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A twenty-four-week, open-label study on Ziprasidone's efficacy and influence on glucolipid metabolism in patients with schizophrenia and metabolic disorder

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Abstract. – BACKGROUND: The risks of antipsychotic drugs on metabolic syndrome (MS) present many challenges for psychiatrists.

AIM: To evaluate the effectiveness and influences on glucolipid metabolism in patients with schizophrenia and metabolic disorders switched from clozapine to ziprasidone.

PATIENTS AND METHODS: Schizophrenic patients with metabolic syndrome who had been treated with clozapine for ≥ 2 years were enrolled in the open-label study. All the patients were switched to ziprasidone from clozapine and followed up for 24-week. The primary endpoints included body mass index (BMI), fasting glucose (FG), triglycerides (TG), HDL cholesterol (HDL-c) and systolic pressure (SP)/diastolic pressure (DP). Secondary endpoints included scores on the Positive and Negative Syndrome Scale (PANSS) and treatment emergent symptom scale (TESS).

RESULTS: A total of 213 cases satisfied the inclusion and exclusion criteria, but only 194 cases eventually completed the 24-week follow-up and were divided into ziprasidone group (n=68, complete substitution) and combined treatment group (n=126, partial substitution). In the ziprasidone group, TG at 4th and 24th week, BMI and HDL-c at 24th week were significantly improved ($p < 0.05$), while cognitive scores and total score of the PANSS at 4th and 24th week, negative factor, the factor of anxiety and depression at 24th week were significantly lower than those at the baseline ($p < 0.05$); In the combined group, cognitive factor scores (4 weekend, 24 weekends) and total score of PANSS (24 weeks) was significantly lower than baseline ($p < 0.05$). There was no significant difference in the TESS score ($p > 0.05$).

CONCLUSIONS: Ziprasidone completely or partially substituting clozapine can improve both glucolipid metabolism disorders, and cognitive disorders and affective disorders of schizophrenia.

Key Words:
Ziprasidone, Clozapine, Schizophrenia, Metabolic syndrome.

Introduction

Earlier studies have revealed people with schizophrenia have metabolic syndrome (MS) highly prevalently[1,2]. Nowadays, increased attention on the therapeutic effectiveness of antipsychotic drugs in schizophrenia has turned to the possible deleterious side-effects of these agents. The risks of antipsychotic drugs on MS present many challenges for psychiatrists; it is necessary to look for an optimal treatment which has better curative effects and less side effects. Among second-generation antipsychotics, clozapine is more strongly associated with metabolic risk, whereas ziprasidone is less associated[3,4]. Ziegenbein et al[5] and Kuwilsky et al[6] had ever combined ziprasidone with clozapine and reported that it would exhibit long-term efficacy without increasing side effects. Furthermore, Henderson et al[7] prove that the addition of ziprasidone does not produce significant improvement in fasting glucose, insulin resistance, hyperlipidemia or lead to weight loss in olanzapine- or clozapine-treated subjects with schizophreniar. However, Pappadopulos et al[4] observe that in short-term trials patient's weight in ziprasidone-treated subjects is higher than that in placebo-treated subjects, in the long-term trials, ziprasidone-treatment induces the weight loss, there are no significant differences in glucose and lipid metabolites between ziprasidone and placebo groups. Martínez-Ortega et al[8] also conclude that antipsychotic-induced body mass index (BMI) increase appears to remain regardless of the specific psychotropic co-treatment. Karayal et al[9] report that subjects switching from quetiapine to ziprasidone show a small but significant decrease in weight as well as improved lipid profiles, regardless of their metabolic status and disease severity at baseline. Compared with patients receiving antipsychotic monotherapy, patients on antipsychotic polyther-

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apy have higher rates of metabolic syndrome and lipid markers of insulin resistance[10]. We found that there was no agreement on the safety and influences of administration of ziprasidone; further studies were needed to confirm this problem.

An open-label study was designed to evaluate the effects of switching from clozapine to ziprasidone on weight, safety and effectiveness, in order to provide options for treating patients with schizophrenia and metabolic disorders.

