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Ziprasidone Does not appear to be Able to Modify the Rise in Blood Lipids Caused by Olanzapine in a Randomised Study

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Abstract

Background: o observe the differences of blood lipids between ziprasidone combined olanzapine and single ziprasidone in inpatients with schizophrenia.

Methods: 220 schizophrenic inpatients were treated with ziprasidone and olanzapine for 5 weeks and then randomly divided into combination group and ziprasidone group. PANSS and TESS were evaluated before treatment, at the 1st weekend, 5th, 7th weekend, 9th weekend and 12th weekend. The blood pressure, weight, waist circumference and hip circumference were measured, respectively at same time points. The fasting blood glucose, glycosylated hemoglobin, high-density lipoprotein, low-density lipoprotein, triglyceride and cholesterol were also tested respectively at same time points.

Results: The high-density lipoprotein, low-density lipoprotein, triglyceride and cholesterol were no significant change before and after treatment at first 5 weeks ($F=0.78\sim1.01$, $p>0.05$).After random grouping, a increasing trends of low-density lipoprotein, triglyceride and cholesterol were found in combination group. Especially, LDL, were higher significantly at 7th, 9th and 12th weekend, and triglyceride were higher at 7th, 9th weekend than that in ziprasidone treatment group. And HDL was lower significantly in combination treatment group at 9th weekend than that in ziprasidone treatment group.

Conclusion: The combination treatment of ziprasidone and olanzapine may increasing some index of blood lipid. It also indicated that ziprasidone did not decrease the higher blood lipids related to olanzaipine.

Abbreviation
SPSS=Statistic product and service solutions
SBP=systolic blood pressure
DBP=diastolic blood pressure
BMI=body mass index
BT=before treatment
ME=month end
BS=blood sugar
GHb=glycosylated hemoglobin
Chol=cholesterol
TG=triglyceride
LDL=low density lipoprotein
HDL=high density lipoprotein
PANSS=positive and negative symptom scale
TESS=treatment emergent symptoms scale
SGA=second generation antipsychotic

Keywords: Ziprasidone, Olanzapine, Schizophrenia, TG, LDL, HDL, Cholesterol

Introduction

The treatment decision of schizophrenia involved many factors, of which were effectiveness of drugs and side effects of treatment [1,2]. For the therapeutic effect, it is important to choose a drug among many atypical antipsychotics, sometimes it needs to choose to combination of atypical antipsychotics. Side effects must also be considered. At present, it is necessary to consider the effect of glucose and lipid metabolism [3,4]. The final decision of clinical treatment is to maximize the therapeutic effect and minimize the side effects, which is the highest goal of clinical treatment, and carry out this goal to the end. In the case

of combined treatment, it's not easy to choose two drugs that match each other among many atypical antipsychotics. Although there is still a relatively high proportion of polypharmacy treatment in psychiatric clinic at present [5-7]. The basic and highest requirement of this kind of combined therapy is that the therapeutic effect is mutually strengthened, while the side effects are relatively reduced or not increased [8,9]. This requires us not only to understand the antipsychotic mechanism and side effect mechanism of drugs, but also to understand the metabolic process of drugs and the interaction between drugs [10]. Only in this way can we achieve the highest level of this combination.

Olanzapine and ziprasidone are atypical antipsychotics, which are widely used in psychiatric clinic. They have ideal effects on positive symptoms, negative symptoms and emotional symptoms of schizophrenia. However, olanzapine often causes obvious glucose and lipid metabolism abnormalities, including weight gain and obesity, while ziprasidone has no or few side effects in this regard, but its sedative and therapeutic effects on irritability are significantly less than olanzapine. Therefore, psychiatrist are concerned about whether the two drugs have the possibility of combination. In fact, there are many clinical studies based on this kind of research [4,11].

A series of studies on the combination and single treatment for schizophrenic patients by olanzapine and ziprasidone by our team. Considering the difference of therapeutic effect and side effects between ziprasidone and olanzapine, we conducted a significant clinical trial, which was a randomized study involving multiple hospitals. First of all, this trial was a combination treatment, which was a basic guarantee to ensure that the treatment can be started and carried out [12-14].The study mainly revealed the following results. First, the improvement of mental symptoms in the first five weeks of combination treatment showed continuous improvement. After the fifth week of random grouping, the two groups continued to improve their mental symptoms, but there was no significant statistical difference between the two groups, while the side effects of ziprasidone group were significantly less than that of the combination treatment group [12]. Second, the waist circumference, body weight and BMI were significantly increased at the end of the fifth weekend. After randomization, the waist circumference, body weight and BMI of the combination treatment group continued to increase significantly, while that of the ziprasidone group decreased slightly. There were significant differences in waist circumference, body weight and BMI between the two groups at the end of 9th and 12th weekends [14]. Third, the blood glucose and glycosylated hemoglobin of the fifth weekend of all inpatients were higher than those before treatment, but there was no statistical difference. After randomization grouping, the blood glucose and glycosylated hemoglobin in the combination treatment group continued to increase, while that in the ziprasidone group did not. Compared with the two groups, the blood glucose in the combination treatment group was significantly higher than that in the ziprasidone group at the 9th and 12th weekends. However, there was no significant difference in glycosylated hemoglobin between the two groups [13].

