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A Pharmacodynamic Modeling and Simulation Study Identifying Gender Differences of Daily Olanzapine Dose and Dopamine D2-Receptor Occupancy

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Abstract

Introduction—Gender differences in treatment response rates for patients treated with antipsychotics are known. However, the literature lacks a pharmacodynamic model to allow for gender-based clinical trial simulations from modeling parameters for Olanzapine and dopamine D2 receptor occupancy. Thus, the primary aim of this analysis is to test and quantify the effect of gender on the pharmacodynamics of Olanzapine.

Methods—Population pharmacodynamic modeling was performed using nonlinear mixed effects modeling in MONOLIX while the Clinical Trial Simulations were performed using R for statistical programming. The pharmacometric analysis is based from a pooled data approach from three clinical studies where patients were diagnosed with schizophrenia and one clinical study where the patients were diagnosed with bipolar disorder.

Results—Olanzapine D2RO was modeled using an Emax model in a study population of seventy patients. Population pharmacodynamic parameters were estimated to be: Emax=85.6% (R.S.E.=3%), ED50-Men=5.15 mg/day (R.S.E.=14) and ED50-Women= 2.38 mg/day (R.S.E.=34%) with the p-value=0.037 for the gender-stratified ED50 results.

Conclusion—Based on the pharmacometrics analysis and model-based dosing simulations suggests that in order to achieve 70% D2RO women require a 10mg/day dose and men require approximately a 20mg/day dose of Olanzapine. Further, clinical implications exist suggesting that clinicians should factor patient gender when considering both a starting dose, as well as, a

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maintenance dose for patients prescribed Olanzapine due to quantifiable gender-differences of striatal dopamine D2 receptor occupancy.

Keywords

olanzapine; gender differences; pharmacodynamics; dopamine; D2RO; psychiatry

Introduction

Gender differences to antipsychotic treatment have been widely reported in the literature (1–5). For example, in a study published by Goldstein and colleagues, at Harvard University, evaluating 1295 men and 700 women reported that women experienced a stronger treatment response to Olanzapine after a six-week trial of treatment, irrespective of chronicity of illness, when compared to men (4). Further, in another study published by Usall and colleagues, conducted in ten European countries, named the Schizophrenia Outpatient Health Outcomes (SOHO) study (men=4,529 and women=3,461), found that women reported an improved quality of life, measured using the EuroQol-5D (EQ-VAS) scale (3). However, despite these clear differences in response to pharmacotherapy between men and women in psychiatry, currently no pharmacodynamic model exists to allow for hypothesis testing for Olanzapine and dopamine D2 receptor occupancy. Thus, the primary aim of this analysis is to test the hypothesis that gender influences the quantifiable Emax equation parameters which govern the pharmacodynamics of daily Olanzapine doses (mg) and the dopamine D2 receptor occupancy (%) in the striatum.

To accomplish this, Olanzapine dose response data will be compiled using a pooled study data approach and analyzed using nonlinear mixed effects modeling (NLME). Further, a final Olanzapine population pharmacodynamic model will be developed for subsequent dose response simulations illustrating the gender-stratified equivalent Olanzapine doses resulting in 70% of dopamine D2 receptor occupancy in the striatum. The rationale for the 70% threshold for D2 receptor occupancy is to avoid extra-pyramidal symptoms, as has been reported at 78% (6). Further, the rationale is to select a 70% receptor occupancy that will minimize prolactin elevation as has been reported at 72% for the same study (6). We hypothesize that an approximate 10% difference in daily doses between men and women will be evident to achieve a 70% D2 receptor occupancy in the striatum.

Methods

Literature Search

A literature search was conducted using MEDLINE/PubMed, PubMed Central, and Google Scholar to identify studies reporting olanzapine doses (mg) and the corresponding dopamine D2 receptor occupancy (%). The keyword search strings included: “olanzapine”, “D2RO”, “receptor occupancy”, “dose response”, and “Positron Emission Tomography” and all relevant articles were included for the final analysis.

