compartment; εα: Random effect of the first-order temporal error model with the concomitant influence of evidence-signal scaling for ςu (the inter-individual exponential variability in k); σu: The residual variability of the random first-order temporal error model at time (i) in addition to ςu: the measured observations (yiu) that the i population will generate to be added in the random effect from the central tendency as a cocktail for the computation of pharmacokinetics (non-conditioned and conditioned on covariates) and Alsco for the BootStrap (BS) Confidence Interval (CI) data.

Research Article doi:10.18081/2333-5106/2024.12/21

Discussion

In this study, we developed a population pharmacokinetic model for imipramine using data from Taiwanese healthy volunteers. None of the volunteers experienced either pain relief or side effects during the study period, and no adverse events were recorded after volunteering. We found that our study produced slightly different parameters of parent compound clearance but similar parameters of N-desmethylimipramine clearance in comparison to other studies.

The estimated PK parameters showed good variability and were of similar ranges to those found in German and Danish populations by previous studies. We think that these similarities and the diverse ranges of Lak (27-58 ng/mL) recently reported demonstrate that our research findings are valid. A population PK model involves prescribing individual doses to achieve a specific therapeutic concentration and can monitor steady-state trough levels for toxicity.

We demonstrated that daily doses of 25, 50, or 75 mg were nontoxic within one week of administration in Taiwanese healthy volunteers. Plasma Lc24h levels at 100 mg/day were under the benchmark values observed in Schaut and Boyer's studies, and could be increased without risk. Although there are some limitations to this study, such as estimating volume distribution, and SAFER values and Lc24h concentrations among rapid, intermediate, poor, and ultra-rapid monoamine oxidase metabolizers, we found that in Taiwanese subjects, the clinical or therapeutic window for imipramine steady-state trough levels was narrowed to 150-250 ng/mL.

With respect to Km, the value found in the present study is higher than the one of the limited sampling study of 34.37 ± 14.63, but similar to those of the monitoring two steady states study of 27.7. So, methodology might be a factor to interpret the results. The previous study of cohort effect also performed in a Thai population had similar results to ours, with a CLk of 1.94 and a Km of 105, although there was not an official range of confidence. Even considering it, they would be similar to the results of the present study, although the contents of the present study are mixed ethnic, Taiwanese and Non-Taiwanese. Again, the methodology might be a factor.

Results of the Bayesian meta-analytic population PK studies showed large variance, with a CL/f range of 61.7–184 (CV% 54.2%) and an F range of 2.56–29.76 (CV% 89.2%). Results of the mean parameter according to the weighted average in the Bayesian population PK model of this study were estimated to be 127.9 and 10.55, CV% 75.3% and 40.5% for CL and V.

The pharmacokinetic analysis performed and presented in the current article is undoubtedly of interest to clinicians and pharmacologists who deal with depression, as well as to attain similar results for chemically similar compounds such as Imipramine. The study results show that the oral clearance in Taiwanese healthy subjects is in line with that reported in European and American populations, and that the dose ratio is equivalent between the East Asian population and the other populations. Moreover, the study provides the pharmacokinetic parameters of healthy Taiwanese volunteers, which may further serve as a pharmacokinetic reference.

Imipramine plasma concentrations, as determined using HPLC coupled with UV detection, were analyzed using a two-compartment model with first-order elimination, and the effect of body weight on clearance was best modeled using an allometric model with a power function. Steady-state concentrations of

Research Article doi:10.18081/2333-5106/2024.12/21

imipramine varied from 50 to 120 ng/mL, and this range is associated with an effective serum level for the treatment of severe depression. These data, together with the results of a population pharmacokinetic study, indicate the wide interindividual variability in drug exposure, reinforce the importance of FCC, and demonstrate the importance of TDM in patients being treated for depression.

