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The effect of bezafibrate in preventing glucolipid abnormalities induced by the antipsychotic risperidone

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ABSTRACT

The present study aimed to investigate the effect of bezafibrate on glucolipid abnormalities induced by antipsychotics in schizophrenia. Patients in the treatment group (group A) were treated with antipsychotics and a daily dose of 200 mg bezafibrate for 12 weeks, and patients in the control group (group B) were treated with antipsychotics; sugar, fat and weight changes before and after the treatment were compared between the two groups. Before treatment the differences in TG, TC, LDL-C, HDL-C, body weight and blood glucose between groups A and B were not statistically significant. However, in group B, levels of TG, TC, LDL-C, body weight and blood glucose after treatment showed statistically significant increases, although levels of HDL-C did not register any statistically significant change. By contract, in group A, there were no statistically significant changes in any of the variables measured. Bezafibrate can prevent an increase in sugar, fat and weight gain in treating schizophrenia patients with antipsychotics, and low doses of bezafibrate are safe in the antipsychotic treatment for schizophrenia.

1. Introduction

At present, more than 16 million people in China suffer from schizophrenia; 46% of these patients have metabolic syndrome (MS), and 37% of these patients have hyperlipidaemia. Mitchell et al. found that patients receiving antipsychotic treatment were more prone to elevated cholesterol and triglycerides levels than those not receiving antipsychotic treatment (Mitchell et al., 2013). Some other studies suggested that antipsychotic drugs such as clozapine, olanzapine, quetiapine and risperidone can affect blood lipid levels (with clozapine having the most impact) and that the incidence of MS induced by second-generation antipsychotics was three times that induced by traditional antipsychotics (Burghardt and Ellingrod, 2013; Li et al., 2010; Osei, 1999; Peng et al., 2010; Wang et al., 2008; Wetterling et al., 2007). At present, most of the clinical first-line drugs in psychiatry are second-generation antipsychotics (Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults, 2007). Therefore, it is worth investigating how to reduce glucolipid abnormalities caused by antipsychotics and exploring drugs that can prevent them. In 2012, the investigators conducted a case-control study on bezafibrate in the treatment of hyperlipidaemia, comparing two groups of patients with schizophrenia, where one group also had hyperlipidaemia but the other did not. The results revealed that bezafibrate could not only treat hyperlipidaemia, but it could also reduce blood glucose (Wei et al., 2014). This study was undertaken in order to further investigate the effect of bezafibrate in preventing glucolipid abnormalities induced by antipsychotics.

2. Materials and methods

2.1. Study subjects

A total of 200 patients, ranging in age from 18 to 60, both male and female, were enrolled in the study from January 2014 to December 2015 and were randomly assigned to two equally-sized groups: groups A and B (both $n = 100$). Patients met the diagnostic criteria for schizophrenia according to the *International Classification of Diseases* (ICD-10); had not taken any antipsychotics in the three months prior to the start of the study; had no serious diseases of the heart, infections, liver or kidney diseases, diabetes mellitus, malignant tumours or trauma; had not received lipid-lowering therapy in the preceding three months; and presented with normal levels of blood lipids, blood glucose and blood pressure. Patients in group A took 200 mg of bezafibrate daily once they entered the study while patients in group B did not. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Xuzhou Oriental People's Hospital, and all

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patients provided informed consent.

2.2. Methods

Patients in group A were treated with 200 mg of bezafibrate for 12 weeks, and treated with risperidone (3 mg to 6 mg per day, averaging 4.6 mg per day) concurrently; patients in group B were treated with risperidone (3 mg to 6 mg per day, averaging 4.5 mg per day), and drug dosage was adjusted by clinicians according to the condition. In both groups, patients with insomnia took a low dose of alprazolam, while patients with extravertebral system reactions were treated with trihexyphenidyl hydrochloride.

2.3. Evaluation method

Before treatment and after 12 weeks of treatment, the patients were assessed using the positive and negative syndrome scale (PANSS) and the Toronto extremity salvage score (TESS) and the following measurements were taken and tests applied: blood lipids, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), liver and kidney functions, electrocardiogram (ECG), electroencephalogram (EEG) and routine blood indices. The blood lipid measurements were conducted as follows: every time 5 ml of fasting venous blood was withdrawn it was tested using a Hitachi 7080 automatic biochemical instrument by the one-step enzyme method.

2.4. Statistical analysis

Data were analysed using SPSS 16.0 statistics software and compared using a *t*-test and an X^2 test.

3. Results

Among the 100 patients in group A, 48 patients had been classified as paranoid type schizophrenics, five patients as tension type schizophrenics, and 47 patients as other types. The patients were between 18 and 60 years old, and they had been suffering for 3 months–13 years. Their body weight ranged from 45 to 95 kg, with an average value of 71.24 ± 19.35 kg. After 12 weeks of treatment, their body weight ranged from 46 to 98 kg, with an average value of 72.34 ± 18.44 kg; their average body weight increased by 1.5% over the course of the study.

The differences in TG, TC, LDL-C, HDL-C, body weight and blood glucose levels before and after administration of risperidone combined with bezafibrate in group A were not statistically significant (Table 1).

