Progress in Neuro-Psychopharmacology & Biological Psychiatry 45 (2013) 178–182

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Hyperprolactinemia and estimated dopamine D2 receptor occupancy in patients with schizophrenia: Analysis of the CATIE data

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ARTICLE INFO

Article history:
Received 13 March 2013
Received in revised form 18 May 2013
Accepted 22 May 2013
Available online 29 May 2013

Keywords:
CATIE
Dopamine D2 receptor occupancy
Hyperprolactinemia
Schizophrenia

ABSTRACT

Background: Large-scale data are still lacking on the relationship between serum prolactin concentration and dopamine D2 receptor occupancy in patients with schizophrenia treated with antipsychotics.
Methods: The dataset from 481 subjects (risperidone, N = 172, olanzapine, N = 211, and ziprasidone, N = 98) who participated in Phase 1 of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) was used in the present analysis. Dopamine D2 receptor occupancy levels on the day of the measurement of serum prolactin level were estimated from plasma antipsychotic concentrations. A multivariate general linear model was used to examine effects of clinical and demographic characteristics, including estimated D2 occupancy levels, on serum prolactin concentrations. Individual subjects were divided into two groups, stratified by the presence of hyperprolactinemia. To evaluate the performance of this binary classification, sensitivity, specificity, and accuracy of consecutive cut-off points in the D2 occupancy were calculated.
Results: The multivariate general linear model revealed that estimated D2 occupancy levels had significant effects on serum prolactin concentrations while any other variables failed to show significant effects. The cut-off point associated with 0.5 or greater, in both sensitivity and specificity with the greatest accuracy, was 73% (sensitivity, 0.58; specificity, 0.68; accuracy = 0.64) (68–70% for risperidone, 77% for olanzapine, and 55% for ziprasidone.).
Conclusion: The threshold for hyperprolactinemia in D2 occupancy may lie somewhat on a lower side of the established therapeutic window with antipsychotics (i.e. 65–80%). This finding highlights the need for the use of the lowest possible dose to avoid this hormonal side effect in the treatment of schizophrenia.

1. Introduction

Hyperprolactinemia is a common side effect induced by antipsychotic agents in the treatment of schizophrenia (Bostwick et al., 2009; Hummer and Huber, 2004) and can result in a number of physical consequences including amenorrhea, galactorrhea, infertility, erectile dysfunction, ejaculation deficiency, and loss of libido (Bostwick et al., 2009; Byerly et al., 2007; Hamner, 2002; Hummer and Huber, 2004; Rettenbacher et al., 2010). Moreover, the long-term elevation of serum prolactin has been associated with decreased bone mineral density and increased risk of breast cancer in post-menopausal women (Kishimoto et al., 2008; Meaney et al., 2004; Wang et al., 2000). The adverse effects of antipsychotics represent an obstacle to adherence to treatment in patients with schizophrenia (Lieberman et al., 2005). Given that the non-adherence is the major cause of relapse and exacerbation (Kane, 2007), every effort should be made to minimize these annoying side effects as much as possible.

Antipsychotic-induced hyperprolactinemia is a result of disinhibition of the lactotroph cells in the anterior pituitary gland (which lie outside the blood–brain barrier) through dopamine D2 receptor antagonism

Abbreviations: CATIE, Clinical Antipsychotic Trials in Intervention Effectiveness; PET, positron emission tomography.

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http://dx.doi.org/10.1016/j.pnpbp.2013.05.010

(Kapur et al., 2002). Arakawa et al. demonstrated that the dopamine D2 receptor occupancy in the pituitary was a predictor of hyperprolactinemia (Arakawa et al., 2010). In this study, 11 healthy men receiving sulpiride and 24 male patients with schizophrenia receiving one of the four different antipsychotics (i.e. risperidone, olanzapine, haloperidol, or sulpiride) underwent positron emission tomography (PET) scanning. Significant positive correlation was observed between serum prolactin concentration and dopamine D2 receptor occupancy in the pituitary ($r = 0.62$, $p = 0.001$). On the other hand, a positive association between dopamine D2 occupancy levels and serum prolactin level has not always been a consistent finding in the literature (Kapur et al., 2000; Mamo et al., 2004; Remington et al., 2006), though this may be attributable to small sample sizes as well as different D2 receptor binding affinity and penetration of the blood brain barrier of the antipsychotic drugs used in the smaller PET studies.

