Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

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

Application of plasma levels of olanzapine and *N*-desmethyl-olanzapine to monitor metabolic parameters in patients with schizophrenia

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ARTICLE INFO

Article history:
Received 12 March 2017
Received in revised form 9 July 2017
Accepted 9 July 2017
Available online xxxx

Keywords:
Olanzapine
N-desmethy-olanzapine
Schizophrenia
Metabolic syndrome
Therapeutic drug monitoring

ABSTRACT

Metabolic disturbance is a common side effect of olanzapine (OLZ); however, the relationships between plasma OLZ concentration (C_{OLZ}) and metabolic disturbance remain unclear. Our previous study revealed that $C_{OLZ} \geqq 22.77$ ng/mL was a positive predictor of therapeutic efficacy in patients with schizophrenia. This study aimed to investigate the roles of OLZ or *N*-desmethyl-olanzapine (DMO) in metabolic outcomes among OLZ-treated patients with schizophrenia. The metabolic syndrome (MS) was diagnosed based on the modified the National Cholesterol Education Program Adult Treatment Panel III criteria for Asians. HPLC-ECD analytical system was applied to determine the C_{OLZ} and DMO concentration (C_{DMO}). The absolute drug levels and concentration-to-dose ratios (C/D ratios) were tested for their correlations to metabolic parameters. Total 151 fasting blood samples from patients with schizophrenia were collected. DMO C/D ratio negatively correlated with weight, body mass index, waist circumference, and C-peptide level. The receiver operator characteristic analysis determined a threshold $C_{DMO} > 5.63$ ng/mL and DMO C/D ratio > 0.35 ng/mL/mg were negative predictors of MS. The C_{OLZ}/C_{DMO} ratio > 6.03 was identified as positive predictor of MS. Combined with previous study result, we proposed that the optimal OLZ treatment should maintain C_{OLZ}/C_{DMO} ratio between 3 and 6 to maximize the clinical efficacy and minimize the metabolic side effects. Our findings suggested that therapeutic drug monitoring on OLZ and DMO is a valuable tool to monitor metabolic side effects in OLZ-treated patients with schizophrenia.

1. Introduction

Schizophrenia is a chronic and disabled mental illness with lifetime prevalence of 0.3–0.66% (McGrath et al., 2008). Antipsychotic drugs are the mainstay treatment for schizophrenia. The second generation antipsychotics (SGAs) such as olanzapine (OLZ), clozapine, and quetiapine have a low risk of extrapyramidal symptoms but are associated with greater likelihood of metabolic abnormalities (Lieberman et al., 2005). World Federation of Societies of Biological Psychiatry suggests that OLZ can be the first-line drug for schizophrenia (Hasan et al., 2012). The Clinical Antipsychotic Trials of Intervention Effectiveness Schizophrenia Trial found that OLZ is one of the most effective antipsychotic drugs, as measured by the length of time to drug discontinuation (Lieberman et al., 2005). However, the superiority in therapeutic efficacy of OLZ should be weighed against metabolic side effects than other antipsychotics (Komossa et al., 2010; Rummel-Kluge et al., 2010; Samara et al., 2016).

OLZ, a thienobenzodiazepine chemical, has high affinity to various receptors (Fulton and Goa, 1997; Maloney and Sikich, 2010). Pharmacokinetic parameters of OLZ indicates that OLZ concentrations (C_{OLZ}) were linear correlated with doses (Batail et al., 2014; Callaghan et al., 1999). C_{OLZ} reaches steady state after continuously doses for seven days (Callaghan et al., 1999). After multiple dosing, the major circulating metabolites are OLZ-10-N-glucuronide and 4′-*N*-desmethyl-olanzapine (DMO) (Callaghan et al., 1999; Kassahun et al., 1997; Maloney and Sikich, 2010).