Olanzapine D2 receptor occupancy data were recorded using Positron Emission Tomography (PET) scans and were pooled from the four following studies: Kapur et al

1998, Kapur et al 1999, Lavalaye et al 1999, and the Attarbaschi et al 2007 (7–10). The Kapur et al 1998 study included a total of fifteen schizophrenia patients with dopamine D2 receptor occupancies measured with [11C]Raclopride Positron Emission Tomography (PET) scans with Olanzapine doses ranging from 5 to 40 mg/day (7). Next, the Kapur et al 1999 study had a total of seventeen schizophrenia patients with Olanzapine doses ranging from 5 to 60 mg/day and dopamine D2 receptor occupancy measured using [11C]Raclopride PET scans (8). The Lavalaye et al 1999 study data included a total of twenty-three schizophrenia patients from the Adolescent Clinic of the Academic Medical Centre in Amsterdam used [123I]Iodobenzamide (IBZM) Single Photon Emission Computed Tomography (SPECT) to measure dopamine D2 receptor occupancy and included Olanzapine doses ranging from 5 to 30mg/day (9). Lastly, the Attarbaschi et al 2007 study used IBZM SPECT to measure the D2RO in a total of seventeen bipolar disorder patients treated with an Olanzapine at a dose range of 5 to 45 mg/day for a minimum of 14 days (10).

Patient demographic data were originally reported in for all four studies. Gender was reported for all four studies; however, olanzapine plasma concentrations were not reported for Lavalaye 1999 alone, and serum prolactin levels were neither reported for the Attarbaschi et al 2006 article nor the Kapur et al 1999 publication.

Population Pharmacodynamic Modeling

Nonlinear mixed effects modeling of the concentration-time data were performed using the MONOLIX (MODèles NOn LINéaires à effets miXtes) software package version 2016R1. The MONOLIX software has been designed for model-based drug development and uses the Stochastic Approximation Expectation-Maximization (SAEM) algorithm with a Markov Chain Monte-Carlo (MCMC) procedure to compute the maximum likelihood estimates of the population estimates and the respective variances (11–15). Model selection was based in a stepwise forward inclusion and subsequent backward elimination step reaching the lowest $-2 \times \text{Log-Likelihood}$ estimate and goodness-of-fit plots. Model validation was computed using the prediction-corrected Visual Predictive Check (VPC). Demographic summary statistics were computed using the R statistical programming language (16).

Dose Response Simulation of Olanzapine and D2 Receptor Occupancy

Daily Olanzapine doses resulting in dopamine D2 receptor occupancies were simulated using the Multiple Comparison Procedure-Modelling (MCP-Mod) package that runs in the R for statistical programming language (version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria) (16,17). The MCP-Mod package has obtained approval by both the European Medicines Agency and the United States Food and Drug Administration (18,19). The method for dose-response simulations have been previously described here (20). Olanzapine dosing simulations were obtained for the following doses: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40 mg/day.

Pharmacokinetic Simulations

Olanzapine pharmacokinetic simulations were conducted using MATLAB Simbiology (Mathworks, Natick, MA, USA). The approach for calculating the equivalent doses using model-based dosing simulations have been previously described here (21–23).

Pharmacokinetic parameters quantifying the concentration-time course of Olanzapine in men and women smokers and non-smokers were referenced from the Bigos and colleagues 2008 article (24). The Bigos and colleagues population pharmacokinetic analysis is from the National Institute of Mental Health (NIMH) funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, that analyzed a subset of patients who were treated with Olanzapine (n=523) (24).

Results

Demographic Data

The pharmacometric analysis included a total of seventy patients (men: n=51, women: n=19) from the original four studies (7–10). Summary statistics of the patient data from the four publications included in this study are provided in Table 1. Based on the results, there was a statistically significant difference in the Olanzapine dose between men and women ($p=0.0493$). However, there were no statistically significant differences found in men and women for age, Dopamine D2 receptor occupancy (%), Olanzapine plasma concentration (ng/mL), or plasma prolactin levels.

Population Pharmacodynamics

From the four datasets, the analysis included a total of seventy D2 receptor occupancy measurements from seventy patients. The Emax model adequately described the dose response data. The maximal dopamine D2 receptor occupancy was estimated to be 85.6% (S.E.=2.8). Statistically significant gender-stratified doses resulting in the half-maximal receptor occupancies (ED50) were estimated to be $ED50_{\text{Males}}=5$ mg/day and $ED50_{\text{Females}}=2.4$ mg/day, $p=0.037$. The final population pharmacodynamic parameter estimates are described in Table 2.