In this series of studies, what has not been summarized and reported is the study results of blood lipids. In this paper, the results will be reported in detail, which will prove ziprasidone whether decrease the higher blood lipids related to olanzapine.

Methods

Study design: The trial was designed in two stage. The first 5 weeks of combined treatment with ziprasidone and olanzapine, in the first 2 weeks, ziprasidone be used the basic therapeutic dose, olanzapine be used 40% - 70% of the therapeutic dose. From the 5th week, they were randomly divided into two groups, one group were continued the original combined treatment and continued to use ziprasidone and olanzapine, the other group were gradually reduced olanzapine, stopped using within 2 weeks, and only be used ziprasidone, if necessary, ziprasidone can be properly added. In this way, the two groups were compared. During the whole clinical trial observation process, clinical evaluation and biological test were conducted at baseline, the first weekend, the fifth weekend, the seventh weekend, the ninth weekend and the twelfth weekend after treatment. Clinical evaluation includes PANSS, CGI, TESS, and biological tests include blood pressure, waist circumference, hip circumference, blood glucose, glycosylated hemoglobin, cholesterol, triglyceride, low-density lipoprotein and high-density lipoprotein. There have been published results of clinical efficacy, glucose metabolism and physical quality [12-14].

Sample: All samples were 220 patients with schizophrenia. The criteria of inpatients tested:(1) The inpatients meet the ICD-10 diagnostic criteria for schizophrenia ; (2) the age of inpatients is greater than or equal to 18 years old, less than or equal to 60 years old; (3) The inpatients had not brain organic diseases and mental disorders caused by them; (4) The inpatients had not dependence on psychoactive substances and mental disorders caused by them; (5) The inpatients had not some diseases for the presence and taking of hormones; (6) The inpatients informed consent of takingziprasidone or ziprasidone combated with olanzapine; (7) The guardian of patients informed consent of trials.

Randomization: the study group and the control group were randomly divided into 1:1 groups according random number Table. The random method was divided into 1:1 groups according to the random table. The random grouping was taken at 5th weekend.

Main index: PANSS, CGI and TESS were evaluated before treatment, at the 1st weekend, 5th, 7th weekend, 9th weekend and 12th weekend. The blood pressure, weight, waist circumference and hip circumference were measured, respectively at same time points. The fasting blood glucose, glycosylated hemoglobin, high-density lipoprotein, low-density lipoprotein, triglyceride and cholesterol were also tested respectively at same time points.

Treatment method: The first 5 weeks of combination treatment with ziprasidone and olanzapine, in the first 2 weeks, ziprasidone be used the basic therapeutic dose (120~160mg/d), olanzapine be used 40% - 70% of the therapeutic dose(10~15mg/d). From the 5th weekend, they were randomly divided into two groups, one group were continued the original combination treatment of ziprasidone and olanzapine, the other group were gradually reduced olanzapine, stopped using within 2 weeks, and only be used ziprasidone, if necessary, ziprasidone can be properly added.

Statistic methods: All data were processed by SPSS18.0 statistical software, and the measurement data between groups were tested by mean t test, $P < 0.05$ was statistically significant. And ANOVA were tested by mean F test, $P < 0.05$ was statistically significant.

7. This study was approved by the ethics committee of jiaxing kangci hospital.

Results

1.The changes of blood lipid after treatment at first 5weeks

The high-density lipoprotein, low-density lipoprotein, triglyceride and cholesterol were no significant change before and after treatment at first 5 weeks (F=0.78~1.01, p>0.05).see Table 1.