Antipsychotic-induced hyperprolactinemia is widely considered inevitable, particularly when using first generation antipsychotics and high potency second generation antipsychotics. This assumption has not been formally tested empirically, and creates a certain therapeutic indifference in the clinical management of hyperprolactinemia in schizophrenia, a position that is no longer tenable given the growing body of literature concerning long-term adverse effects of prolactin elevation.

We have developed a model with which the dopamine D2 receptor occupancy by antipsychotic drugs, including risperidone, olanzapine, and ziprasidone, can be reliably estimated from plasma concentrations of these drugs (Uchida et al., 2011b). In addition, recent advances in nonlinear, mixed-effects population pharmacokinetic methods have made it possible to estimate individual pharmacokinetic parameters for antipsychotic drugs, including peak and trough plasma concentrations, using two or more sparsely collected blood samples (Bigos et al., 2006). By combining these models, the dopamine D2 receptor occupancy levels at any given point in time can be reliably estimated, using the measurement of antipsychotic plasma concentrations at two separate random time points (Uchida et al., 2009a).

For the purpose of providing robust findings on the relationship between dopamine D2 receptor blockade and serum prolactin concentration in a large sample, the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) (Stroup et al., 2003) provides an ideal dataset in light of its unprecedented large sample size and availability of plasma antipsychotic concentrations for which population pharmacokinetic models have already been developed with respect to risperidone, olanzapine, and ziprasidone (Bigos et al., 2008; Feng et al., 2008; Wessels et al., 2011). The objective of this report was to evaluate the relationship between estimated dopamine D2 receptor occupancy with risperidone, olanzapine, and ziprasidone and hyperprolactinemia in patients with schizophrenia in the CATIE.

2. Methods

2.1. Study design

The CATIE was funded by the National Institute of Mental Health to compare the effectiveness of second-generation antipsychotics and a first-generation antipsychotic medication in patients with schizophrenia; the details of the study were reported elsewhere (Stroup et al., 2003). Briefly, the study was performed between January 2001 and December 2004 at 57 clinical sites in the United States. One thousand four hundred and ninety-three patients between ages 18 and 65 with a diagnosis of schizophrenia on the basis of the Structured Clinical Interview of the DSM-IV participated in the CATIE. Patients were initially randomized to risperidone (1.5–6.0 mg/day), olanzapine (7.5–30 mg/day), ziprasidone (40–160 mg/day), quetiapine (200–800 mg/day), or perphenazine (8–32 mg/day) under double-blind conditions and received treatments for up to 18 months or until treatment was discontinued for any reason (Phase 1).

Data used in the present analysis were derived from subjects who were receiving risperidone, olanzapine, or ziprasidone, had serum prolactin concentration measured at 3 months in Phase 1a, and provided plasma samples for the assessment of antipsychotic concentrations. Subjects randomized to these three drugs were included in the present study since the prediction models of dopamine D2 receptor occupancy from plasma drug concentrations were available for those three drugs (Bigos et al., 2008; Feng et al., 2008; Wessels et al., 2011). All participants gave written informed consent to participate in the protocols approved by the local institutional review boards.