The prevalence of metabolic syndrome (MS) in schizophrenic patients was estimated to be two-fold higher than that in general population (Huang et al., 2009; Hwang et al., 2006; McEvoy et al., 2005; Mitchell et al., 2013). The risk of MS was significantly higher with clozapine and olanzapine than other antipsychotic drugs (Melkersson and Dahl, 2004; Vancampfort et al., 2015). Therefore, it is important to monitor the metabolic parameters among subjects during olanzapine treatment.

In order to assure effectiveness and minimize the adverse reactions of OLZ, AGNP-TDM (Arbeitsgemeinschaft für Neuropsychopharmakologie

Abbreviations: AUC, Area under curve; BMI, body mass index; CYP, Cytochrome P450; DMO, *N*-desmethyl-olanzapine; MS, metabolic syndrome; OLZ, olanzapine; ROC, receiver operator characteristic; TDM, therapeutic drug monitoring.

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http://dx.doi.org/10.1016/j.schres.2017.07.022
0920-9964/

und Pharmakopsychiatrie - therapeutic drug monitoring) consensus guidelines suggest that OLZ-treated patients may benefit by TDM and C_{OLZ} is recommended to be within 20–80 ng/mL (Hiemke et al., 2011). Patients whose C_{OLZ} higher than 23.2 ng/mL would have clinical responses to OLZ therapy (Perry et al., 2001). Our previous study result showed that $C_{OLZ} \geqq 22.77$ ng/mL was a predictor of maintaining an at least mildly ill status (Positive and Negative Syndrome Scale (PANSS) score ≦ 58) in schizophrenic patients (Lu et al., 2016). However, previous study also reported that a threshold C_{OLZ} of 20.6 ng/mL was associated with significant weight gain (an increase from baseline weight of ≧7%) during olanzapine therapy (Perry et al., 2005). Toxicity could be induced when C_{OLZ} is >100 ng/mL and increased risk of mortality when C_{OLZ} reaches 160 ng/mL (Robertson and McMullin, 2000). The utility of TDM for OLZ might improve the delivery of cost-effective care and approach the goal of personalized medicine (Lopez and Kane, 2013).

Our previous study (Lu et al., 2013) revealed that DMO concentration (C_{DMO}), but not C_{OLZ}, was inversely associated with concentrations of glucose and insulin, and positively correlated with homocysteine levels among patients with schizophrenia. These findings, which agree with previous study results (Melkersson and Dahl, 2003; Melkersson et al., 2000), revealed that DMO might have an antagonistic effect on OLZ-induced metabolic abnormalities. The aim of this study was to explore the roles of C_{OLZ} and C_{DMO} in metabolic parameters among OLZ-treated patients with schizophrenia.

2. Materials and methods

2.1. Patients

This study was approved by the institutional review board and the ethics committee of Taipei Medical University (approval number: F950206). All aspects of this study were conducted according to the principles expressed in the Declaration of Helsinki. Patients, who aged 20–65 years, fulfilled the DSM-IV diagnostic criteria of schizophrenia, and used a stabilized dose of OLZ for at least three months, were recruited. The participants who had full capacity and willingness to provide written informed consent were included. Patients who had addictions, pregnancy, during lactation periods, other disease conditions which may interfere this monitoring were excluded. The patients were inpatients or outpatients at Taipei Medical University-Wan Fang Hospital and recruited between July 2006 and June 2009.

2.2. Measures

Sitting blood pressure (BP) and anthropometrical parameters were measured. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing. Body mass index (BMI) was defined as weight in kilograms divided by the square of the body height in meters. Blood was drawn after overnight fasting, around 12 h after the last OLZ dose. Fasting plasma levels of glucose (FPG), high-density lipoprotein cholesterol (HDL—C), homocysteine, and triglycerides (TG) were measured by standardized automated enzymatic methods. The plasma levels of insulin and C-peptide were measured immunologically. Metabolic syndrome (MS) was diagnosed based on the modified National Cholesterol Education Program Adult Treatment Panel III criteria for Asians (Tan et al., 2004). Three or more of the following five criteria are required: (1) waist circumference > 90 cm in men or >80 cm in women; (2) fasting TG levels ≧ 150 mg/dL; (3) fasting HDL-C levels < 40 mg/dL in men or <50 mg/dL in women; (4) BP ≧ 130/85 mm Hg; and (5) FPG levels ≧ 100 mg/dL. The quantification of OLZ and DMO levels employed a modified HPLC coupled with ECD of our previous study (Lu et al., 2013).