Table 1: Blood libidos before and after treatment first 5 weeks (n=196)

	Baseline	First week end	Fifth week end
Chol(mmol/L)*	4.28±0.88	4.26±0.78	4.30±0.85
TG(mmol/L)*	1.47±0.95	1.50±0.82	1.54±0.76
LDL(mmol/L)*	2.18±0.77	2.13±0.74	2.17±0.76
HDL(mmol/L)*	1.32±0.34	1.30±0.25	1.31±0.28

Chol=cholesterol;TG=triglyceride;
LDL=low density lipoprotein;
HDL=high density lipoprotein
F=0.78~1.01,p>0.05

2.The changes of blood lipids between combination treatment group and ziprasidone group.

After random grouping, a increasing trends of low-density lipoprotein, triglyceride and cholesterol were found in combination group. Especially, LDL, were higher significantly at 7th, 9th and 12th weekend, and triglyceride were higher at 7th,9th weekend than that in ziprasidone treatment group. And HDL was lower significantly in combination treatment group at 9th weekend than that in ziprasidone treatment group, see table 2.

Table 2: Comparison Blood libido Between two groups

	Ziprasidone(n=99)	Ziprasidone+ Olanzapine(n=97
Chol(mmol/L)*		
5th Weekend	4.24±0.78	4.37±0.91
7th Weekend	4.22±0.82	4.35±0.93
9th Weekend	4.22±0.84	4.47±1.07*
12th Weekend	4.20±0.95	4.34±1.04
TG(mmol/L)*		
5th Weekend	1.44±0.60	1.65±0.88
7th Weekend	1.50±0.61	1.79±0.93**
9th Weekend	1.47±0.61	1.81±0.99***
12th Weekend	1.69±0.98	1.93±1.06
LDL(mmol/L)*		
5th Weekend	2.05±0.73	2.29±0.77
7th Weekend	2.02±0.72	2.33±0.78***
9th Weekend	2.05±0.72	2.41±0.80***
12th Weekend	2.06±0.76	2.32±0.95****
HDL(mmol/L)*		
5th Weekend	1.34±0.27	1.28±0.27
7th Weekend	1.30±0.25	1.26±0.27
9th Weekend	1.40±0.61	1.34±0.29*
12th Weekend	1.33±0.27	1.31±0.27

Discussion

Metabolic syndrome was a important side effect during treatment by atypical antipsychotic drugs

Gül Dikeç (2018) found that 73.8% of patients stated they experienced side effects from antipsychotic medications and 20.7% of patients experienced weight gain in 271 inpatients using atypical antipsychotic medications in a psychiatric hospital in Turkey [15]. Osama Abo Alrob (2019)found that after six months of taking the SGA, 44% of patients experienced elevated systolic pressure, 54.9% had elevated triglyceride, and 31.9% had impaired glucose levels (p value < 0.05). Prior to initiating SGA therapy, 14.3% of patients had metabolic syndrome, while 37.4% had metabolic syndrome after six months of therapy, and it was more prominent in males compared to female patients (p value < 0.05)[16]. Omer Saatcioglu (2016) also found that frequency of MS according to IDF criteria was 42.2 % among the patients. There was no significant difference between patients with and without MS in terms of age. The ratios of MS were 62.5 % for the group taking typical and atypical antipsychotics together and 35.7 % for the group taking two or more atypical antipsychotics together [17].These suggested that atypical antipsychotics play important role in developing of metabolic syndrome in some patients [18].Atypical antipsychotic drug induced metabolic syndrome by increasing of low-density lipoprotein, triglyceride and cholesterol, weight, blood sugar [18]. So the metabolic index as side effects selected for the serious study also refer to clinical practice.

The different atypical antipshotics had different effects on metabolic syndrome.

Subin Park(2013)found that olanzapine-treated patients showed significant weight gain, particularly fat gain, with increased low density lipoprotein-cholesterol and decreased high density lipoprotein-cholesterol concentrations after 12 weeks,. In contrast, ziprasidone-treated patients showed no significant weight gain with increased high density lipoprotein-cholesterol concentration [4]. A study also found that only olanzapine was associated with significantly increased glucose levels compared to a placebo (mean difference (MD) = 3.95, 95% confidence interval (CI) = 0.14 to 7.76). Moreover, olanzapine was associated with a significantly greater change in the glucose levels than ziprasidone (MD = 5.51, 95% CI = 1.62 to 9.39), lurasidone (MD = 5.58, 95% CI = 0.53 to 10.64) or risperidone (MD = 3.05, 95% CI = 0.87 to 5.22). Ziprasidone and lurasidone were associated with minimal glucose changes compared to the other antipsychotics [3]. So some psychiatrists designed combination treatment of ziprasidone and olanzaping to avid the syndrome [11]. To some extent, this study also has such a design concept. But this study not only aimed at the problem of metabolic syndrome but also proved the treatment decision-making in the early stage of the disease and the subsequent treatment methods[12-14]. differences on blood lipids between ziprasindone and olanzapine in schizophrenic patients should be reported.