2.2. Population pharmacokinetic analysis

Subjects who participated in the CATIE provided plasma samples for the measurement of concentrations of risperidone plus 9-hydroxyrisperidone (active moiety), olanzapine, or ziprasidone at more than one time point. Using these samples, plasma antipsychotic concentrations at peak and trough that corresponded to the dose given at 3 months were calculated for each individual, using the established population pharmacokinetic models and extracting the Empirical Bayes Estimates for the pharmacokinetic parameters from each of these individuals (Sheiner et al., 1977; Beal and Sheiner, 1992). The precision and reliability of this estimation has recently been confirmed in our population pharmacokinetic study (Uchida et al., 2012). The nonlinear mixed-effect models for risperidone, olanzapine, and ziprasidone were previously established using the CATIE data (Bigos et al., 2008; Feng et al., 2008; Wessels et al., 2011). These original studies used to establish the population pharmacokinetic models comprised 1236 risperidone plus 9-hydroxyrisperidone concentrations from 490 subjects, 1527 olanzapine concentrations from 523 subjects, and 568 ziprasidone concentrations from 233 subjects, respectively. All three compounds were adequately described by using a one-compartment linear model with first order absorption. The previously established models utilized exponentiated or log-normal interindividual variability on each pharmacokinetic parameter, a mixture distribution to assign the tri-modal distribution of risperidone of clearance as CYP 2D6 genotype was not available for that drug, an age effect on clearance of the 9-hydroxyrisperidone moiety, and sex, race, and age effects on olanzapine disposition.

2.3. Estimation of dopamine D2 receptor occupancy

By using the estimated plasma concentrations of antipsychotics at peak and trough at 3 months, corresponding dopamine D2 receptor occupancy levels were estimated, using the model that we recently developed (Uchida et al., 2011b). Briefly, dopamine D2 receptor occupancy levels were estimated by incorporating the estimated plasma concentration of risperidone active moiety, olanzapine, or ziprasidone into the following one-site binding model: $\text{occupancy}\ (\%) = a \times [\text{plasma level} / (\text{plasma level} + ED_{50})]$, where a is the maximum receptor occupancy attributable to the antipsychotic drug and ED_{50} is the estimated plasma concentration of the antipsychotic drug associated with 50% of receptor occupancy, which was obtained in the systematic review and pooled analysis (risperidone active moiety: $a = 88.0\%$, $ED_{50} = 4.9$ ng/mL; olanzapine: $a = 90.7\%$, $ED_{50} = 7.1$ ng/mL; ziprasidone: $a = 88.2\%$, $ED_{50} = 32.9$ ng/mL) (Uchida et al., 2011b). Mean values of peak and trough dopamine D2 receptor occupancy levels were obtained for further analyses.

2.4. Statistical analysis

Statistical analyses were carried out by using the SPSS Version 19.0 (SPSS Inc., Chicago). A multivariate general linear model was used to examine the effects of estimated dopamine D2 receptor occupancy levels, age, sex, race, and smoking status on serum prolactin

concentration. In addition, subjects were divided into two groups, based on the presence of hyperprolactinemia (i.e. >18.77 ng/mL and >24.20 ng/mL for men and women, respectively) (Marken et al., 1992) The mean estimated dopamine D2 receptor occupancy levels were compared between the hyperprolactinemia and the non-hyperprolactinemia groups, using the independent t-test. A p-value of <0.05 was considered statistically significant (two-tailed). To evaluate the performance of this binary classification, sensitivity and specificity of the consecutive cut-off points in increments of 1% between 50% and 85% in the estimated dopamine D2 receptor occupancy for hyperprolactinemia were calculated. Accuracy, which is defined as [True Positive + True Negative] / Total N, was also calculated. Accuracy depends on the number of observations, which may render it inferior to the careful and balanced consideration of sensitivity and specificity (Alberg et al., 2004). To address this potential pitfall, cut-off points that demonstrated a level of 0.5 or greater in both sensitivity and specificity with the highest degree of accuracy were examined.

3. Results

3.1. Subject characteristics

Four hundred and eighty-one subjects who provided blood samples for the assessments of plasma concentrations of risperidone plus 9-hydroxyrisperidone, olanzapine, or ziprasidone and serum prolactin concentration at 3 months were included. Demographic and clinical characteristics of these subjects were summarized in Table 1. Mean ± SD daily doses of risperidone, olanzapine, and ziprasidone at 3 months were 4.0 mg ± 1.4 mg, 19.9 ± 7.4 mg, and 120.4 ±35.8 mg, respectively. Mean ± SD serum prolactin concentration was 21.0 ± 22.0 ng/mL (20.9 ± 22.4 ng/mL for males and 21.5 ±21.0 ng/mL for females).