Table 1
Demographic and metabolic characteristics of study subjects.

Parameters	n = 151
Age (years)	41.3 ± 12.1
OLZ dose (mg)	14.2 ± 5.4
Weight (kg)	68.1 ± 15.1
BMI (kg/m^2)	25.9 ± 6.4
Waist circumference (cm)	88.3 ± 13.2
Systolic BP (mm Hg)	120.3 ± 14.5
Diastolic BP (mmHg)	75.0 ± 9.5
Glucose (mg/dL)	94.4 ± 33.1
Insulin (μU/mL)	12.5 ± 11.3
C-peptide (ng/mL)	3.0 ± 1.6
Triglyceride (mg/dL)	150.1 ± 88.4
HDL (mg/dL)	48.0 ± 13.8
Cholesterol (mg/dL)	189.9 ± 35.4
Homocysteine (μmol/L)	13.6 ± 6.5
DMO levels (ng/mL)	6.9 ± 4.7
OLZ levels (ng/mL)	37.0 ± 25.6
DMO C/D (ng/mL/mg)	0.6 ± 0.4
OLZ C/D (ng/mL/mg)	2.9 ± 2.3
Ratio of OLZ/DMO	7.0 ± 6.16

2.3. Statistical analyses

Descriptive statistics were presented as the mean ± standard deviation (SD) for continuous variables and rate for discrete variables. The concentration-to-dose (C/D) ratio was calculated by dividing drug concentration by the administered dose. The Spearman's rank order correlation method was applied to analyze the correlations of various indicators of OLZ or DMO to metabolic parameters. To correct possible errors during multiple comparisons, the modified Bonferroni's method was used (Benjamini et al., 2001). To quantify the abilities of various indicators of OLZ or DMO to identify MS, we performed receiver operating

Table 2
Correlation tests for metabolic measures and levels of olanzapine and its metabolite DMO.

	OLZ	OLZ C/D	DMO	DMO C/D	OLZ/DMO
Weight					
r_s =	−0.002	−0.135	−0.109	−0.281*,a	0.055
p =	0.976	0.097	0.184	0.000	0.500
BMI					
r_s =	0.103	−0.015	−0.144	−0.327*,a	0.174*
p =	0.209	0.856	0.077	0.000	0.033
Waist					
r_s =	−0.013	−0.093	−0.219*	−0.321*,a	0.078
p =	0.877	0.254	0.007	0.000	0.341
Glucose					
r_s =	−0.048	−0.116	−0.090	−0.173*	0.050
p =	0.562	0.157	0.273	0.034	0.539
Insulin					
r_s =	−0.104	−0.174*	−0.109	−0.186*	−0.033
p =	0.202	0.033	0.184	0.034	0.687
C-peptide					
r_s =	−0.045	−0.133	−0.158	−0.217*,a	0.022
p =	0.581	0.103	0.184	0.007	0.793
Cholesterol					
r_s =	−0.030	−0.019	0.049	−0.061	0.008
p =	0712	0.821	0.551	0.459	0.919
Triglycerides					
r_s =	−0.126	−0.087	−0.170*	−0.121	−0.038
p =	0.134	0.287	0.037	0.140	0.645
HDL					
r_s =	0.050	0.022	0.152	0.125	−0.055
p =	0.538	0.787	0.063	0.126	0.503
Homocysteine					
r_s =	0.210*	0.164*	0.053	−0.018	0.176*
p =	0.010	0.044	0.518	0.823	0.031

* p value < 0.05; Spearman's rank order correlation method.
[a] r_s remained significant after FDR correction.

Please cite this article as: Lu, M.-L., et al., Application of plasma levels of olanzapine and *N*-desmethyl-olanzapine to monitor metabolic parameters in patients with schizophrenia..., Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.07.022