The combination treatment of ziprasidone and olanzaping did not avoid blood lipids metabolic abnormal

The high-density lipoprotein, low-density lipoprotein, triglyceride and cholesterol were no significant change before and after treatment at first 5 weeks (F=0.78~1.01, p>0.05), which may be related to that time of taking drugs was short. The difference in changes of blood lipids between combination treatment group and ziprasidone group provide the suggestion. After random grouping, a increasing trends of low-density lipoprotein, triglyceride and cholesterol were found in combination group. Especially,LDL, were higher significantly at 7th,9th and 12th weekend, and triglyceride were higher at

7th,9th weekend than that in ziprasidone treatment group. And HDL was lower significantly in combination treatment group at 9th weekend than that in ziprasidone treatment group. These results showed that olanzapine can increased the low-density lipoprotein, triglyceride and cholesterol, which not related the dose, combination with other antipschotic drug. So combination of olanzapine and ziprasidone cannot avoid increasing of blood lipids.

Ziprasidone was associated with a lower propensity for weight gain and central fat deposition than olanzapine [4]. And at base of olanzapine or clozapine, ziprasidone also increase blood lipids afar combination treatment [11]. But olanzapine or clozapine still induce blood sugar and blood lipids abnormal and body weight gain after their management [13,14,]. This results also provided same view. But at same time, it also indicated that ziprasidone did not decrease the higher lipids related to olanzapine.

The significance of the series study provided both therapeutic concept and avoidance of metabolic syndrome.

Mon pharmacy or polypharmacy were related to many factor. First, some patients indeed needed polypharmacy, such as treatment-resistant schizophrenia, chronic schizophrenia void side effects or better therapeutic effects [5,7-11]. Second, which two drugs were combined was also one of the important selection. It needed understand for pharmacology of two drugs. In therapeutic effects, amisulpride and olanzapine were first line two antipsychotic drug for schizophrenia [19]. In less side effect of metabolic syndrome, ziprasidone, aripiprazole and amisulpride were first three antipsychotic drugs [3,11,20]. So it were considered as a best selection that ziprasidone, aripiprazole combined with olanzapine or clozapine [10,11].This study was designed as ziprasione combined with olanzapine. The last or third, was using policy for combination of ziprasidone and olanzapine. In this study, the ziprasidone was used as main therapeutic drug to higher dose and olanzapine was used as an adjuvant of 40%~70% treating dose. The first stage was combination treatment for 5 weeks and then random second stage were single ziprasidone and ziprasidone combined with olanzapine. The conclusion was that single ziprasidone was best selection after grouping because the blood lipids were higher that in combination of ziprasidone and olanzapine, which means that perfect methods was previous combination therapy and following single therapy.

The insufficient of this study

First, thought this was multicenter, random, compared study, but not blind, which was obvious defects and maybe influenced the results of study, which maybe just influence the changes of symptoms rather than blood lipids that were biological index. Second, the single olanzapine group should be designed compared to single ziprasione and combination treatment group of ziprasidone and olanzapine. Third, the correlation among blood lipids, body composition and blood sugar was not analyzed. Forth, the relationship of clinical symptoms and biological index was not analyzed.