3.2. Association between estimated D2 receptor occupancy and serum prolactin concentration

The multivariate general linear model revealed that while age, sex, race, and smoking status failed to demonstrate any statistically significant effect on serum prolactin concentration, the estimated dopamine D2 receptor occupancy levels statistically showed a positive association with the serum prolactin concentration (Corrected model: $F_{[1,\ 458]} = 43.0$, $p < 0.001$, $R^2 = 0.12$). When the subjects were divided into the two groups according to the presence of hyperprolactinemia, the mean ± SD estimated dopamine D2 receptor occupancy was significantly higher in subjects who experienced hyperprolactinemia (N = 170) than those who did not (N = 311) (72.4 ± 8.7% vs. 64.1 ± 14.9%, $p < 0.001$). We then conducted additional analyses to find the threshold. Sensitivity and specificity of a series of cut-off points for estimated dopamine D2 occupancy are presented in Table 2. The cut-off point of 73% resulted in 0.5 or greater in both sensitivity and specificity with the highest degree of accuracy. When they were separately analyzed in the same way, the cut-off points for hyperprolactinemia were 68–70% for risperidone, 77% for olanzapine, and 55% for ziprasidone. Plasma concentrations of risperidone plus 9-hydroxyrisperidone, olanzapine, and ziprasidone corresponding to those cut-off point were 16.7–19.1 ng/mL, 39.9 ng/mL, and 54.5 ng/mL, respectively, using the one-site binding models described above.

Table 1
Demographic and clinical characteristics of the patients (N = 481).

Characteristics	Values
Age, years, mean ± SD (range)	41.4 ± 10.8 (18–66)
Male, N (%)	349 (72.6%)
Race	
Caucasian, N (%)	295 (61.3%)
African-American, N (%)	160 (33.3%)
Native American, N (%)	4 (0.8%)
Asian, N (%)	12 (2.5%)
Native Hawaiian or other Pacific Islander, N (%)	1 (0.2%)
Mixed, N (%)	9 (1.9%)
Smoking, N (%)	324 (67.4%)
Medication	
Risperidone, N (%)	172 (35.8%)
Olanzapine, N (%)	211 (43.9%)
Ziprasidone, N (%)	98 (20.4%)

4. Discussion

To our knowledge, this is the largest study to investigate the relationship between serum prolactin concentration and estimated dopamine D2 receptor blockade with risperidone, olanzapine, or ziprasidone in patients with schizophrenia. Our results support previous reports of a significant association between dopamine D2 receptor occupancy levels and serum prolactin concentration. Our data extend these observations through the demonstration of a threshold of hyperprolactinemia at 73% of striatal dopamine D2 receptor occupancy; moreover, it seems to differ among antipsychotic drugs. These differences in the cutoff points might be derived from the dissociation between central and peripheral dopamine D2 occupancy levels (Kapur et al., 2002).

Previous brain imaging studies have consistently shown the presence of a therapeutic window of 65–80% occupancy in the striatal dopamine D2 receptors (Farde et al., 1995; Kapur et al., 2000; Uchida et al., 2011a); it is associated with optimal therapeutic efficacy during acute treatment in younger patients while minimizing risks of extrapyramidal symptoms (Farde et al., 1992; Kapur et al., 2000) and cognitive impairments (Sakurai et al., 2013). Data from the present study provide further support of this therapeutic range from the perspective of antipsychotic-induced hyperprolactinemia. Among previous studies that investigated the relationship between dopamine D2 receptor occupancy and hyperprolactinemia (Baron et al., 1989; Kapur et al., 2000; Schlegel et al., 1996), Kapur et al. demonstrated in their PET study that the likelihood of hyperprolactinemia increased significantly as the dopamine D2 occupancy exceeded 72% for haloperidol. As described in the Introduction, Arakawa et al. also conducted a PET study and reported that significant positive correlation was observed between the plasma concentration of prolactin and the dopamine D2 receptor occupancy in the anterior pituitary, suggesting that 50% dopamine D2 occupancy in the pituitary as the threshold level of

Table 2
Sensitivity and specificity of a series of cutoff points in the estimated dopamine D2 receptor occupancy for hyperprolactinemia.