Figure 1 displays the model diagnostics of the observed versus predicted goodness-of-fit plots for the population and individual olanzapine D2 receptor occupancy predictions. Further model evaluation was based on the normalized prediction distribution error plot and the individual weighted residual plots shown in Figure 2. The overall final diagnostic plot, the visual predictive check (VPC), is displayed in Figure 3 for the population.

Dose Response Simulation Results

Olanzapine and dopamine D2 receptor occupancy simulations were conducted at the following doses: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40 mg/day. The Clinical Trial Simulation included a virtual population of 40-men and 40-women resulting in 1,680 data points that represent the striatal D2 receptor occupancy levels at the aforementioned doses. Gender-stratified dose response data following the simulations are illustrated in Figure 4. The differences in shapes of the dose-response curves between men and women illustrate that women achieve a very rapid rise in D2 receptor occupancy up to 10mg/day and then the curve stabilize. Contrastingly, the dose-response curve in men illustrates a continual increase in response, achieving higher percentages of D2 receptor occupancy at much higher doses than that found in women. Based on the results, a 70% D2

receptor occupancy in women would require approximately 10mg/day of Olanzapine while men would require approximately, double the dose, 20mg/day.

Olanzapine Pharmacokinetic Simulations

Using the average doses for men and women as provided in Table 1, pharmacokinetic dosing simulations were conducted for theoretical doses of 17.8mg/day for men and 12.4mg/day for women. The simulated Olanzapine pharmacokinetic parameters were as follows: gender-specific clearance rates were (CL): CL-Men=28.83 L/hour (CV=38%) and CL-Women=20.96 (CV=42%), the volume of distribution was 2150 L (CV=86%), and the absorption rate constant was $K_a=0.5$ (1/hour). The dosing simulations and analysis in this section of the paper provides insight for understanding the pharmacodynamic modeling and simulation results in this paper. Figure 5 shows the graphical illustrations of Olanzapine concentration-time courses in men and women. The tabular comparisons of the area under the curve (AUC) and maximal plasma concentration (C_{max}) are shown in Table 3.

Discussion

In this pharmacometric study evaluating the pharmacodynamics of Olanzapine, women were found to require a significantly ($p=0.037$) lower dose of Olanzapine when compared to men (ED50-Women= 2.38 mg/day versus ED50-Men=5.15 mg/day). So, a greater percent difference was seen between genders from our original hypothesis of 10%. Thus, an approximate 50% dose adjustment would be required to achieve an equivalent 70% striatal D2 receptor occupancy between men and women. In comparing our results with a previous Olanzapine dose response (dopamine receptor occupancy) study by Bishara and colleagues, that article reported an E_{max} of 87.3% and a half-maximal receptor occupancy, ED50, of 4.1mg (25). It is important to note that the study which led us to select the 70% threshold for D2 receptor occupancy aimed at avoiding both patient extra-pyramidal symptoms and minimizing prolactin increases in the serum was based on a study with twenty-two patients and that some patients with striatal occupancies below 70% showed response (6).

Overall, the results suggest that the second generation antipsychotic, Olanzapine, is more potent in women as compared to men at similar doses. Moreover, men require higher doses to achieve the desired striatal occupancy effects that would be found in women at lower doses. These quantifiable gender-differences in striatum suggests that both gender-specific starting doses and maintenance doses be considered when prescribing Olanzapine. As with all pharmacological management, careful dose titration is of importance to screen for patient adverse drug effects and the use of various treatment response scales in psychotic disorders that are in remission (26).