Patients and Methods

Subjects

All the subjects were collected from Outpatients with schizophrenia and metabolic syndrome (MS) in Shanghai Xuhui District Mental Health Center from 2009.09 to 2011.11. Inclusion criteria were: (1) conforming to 10th International Classification of diseases-10 (the ICD-10) for schizophrenia's diagnostic criteria; (2) aging from 18-60 year-old, and having been treated with clozapine in a conventional dose range for ≥ 2 years and total score of Positive and Negative Syndrome Scale (PANSS) ≥ 60; (3) conforming to the diagnosis of MS recommended by Chinese Diabetes Society in 2004: obesity, BMI ≥ 25.0 kg/m^2; hyperglycemia, fasting plasma glucose ≥ 6.1 mmol/L and (or) plasma glucose after glucose load ≥ 7.8 mmol/L and (or) already being diagnosed with diabetes; hypertension, systolic pressure (SP)/diastolic pressure (DP) ≥ 140/90 mmHg and (or) being identified as hypertension; dyslipidemia, fasting blood triglycerides (TG) ≥ 1.7 mmol/L and (or) fasting plasma HDL cholesterol (HDL-c) < 0.9 mmol/L for male, < 1.0 mmol/L for female. Patients who met three or four conditions above were diagnosed with MS. All the subjects or their family were informed consent. Exclusion criteria were: (1) being unable to provide informed consent; (2) organic mental disorders and psychoactive drug substances abuse or dependence; (3) serious body disease; (4) women in pregnancy or lactation; (5) participating in other researches.

Switching Strategy

All the patients were switched from clozapine to ziprasidone (Nhma Pharmaceutical Group, 20 mg per pill) according to reference[11], and the duration of the treatment was divided into changing drug period (1-4 weeks) and observational period (5-24 week). In the first week, stable dosage of clozapine was used in the patients who were placed on ziprasidone (40 mg, bid for 2 days, followed by incremental dose for 60-80 mg, bid within 3rd day to 7th day, eg. at 4th day, 60 mg, bid; at 7th day, 160 mg/d). In the following 2nd-4th week, clozapine was reduced or withdrawn from 450 mg/d to 0 mg/d according to clinical diagnosis. Patients were naturally divided into ziprasidone group and combination group. In 5th-24th week, the dosage of ziprasidone and clozapine could be adjusted ranging from 80 to160 mg/d, 0 to 450 mg/d, respectively.

During the switching treatment, benzodiazepines, adrenaline beta blockers or anticholinergic drug can be used periodically to treat side effects of drug withdrawal and activation induced by ziprasidone. At the same time, patients were allowed to taking other medications, including antihypertensive drugs, oral hypoglycemic drugs, antiacid drugs (excluding cimetidine), antibiotics, vitamins and mineral supplements, etc.

Assessment

The primary endpoints included body mass index (BMI = weight/height^2, kg/m^2), systolic pressure (SP)/diastolic pressure (DP), fasting glucose (FG), triglycerides (TG), HDL cholesterol (HDL-c) which were obtained from a fasting blood sample at 7:00 am. The second endpoints included PANSS and Treatment Emergent Syndrome Scale (TESS). PANSS (including 33 items, 4 subscales, positive symptom, negative symptom, general psychopathology symptom and accessory symptom) was used to assess the psychopathologic severity of the patients. The severity of each symptom was scored with one of seven grades (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate severe, 6 = severe, 7 = extreme). TESS (including 33 symptoms and laboratory examinations) was used to assess side effect of drugs. All the outcome measures were obtained at baseline (just before switching toziprasidone) and at 4 and 24 weeks.

Statistical Analysis

All data were analyzed by SPSS 15.0 software (SPSS Inc., Chicago, IL, USA) and were displayed by mean ± SD or rate (%). Pair-*t* test was used to compare data before and after the treatment, *t* test was used to compare data among groups, and quantitative data was analyzed by c^2. Significance was set at $p < 0.05$.