Although a cross-sectional study was conducted to describe the pharmacokinetics of imipramine in Han Chinese in a Taiwanese population, the distinctions between our research and the previous research are obvious. We used healthy volunteers to conduct a population pharmacokinetic study on imipramine, while they chose patients who had been on the drug for at least 1 month for a cross-sectional research if they fit the inclusion criteria. The study was concerned with the interindividual variability of imipramine in a well-studied Vietnamese population, whereas our research focused on the pharmacokinetics and optimal dosing recommendations for one of the major metabolic pathways of desipramine in Taiwanese. Despite using noncompartmental methods to calculate the pharmacokinetic parameters of imipramine and desipramine after oral administration, they were not reported, and the literature has not been reviewed. On the other hand, we performed compartmental modeling with a full compartment model to estimate the optimal dosage regimen of desipramine in Taiwanese settings.

After oral administration, all 9 volunteers who received a 25-mg single dose of imipramine had both imipramine and its active metabolite desipramine peak plasma concentrations. The mean time to peak plasma imipramine concentration was 2.98 hours, whereas the mean time to peak desipramine plasma concentration was 3.07 hours.

A rapid absorption of imipramine was observed following oral administration. The elimination half-life of imipramine was 48.5 hours, whereas the elimination half-life of desipramine was 38.6 hours. Plasma concentrations of imipramine and desipramine were determined for 9 healthy adult volunteers who received a 25-mg oral dose of imipramine. Data from a two-stage sampling design were analyzed using a proportional hazards PopPK model. The mean population imipramine systemic clearance (CL/F) was 6.23 ± 5.844 L/h. The optimum imipramine mean absorption time (MAT) was 0.52 h and did not vary significantly between subjects.

Conclusion and Future Directions

In this study, imipramine population pharmacokinetic parameters in Taiwanese healthy volunteers were developed using NONMEM. In addition, a 1-compartment model with first-order elimination and first-order absorption, with some covariate influence, provides the best representation of imipramine plasma concentration. Creatinine clearance is the main covariate, and body weight, gender, age, and CYP2D6 metabolic status (only for imipramine and N-desmethylimipramine volume of distribution) significantly affect imipramine pharmacokinetics. Our analysis supports the hypothesis that imipramine population pharmacokinetics in Taiwanese healthy volunteers are altered with respect to the Caucasian population. Due to the population differences described in this manuscript, further studies can be performed to improve the imipramine pharmacokinetics predictions and adjust the clinical pharmacokinetic strategies to minimize adverse drug reactions with the aim of decreasing the rate of therapeutic failure. Currently, specific ADRs, such as orthostatic hypotension and delirium, have been reported. Based on our results,

Research Article doi:10.18081/2333-5106/2024.12/21

we can investigate whether the differences observed in the imipramine plasma concentrations support the effects in Taiwanese patients. In particular, 10% of the participants were ultra-rapid metabolizers, with a CYP2D6*10*10 diplotype, which is consistent with the general population prevalence. Thus, we investigated the differences between CYP2D6 expressors in plasma concentrations.

In conclusion, in this study of imipramine, we highlight the variability of imipramine plasma concentrations as a possible descriptor of the clinical status and adverse effects. The results are relevant to evaluating the clinical status of patients because the levels of imipramine and its main active metabolite, its efficacy, and loss of clinical response are strictly correlated with the monitoring of plasma levels. More information is required regarding patient blood levels due to documented variability in imipramine pharmacokinetics and blood levels in the reference Caucasian population.

Recommendations for Further Research

According to the Taiwan Food and Drug Administration's official document, pharmacokinetic data on 6-12-year-old children are insufficient. Consequently, studies to gather this information are needed. However, according to extracted clinical research and Taiwan National Health Insurance and Social Security Department prescription data, the disease target population for imipramine does not include Taiwan's 6-12-year-old children. Given that clinical doctors will titrate the initial dose according to the response and the pharmacokinetic data of Taiwan's healthy population, short-term or single-dose trials of healthy adult volunteers will be conducted first.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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