It is important to note that dose response simulation results illustrate that in male patients with psychosis, therapeutic efficacy of Olanzapine may not be even achieved until daily doses of 15–25 mg/day (60–75% D2 receptor occupancy) are achieved. A study by Rabinowitz and colleagues pooled data from five large pharmaceutical companies and reported that being female showed statistically significant favorable outcomes when managing schizophrenia (27). A 2009 article by Citrome and Kantrowitz analyzed Olanzapine efficacy data from double-blind randomized clinical trials, case reports/series,

and observational studies found that from the years 1997 to 2006 over 50% of patients received Olanzapine doses exceeding 20 mg/day and even some case reports reporting doses up to 60 mg/day (28). Though the Citrome and Kantrowitz article does not comment on gender-differences, using the clinical trial simulation findings from Figure 4 allows a pharmacodynamic deduction to show why therapeutic efficacy may be seen at doses above 20 mg/day in men; however, the same does not hold true for women. With these differences, there may be a possibility that the variations in treatment response in psychiatry may even contribute to what Soerensen and colleagues calls the 'potentially inappropriate prescribing' of psychotropic medications where the author has a clinical pharmacologist evaluate thousands of patient records for appropriateness of psychotropic prescribing in psychiatry (29).

Our study results align with an electroencephalography (EEG) neuroimaging study that analyzed twenty-two age matched men and women diagnosed with schizophrenia and concluded that women experience greater dopamine serotonin 5-HT₂ and D₂ receptor blockade when compared to age-matched male patients (30). This same study reported that female schizophrenia patients had increased delta slow-wave frequencies localized to the dorsolateral prefrontal cortex ($p < 0.04$) when compared to age-matched male schizophrenia patients suggesting gender-specific pharmacodynamics as measured by the EEG brain mapping study (30).

It is important to note that in in three, Kapur et al 1998, Kapur et al 1999, and Lavalaye et al 1999, of the four studies patients were diagnosed as suffering from schizophrenia while the Attarbaschi et al study included patients diagnosed with bipolar disorder (7–10). In the interest of obtaining a large enough sample-size from the literature, the chronicity of schizophrenia or bipolar disorder was not factored into the dose response modeling and simulation analysis. However, of the studies two patients were reported to be drug-naïve and another two patients were of neuroleptics for two-months (7–10).

The study by Bigos and colleagues in 2008, analyzed 1527 plasma samples and found that Olanzapine clearance rates were $CL_{Men} = 20.96 \pm 8.77$ L/hour and $CL_{Women} = 28.83 \pm 11.02$ L/hour ($p < 0.0001$) (24). Using the Bigos et al pharmacokinetic model parameters and the average male and female Olanzapine doses in this study, we found no major differences in the maximum Olanzapine concentrations nor the total drug exposure that could explain the significant gender-specific differences seen in the dopamine D₂ receptor occupancies approximated in this paper. Further, it is important to note that the Bigos et al article states that neither body weight, nor height, nor age, nor concomitantly administered medications had any effect on the Olanzapine clearance rates (24). Therefore, pharmacokinetics alone does not explain the gender differences calculated in the D₂ receptor within the striatum. These results suggests that testosterone and estrogen modulate the pharmacodynamics of psychotropic medications at dopamine D₂ receptors in the brain. Lastly, a gender-by-genotype interaction with the cytochrome P450 1A2 (CYP1A2), CYP2D6, and CYP3A4 pharmacogenes and the D₂ receptors in the brain may very well contribute to the variation in clinical response that have been reported and encountered when treating patients with psychosis.

Conclusion

Based on the pharmacodynamic modeling and simulation results, implications exist suggesting that clinicians should factor patient gender when considering both a starting dose, as well as, maintenance doses for patients prescribed Olanzapine. The dose resulting in the half-maximal dopamine D2 receptor occupancy is 2.5 mg/day for women and 5 mg/day for men and considering the available doses for Olanzapine, male patients may benefit from a 5 mg/day starting dose. In turn, female patients may better proceed with lowest available dose of 2.5 mg/day. Further, to reach a 70% dopamine D2 receptor occupancy threshold in the striatum, which minimizes the extrapyramidal effects and an elevation in serum prolactin, translates into a dose of approximately 20 mg/day for men and 10 mg/day for women. These aforementioned doses provide insight to potential maintenance doses for olanzapine based on gender.