Results

General Information

Totally, 213 cases were enrolled into the study, but 6 cases during 1-4 week quitted because their conditions deteriorated, 3 cases quitted because of other physical diseases and 3 cases quitted because of their mental symptoms worsening during 5-24 week. A total of 194 cases completed the study, including 68 cases in ziprasidone group, 126 cases in combination group. Demographics for the 194 patients included in the analyses are shown in Table I. The dosage of ziprasidone in ziprasidone group was 131.4 ± 33.5 (40-160) mg, and the dosage of ziprasidone and clozapine in combination group were 68.7 ± 30.9 (20-120) mg, 239.2 ± 108.2 (25-375) mg, respectively.

Effect on BMI, Glucose and Lipid Metabolism

At the end of 4th week, TG level in ziprasidone group was significantly lower than the baseline and that in combination group ($p > 0.05$). There was no difference of indexes in combination group compared with the baseline. At the end of 24th week, BMI and TG both in ziprasidone group and combination group was significantly lower than the baseline ($p < 0.05$). HDL-c in ziprasidone group was significantly higher than that in combination group ($p < 0.05$).

Efficacy and Safety

At the end of 4th week, statistically significant improvement from pre-switch baseline to endpoint was observed in cognition factor in both ziprasidone group and combination group, and PANSS total score in ziprasidone group ($p < 0.05$). At the end of 24th week, negative factor, cognition factor, anxiety factor and PANSS total score was significantly lower in ziprasidone group than not only baseline but also those in combination group ($p < 0.05$). In combination group, cognition factor and PANSS total score was lower than baseline. But TESS score did not change within or among the group.

Discussion

Clozapine is considered to be second-line drugs for schizophrenia. However, due to historical reasons and socioeconomic factors, clozapine is still widely used in China mainland, even in elderly patients. Its use has been limited by its potentially serious adverse effects, because clozapine is more likely to cause weight gain, glucolipid metabolic disorders, and even induces MS[4]. We devoted ourselves to an optional treatment to reduce the risk for the metabolic side effects. An open trial reveals that ziprasidone appears well tolerated in schizophrenic patients, with mild or moderate adverse events[12]. It is worthy evaluating

Table I. Demographics and illness characteristics.

Item	ziprasidone group (n=68)	Combination group (n=126)	T/χ^2	p
Gender			3.60	0.058
Male	27 (39.7%)	68 (54.0%)		
Female	41 (60.3%)	58 (46.0%)		
Age (year)	42.90 ± 9.16	41.37±9.13	1.11	0.269
Marriage			3.44	0.329
Unmarried	52 (76.5%)	95 (75.4%)		
Married	9 (13.2%)	24 (19.0%)		
Divorce/windowed	7 (10.3%)	7 (5.6%)		
Education			3.95	0.267
Primary or below	2 (2.9%)	1 (0.8%)		
Junior	15 (22.1%)	40 (31.7%)		
Senior/secondary school	38 (55.9%)	69 (54.8%)		
College or above	13 (19.1%)	16 (12.7%)		
Employment status			0.26	0.612
Employed	57 (83.8%)	109 (86.5%)		
Unemployed	11 (16.2%)	17 (13.5%)		
Age of onset (year)	28.12 ± 6.80	29.29 ± 7.33	-1.09	0.279
Duration of schizophrenia (year)	14.78 ± 9.85	12.09 ± 8.82	1.94	0.053
Duration of MS (year)	4.13 ± 1.26	4.25 ± 1.04	1.22	0.191

Table II. Outcomes of BMI, glucose and lipid metabolism.