Cutoff points, %	Sensitivity	Specificity	Accuracy
85	0.01	1.00	0.66
80	0.16	0.91	0.65
75	0.45	0.71	0.62
74	0.52	0.69	0.63
73	0.58	0.68	0.64
72	0.62	0.64	0.63
71	0.69	0.6	0.63
70	0.76	0.58	0.63
69	0.73	0.56	0.62
68	0.75	0.52	0.60
67	0.78	0.48	0.59
66	0.81	0.46	0.58
65	0.84	0.42	0.57
60	0.90	0.32	0.52
55	0.95	0.23	0.49
50	0.98	0.18	0.46

Bold values represent cutoff point associated with >0.5% in both sensitivity and specificity.
The italicized value represent the cutoff point associated with >0.5% in both sensitivity and specificity with the highest degree of accuracy.

hyperprolactinemia (Arakawa et al., 2010). However, previous brain imaging data have not always shown such an association (Mamo et al., 2004; Remington et al., 2006) probably, in part, due to small sample sizes (16 at the largest). Although the dopamine D2 receptor occupancy was not measured but estimated, the present study with the large sample size of 481 confirmed the significant association between hyperprolactinemia and dopamine D2 receptor occupancy levels in patients with schizophrenia. Furthermore, the results suggest that the 73% of dopamine D2 receptor occupancy figure with antipsychotics could serve as a threshold of hyperprolactinemia in the treatment of schizophrenia.

Minimizing exposure to antipsychotics is important in light of their dose dependent side effects such as sudden cardiac death (Ray et al., 2009), negative subjective well-being (Mizrahi et al., 2007), and extrapyramidal side effects (Kapur et al., 2000; Uchida et al., 2011a). The findings in the present study also corroborate such strategy to counteract hyperprolactinemia and emphasize the relevance of using low antipsychotic dosage to minimize the risk of this D2 occupancy-dependent side effect in the treatment of schizophrenia. However, although a meta-analysis indicates that a lower antipsychotic dosage strategy for relapse prevention in schizophrenia may not compromise effectiveness (Uchida et al., 2011c), this treatment approach should be employed in careful consideration of inter-individual differences in dose requirements (Uchida et al., 2009b, 2009c).

The results of this study should be interpreted in light of various limitations. First, only patients treated with risperidone, olanzapine, or ziprasidone were included in this study since both the population pharmacokinetic models (Bigos et al., 2008; Feng et al., 2008; Wessels et al., 2011) and the prediction model of dopamine D2 receptor occupancy from plasma concentrations (Uchida et al., 2011b) were available only for those three drugs. Although these drugs represent commonly prescribed atypical antipsychotics, any extrapolation of the findings to other antipsychotics must be made within this context. Second, dopamine D2 receptor occupancy was not measured with brain imaging techniques, but it was calculated with the model we developed although the predictive performance of the model has been shown to be reliable (Uchida et al., 2011b). Moreover, the region of interest in 97% of the PET data used for the development of this prediction model was the striatum of basal ganglia (Uchida et al., 2011b). The findings in the present study need to be replicated in future investigations, using radiotracers that can directly be assessable to extrastriatal dopamine receptors, especially those in the anterior pituitary, which is located outside the blood–brain barrier (Kapur et al., 2002). Third, the incidence of hyperprolactinemia differs among antipsychotics. It has been reported that risperidone presented a high risk of hyperprolactinemia, while olanzapine and ziprasidone showed a relatively low risk (Volavka et al., 2004; Melkersson, 2005; Komossa et al., 2009). In contrast, in the present study, the cut-off point for hyperprolactinemia in patients receiving ziprasidone was lower than the other two drugs. One possible reason of this unexpected finding may be a relatively short peripheral and central half-life of this drug. Our group recently demonstrated in a PET study that the time-course of receptor occupancy across the regions indicated a D2 occupancy half-life of 8.3 h (Suzuki et al., in press), suggesting rapid fluctuation in prolactin level as well. Moreover, there were only 17 subjects (17.3%) who presented hyperprolactinemia in the ziprasidone group with only 2 of them showing estimated D2 occupancy levels over 70%. These issues may make it difficult to find a robust threshold for this particular agent. Forth, there are previous studies that found increased prolactin concentrations in antipsychotic-naïve patients with schizophrenia (Aston et al., 2010; Lee and Kim, 2006), which indicates that hyperprolactinemia that we observed in this study may not be solely attributable to blockade of dopamine D2 receptors with antipsychotic drugs. Finally, we did not take into account normal fluctuations of serum prolactin concentrations; it is widely known that serum prolactin concentrations rise during sleep and decrease during the day (Van Cauter et al., 1981). Furthermore, menstrual cycle phases also affect its concentration in premenopausal women (Musey et al., 1987).