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References

1. Leslie Citrome (2017) Activating and Sedating Adverse Effects of Second-Generation Antipsychotics in the Treatment of Schizophrenia and Major Depressive Disorder: Absolute Risk Increase and Number Needed to Harm. J Clin Psychopharmacology 37: 138-147.
2. Felix-Martin Werner, Rafael Coveñas (2014) Safety of Antipsychotic Drugs: Focus on Therapeutic and Adverse Effects.Expert Opin Drug Saf 13: 1031-42.
3. Yangyu Zhang, Yingyu Liu, Yingying Su, Yueyue You, Yue Ma, et al. (2017) The Metabolic Side Effects of 12 Antipsychotic Drugs Used for the Treatment of Schizophrenia on Glucose: A Network Meta-Analysis. BMC Psychiatry 17: 373.
4. Subin Park, Ki Kyoung Yi, Min-Seon Kim, Jin Pyo Hong (2013) Effects of Ziprasidone and Olanzapine on Body Composition and Metabolic Parameters: An Open-Label Comparative Pilot Study. Behav Brain Funct 9: 27.
5. Giouliana Kadra, Robert Stewart, Hitesh Shetty, James H MacCabe, Chin-Kuo Chang, et al. (2018) Antipsychotic Polypharmacy Prescribing and Risk of Hospital Readmission. Psychopharmacology (Berl) 235: 281-289.
6. Stephanie Lock Man Lung, Ho Ming Edwin Lee, Yu Hai Eric Chen, Kit Wa Sherry Chan, Wing Chung Chang, Lai Ming Christy Hui (2018) Prevalence and Correlates of Antipsychotic Polypharmacy in Hong Kong.Asian J Psychiatr 33: 113-120.
7. Kristensen D, Hageman I, Bauer J, Jørgensen MB, CorrellCU (2013) Antipsychotic polypharmacy in a treatment-refractory schizophrenia population receiving adjunctive treatment with electroconvulsive therapy. J ECT 29: 271-276.
8. Thompson JV, Clark JM, Legge SE, Kadra G, Downs J, Walters JT, et al. (2016) Antipsychotic polypharmacy and augmentation strategies prior to clozapine initiation: a historical cohort study of 310 adults with treatment-resistant schizophrenic disorders. J Psychopharmacol 30: 436-43.
9. Huai-Hai Wang, Min Cai, Hua-Ning Wang, Yun-Chun Chen, Rui-Guo Zhang, et al. (2017) An Assessor-Blinded, Randomized Comparison of Efficacy and Tolerability of Switching From Olanzapine to Ziprasidone and the Combination of Both in Schizophrenia Spectrum Disorders. J Psychiatr Res 85: 59-65.
10. Jari Tiihonen, Heidi Taipale, Juha Mehtälä, Pia Vattulainen, Christoph U Correll, Antti Tanskanen (2019) Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. JAMA Psychiatry 76: 499-507.
11. David C Henderson, Xiaoduo Fan, Paul M Copeland, Bikash Sharma, Christina P Borba, et al. (2009) Ziprasidone as an Adjuvant for Clozapine- Or Olanzapine-Associated Medical Morbidity in Chronic Schizophrenia. Hum Psychopharmacology 24: 225-232.
12. Tang Jianliang, Jin Weidong, Jiang Changwang, Jiang Yonghong (2016) The control study of ziprasidone and alanzapine in consolidation therapy of schizophrenic patients. Chinese J General Practice 14: 1083-1085.
13. Zhou Yong, Huang Hanjin, Tang Jianliang (2015) Efficacy of ziprasidone and olanzapine in treating patientswith schizophrenia and their influences on blood glucose and glycosylated hemoglobin at early stage of course of

treatment. Journal of Wenzhou Medical University 45: 674-678.
14. Lin Yong, Yaomingrong, Jin Weidong, Tang Jianliang (2015) Change of body mass index and waistline of schizophrenic patients in maintennance therapy with ziprasidone. Chinese J of General Practice 13: 1594-1596.
15. Gül Dikeç, Leyla Baysan Arabaci, Gülçin Bölük Uzunoglu, Selin Demet Mizrak (2018) Metabolic Side Effects in Patients Using Atypical Antipsychotic Medications During Hospitalization. J Psychosoc Nurs Ment Health Serv 56: 28-37.
16. Osama Abo Alrob, Sayer Alazzam, Karem Alzoubi (2019) The Effect of Long-Term Second-Generation Antipsychotics Use on the Metabolic Syndrome Parameters in Jordanian Population [J]Medicina 55: 320.
17. Omer Saatcioglu, Murat Kalkan, Nurhan Fistikci, Sakire Erek, Kasim Candas Kilic (2016) Relationship Between Metabolic Syndrome and Clinical Features, and Its Personal-Social Performance in Patients With Schizophrenia. Psychiatr Q 87: 265-280.
18. Ren Zhibin, Jin Weidong, Wang Naixin (2010) atypical antipsychotics and metabolic syndrome. Journal OF Clinical Psychosomatic Disease 16: 186-187.
19. Yikang Zhu, Marc Krause, Maximilian Huhn, Philipp Rothe, Johannes Schneider-Thoma, et al. (2017) Antipsychotic Drugs for the Acute Treatment of Patients With a First Episode of Schizophrenia: A Systematic Review With Pairwise and Network Meta-Analyses. Lancet Psychiatry 4: 694-705.
20. Dahlia Rosally Turangan, Bahagia Loebis, Surya M Husada, Nazli Mahdinasari Nasution (2019) Differences of Fasting Blood Glucose Level in People With Schizophrenia Between Before and After Getting Aripiprazole Treatment. Open Access Maced J Med Sci 7: 2607-2611.

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