		ziprasidone group (n=68)	Combination group (n=126)	t	*p*
Baseline	BMI (kg/m^2)	23.73 ± 2.95	23.34 ± 2.34	1.37	0.172
	FPG (mmol/L)	5.94 ± 0.81	5.83 ± 0.95	1.19	0.237
	HDL-c (mmol/L)	0.94 ± 0.37	0.95 ± 0.26	-0.16	0.870
	TG (mmol/L)	1.68 ± 0.37	1.69 ± 0.28	-0.65	0.514
	SP (mmHg)	131.71 ± 12.28	133.88 ± 17.48	-1.01	0.314
	DP (mmHg)	81.27 ± 10.04	83.38 ± 11.95	-1.31	0.193
4th weekend	BMI (kg/m^2)	23.11 ± 3.28	23.59 ± 2.73	-0.97	0.332
	FPG (mmol/L)	5.87 ± 0.87	5.76 ± 0.83	0.81	0.418
	HDL-c (mmol/L)	0.95 ± 0.44	0.94 ± 0.45	0.21	0.726
	TG (mmol/L)	1.50 ± 0.51*	1.68 ± 0.67	-2.01	0.044
	SP (mmHg)	133.28 ± 13.90	132.53 ± 15.47	0.88	0.379
	DP (mmHg)	82.95 ± 11.13	82.66 ± 13.76	0.70	0.483
24th weekend	BMI (kg/m^2)	21.96 ± 2.18#	22.10 ± 3.13#	-0.14	0.886
	FPG (mmol/L)	5.83 ± 0.91	5.82 ± 0.89	0.39	0.679
	HDL-c (mmol/L)	1.12 ± 0.38#	0.96 ± 0.64	3.69	0.005
	TG (mmol/L)	1.52 ± 0.56#	1.54 ± 0.63#	0.58	0.615
	SP (mmHg)	131.75 ± 12.77	132.03 ± 17.09	-0.78	0.434
	DP (mmHg)	79.95 ± 12.21	82.50 ± 12.79	-1.83	0.054

Note:*p <0.05, compared within the group at 4 the weekend; #p < 0.05, compared within the group at 24 the weekend

the clinical efficacy and side effects of a switched strategy to ziprasidone from clozapine.

According to China's mental disorder prevention manual, if clozapine is replaced by other drugs, it can't be dropped sharply due to rebound effect. At the same time, to ensure the steady clinical efficacy, patients in our study received a steady-state switching strategy for 4 weeks. A total of 213 patients were enrolled into the group, about 93.7% (193/213) patients received a complete or partial substitution of ziprasidone and finished the 24-weeks study. Only 6.3% (13/213) patients quitted the study due to their instability or worsening symptoms. No serious drug side effects were observed during 24-week follow-up. The data showed it was operable and practicable for ziprasidone to replace clozapine. There is a highlight that both the short-term (4 week) and long-term (24 week) observation of weight and glucolipid changes associated with a therapeutic substitution of ziprasidone were included in our research.

No matter clozapine was completely or partially replaced by ziprasidone, patients got varying improvements in metabolic index. The previous short-term studies have showed improvement in weight, BMI, and lipid profiles after substitution of ziprasidone for olanzapine or risperidone or aripiprazole[13-15]. In our study, BMI did not change at 4th weekend compared with the baseline in both ziprasidone group and combination group, and was significantly lower than baseline until 24th weekend. It indicates that it takes time for ziprasidone to correct the weight gain induced by clozapine. In ziprasidone group, TG level was significantly lower than baseline at 4th weekend and HDL-c was also significantly increased at 24th weekend. In combination group which ziprasidone partially replaced clozapine, BMI and TG level displayed the same significant change at 24th week as the ziprasidone group. A recent study[16] has confirmed that associations between fat mass and appetite are not disrupted in the ziprasidone group but in olanzapine-treated patient. It may be one of the contributing factors that ziprasidone causes mild or even no metabolic disorders. Partial substitution of ziprasidone limits sustained beneficial effects of ziprasidone.

In terms of efficacy of mental symptoms, completely and partially switching to ziprasidone showed different results. In combination group, cognitive function was improved continually compared to the baseline from 4th weekend. While in ziprasidone group the cognitive function and total scores of PANSS were significantly reduced at 4th weekend, at 24th weekends, cognitive factor, negative symptom factor, emotional factor and total scores of PANSS were further improved. These data indicated that ziprasidone had better curative effect than clozapine, which was in consistent with Harvey et al[17] and Loebel et al[18]. We speculate that there must be some refractory potency which exists in some patients

and needs to be further investigated so that ziprasidone combined with clozapine could not be completely replaced with ziprasidone. Meantime, drug combination could offset adverse impacts caused by MS or clozapine.

Conclusions

We are lacking of the data when patients did not experienced weight gain or glucolipid metabolic indices changes on their prior medications. Moreover, there is a lack of information for patient lifestyle factors such as diet and exercise regimens. But our study demonstrates that it is an optimal treatment of switching to ziprasidone from clozapine for patients with schizophrenia and MS to get good efficacy and tolerability.

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