In conclusion, the threshold for hyperprolactinemia in dopamine D2 receptor occupancy was found to be 73%, which lies somewhat on a lower side of the established therapeutic window with antipsychotics (65–80%). Given that this often invisible side effect could cause a variety of serious consequences in the both short and long runs, minimizing exposure to antipsychotics while keeping their clinical effectiveness is critically important in the treatment of schizophrenia. Although the findings in the present study need to be replicated in prospective brain imaging studies that focus on the pituitary in particular, they endorse the clinical relevance of using the lowest possible dose of antipsychotics.

Conflicts of interest

Dr. Tsuboi has received manuscript fees from Dainippon Sumitomo Pharma and speaker's honoraria from Otsuka Pharmaceutical, Eli Lilly and Tsumura within the past two years. Dr. Bies has received NIH, CAMH, Lilly and Indiana University based grant funding. Dr. Suzuki has received manuscript fees or speaker's honoraria from Dainippon Sumitomo Pharma, Eli Lilly, Astellas Pharma, Novartis Pharma, and Meiji Seika Pharma within the past two years. Dr. Pollock receives research support from the National Institute of Health and the Canadian Institutes of Health Research. Within the past five years, he has been a member of the advisory board of Lundbeck Canada (final meeting was May 2009) and Forest Laboratories (final meeting was March 2008). Dr. Pollock has served one time as a consultant for Wyeth (October 2008). He was also a faculty member of the Lundbeck International Neuroscience Foundation (LINF) (final meeting was April 2010). Dr. Graff receives grant support from National Institute of Health, Canadian Institute of Health Research, Ontario Mental Health Foundation, CONACyT, ICyTDF and Janssen. He has served as consultant for Abbott Laboratories, Gedeon Richter Plc, and Eli Lilly within the past two years. Dr. Mimura has received grants, or consultant fees from Eisai, Astellas Pharma, GlaxoSmithKline and Meiji, and received speaker's honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomiyakuhin within the past two years. Dr. Uchida has received grants from Pfizer, Astellas Pharmaceutical, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shiohogi, and Dainippon-Sumitomo Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji-Seika Pharma, Janssen Pharmaceutical, and Yoshitomi Yakuhin and speaker's honoraria from Otsuka Pharmaceutical, Janssen Pharmaceutical, Novartis Pharma, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, and Janssen Pharmaceutical within the past two years.

Acknowledgments

Data used in the preparation of this article were obtained from the limited access datasets distributed from the NIH-supported “Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia” (CATIE-Sz). This is a multisite, clinical trial of persons with schizophrenia, comparing the effectiveness of randomly assigned medication treatment. The study was supported by NIMH Contract # N01MH90001 to the University of North Carolina at Chapel Hill. The ClinicalTrials.gov identifier is NCT00014001. The version of the dataset used was 1.0. This study was also supported by grant R01MH064173 from the National Institute of Mental Health and was ancillary to Clinical Antipsychotic Trials of Intervention Effectiveness, N01MH90001, from the National Institute of Mental Health.

This manuscript reflects the views of the authors and may not reflect the opinions or views of the CATIE-Sz Study Investigators or the NIH. No funding was provided for the present analysis.

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