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List of abbreviations

5-HT₂	Serotonin Receptor
D₂	Dopamine D2 Receptor
D₂RO	Dopamine D2 Receptor Occupancy
ED₅₀	Half-maximal Receptor Occupancies
EEG	Electroencephalography
E_{max}	Percent Maximal Effect
MCMC	Markov Chain Monte-Carlo procedure
MONOLIX	MODèles NON Linéaires à effets mixtes
NLME	Nonlinear Mixed Effects Modeling
SAEM	Stochastic Approximation Expectation-Maximization

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Figure 1. Observed versus Predicted Plots

Goodness-of-fit plots for the observed versus predicted model diagnostics of the population (a) fit and the individual (b) fit for the Olanzapine D2 Receptor Occupancy.

Figure 2. Weighted Residual Plots

Goodness-of-Fit plots illustrating the individual weighted residuals (IWRES) (a) and the normalized prediction distribution errors (NPDE) over time (b) and the IWRES (c) and NPDE over the predicted D2 Receptor Occupancy (d). The bottom two graphs illustrate the probability density function distributions for the IWRES (e) and NPDE (f).

Figure 3. Visual Predictive Check

The Visual Predictive Check for the final population pharmacodynamic model for D2 receptor occupancy illustrating percentile distribution bands. The solid green lines represent the 90th (upper green), 50th (middle green) and 10th (bottom green) percentiles. The upper and lower blue shaded are represent the 95% confidence interval for the 90th and 10th percentiles, while the middle peach band shaded band represents the 95% confidence interval for the population median predictions.

Figure 4. Dose Response Simulations

Simulation results illustrating gender-stratified Olanzapine doses (mg/day) and the corresponding dopamine D2 receptor occupancy (%) levels. The ED50-Female=2.38 mg/day while the ED50-Male=5.15 mg/day. The solid line represents the average population receptor occupancy profile while the shaded bands represent the 95% confidence intervals for the population mean.

Figure 5. Olanzapine Pharmacokinetic Dosing Simulations

Simulated concentration-time curves for virtual populations of 4000 men (top) and 4000 women (bottom) administered 14-days of Olanzapine at the average doses calculated from the pooled data included in the four studies.

Table 1

Summary of patient data from studies included in the analysis.

	Men	Women	p-value
Sample Size	n=53	n=19	
Age	25.6 ± 7.9	28.9 ± 9.1	0.139
Dose (mg)	17.8 ± 11.3	12.4 ± 5.9	0.0493
Dopamine D2 Receptor Occupancy (%)	67 ± 16	67 ± 12	0.887
Plasma Concentration (ng/mL)	38.6 ± 41.7 (n=33)	20.7 ± 19.7 (n=14)	0.134
Plasma Prolactin (ng/mL)	13.0 ± 7.0 (n=25)	14.6 ± 7.6 (n=8)	0.578

Values are expressed as mean ± standard deviation.

TABLE 2

Final Population Pharmacodynamic Parameter Estimates for Olanzapine.

Parameter	Estimate	S.E.	R.S.E.(%)	p-value
E_{max} (%): D2 Receptor Occupancy	85.6	2.8	3	
ED₅₀_{Females} (mg/day): Dose at half-maximal receptor occupancy in Women	2.38	0.81	34	
ED₅₀_{Males} (mg/day): Dose at half-maximal receptor occupancy in Men	5.15	0.74	14	
β ED₅₀_{Male} (%):increase daily Olanzapine dose for in Men	77.3%	0.37	48	0.037
Interindividual Variability				
ω_{E_{max}}, variance for E_{max}	0.0441	0.026	59	
ω_{ED₅₀}, variance for EC₅₀	0.524	0.085	16	
Constant error model	0.034	–	–	

CV (%), interindividual deviation of each parameter; RSE (%), percentage of relative standard error (100%×SE/EST).

Table 3

Pharmacokinetic simulation comparisons for average doses in men and women from the four Olanzapine studies included in this pharmacodynamic study.

Pharmacokinetic Parameter Descriptions for Olanzapine	Men	Women
Daily Dose for 14-days	17.8 mg/day	12.4 mg/day
AUC, Area Under the Curve (ng/mL*hr)	268.4	230.9
Cmax, maximum Olanzapine Plasma Concentration (ng/mL)	26.8	23.6