Of the 100 patients in Group B, 50 patients had been classified as paranoid type schizophrenics, four patients as tension type schizophrenics, and 46 patients as other types. The patients were between 18 and 59 years old and had been suffering for 3 months–17 years. Their body weight ranged from 45 to 98 kg, with an average value of 72.20 ± 18.71 kg. After 12 weeks of treatment, their body weight ranged from 50 to 105 kg, with an average value of 79.37 ± 19.65 kg; their average body weight increased by 9.9% over the course of the study.

In group B, the differences in TG, TC, LDL-C, body weight and blood glucose levels before and after administration of risperidone were statistically significant, while the difference in the level of HDL-C was not statistically significant (Table 1).

Before administration, the differences in TG, TC, LDL-C, HDL-C, body weight and blood glucose levels between groups A and B were not statistically significant (Table 2).

After treatment, the differences in TG, TC, LDL-C, body weight and blood glucose levels between groups A and B were statistically significant, while the difference in the level of HDL-C was not statistically significant (Table 2).

The side effects of groups A and B were compared. The differences in body weight, blood lipids and blood glucose between groups A and B were statistically significant, but the differences in other items between groups A and B were not statistically significant (Table 3).

4. Discussion

Schizophrenia is a term for a group of diseases that are lifelong in nature, are strongly associated with disability, and have a high rate of recurrence. Recent studies have shown that because patients with schizophrenia are lonely, inactive and indifferent they follow unhealthy lifestyles. Combined with the long-term use of high doses of antipsychotics, this causes a higher incidence of MSs such as hyperlipidaemia, type 2 diabetes mellitus, hypertension and increased body weight than in the normal population. The risk of cardiovascular disease is increased, and the quality of life of patients with schizophrenia is seriously compromised (Burghardt and Ellingrod, 2013; Wang et al., 2008; Wetterling et al., 2007). The means of reducing and preventing hyperlipidaemia, type 2 diabetes mellitus, hypertension, increased body weight and other MSs in patients with schizophrenia during treatment is a current clinical research topic. Preventing the occurrence of glucolipid abnormalities and MS through lifestyle adjustments in patients with schizophrenia is difficult due to the effects of pathological factors. Bezafibrate can reduce TG and LDL-C and increase HDL-C, has a significant curative effect on hyperlipidaemia, and can enhance the sensitivity of target tissue to insulin, so it can theoretically prevent diabetes mellitus (Wang et al., 2008). In recent years, there have been many studies on the effects of bezafibrate on blood lipids and blood glucose; however, there are fewer studies on the preventive effect of bezafibrate on glucolipid abnormalities induced by antipsychotics (Arbel et al., 2016; De Marco et al., 2017; Franko et al., 2017; Grings et al., 2017; Handelsman and Shapiro, 2017; Jasim et al., 2018; Koopal et al., 2017; Parmeggiani et al., 2019; Shipman et al., 2016; Waskowicz et al., 2019). In the present study, patients with schizophrenia and normal blood lipid and blood glucose levels were additionally treated with a low dose of bezafibrate during treatment with antipsychotics and compared with patients in the control group who were not additionally treated with it, to assess the preventive effects of bezafibrate on glucolipid abnormalities and increased body weight. The present study demonstrated that, before treatment, in both groups, TG,

Table 1
Comparison of TG, TC, LDL-C, HDL-C, body weight and blood glucose between before and after administration in group A and B.

		TG (mmol/L)	TC (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	Body weight (kg)	Blood glucose (mmol/L)
Group A	Before	0.98 ± 0.56	4.37 ± 1.23	3.76 ± 2.01	1.35 ± 0.67	71.24 ± 19.35	5.23 ± 2.14
	After	1.12 ± 0.66	4.82 ± 1.40	3.98 ± 1.68	1.30 ± 0.58	72.34 ± 18.34	5.87 ± 2.38
	T value	0.52	0.77	0.42	0.23	0.31	0.56
	P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Group B	Before	0.94 ± 0.63	4.56 ± 1.34	3.56 ± 1.97	1.41 ± 0.63	72.20 ± 18.71	5.35 ± 2.22
	After	2.45 ± 0.73	7.87 ± 1.74	4.87 ± 1.67	1.22 ± 0.54	79.37 ± 19.63	7.29 ± 2.54
	T value	3.56	4.35	2.32	0.48	3.56	3.12
	P value	<0.01	<0.01	<0.01	>0.05	<0.01	<0.01

Table 2
Comparison of TG, TC, LDL-C, HDL-C, body weight and blood glucose between group A and B before and after administration.

		TG (mmol/L)	TC (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	Body weight (kg)	Blood glucose (mmol/L)
Before	Group A	0.98 ± 0.56	4.37 ± 1.23	3.76 ± 2.01	1.35 ± 0.67	71.24 ± 19.35	5.23 ± 2.14
	Group B	0.94 ± 0.63	4.56 ± 1.34	3.56 ± 1.97	1.41 ± 0.63	72.20 ± 18.71	5.35 ± 2.22
	T value	0.47	0.51	0.41	0.37	0.42	0.64
	P value	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
After	Group A	1.12 ± 0.66	4.82 ± 1.40	3.98 ± 1.68	1.30 ± 0.58	72.34 ± 18.34	5.87 ± 2.38
	Group B	2.45 ± 0.73	7.87 ± 1.74	4.87 ± 1.67	1.22 ± 0.54	79.37 ± 19.63	7.29 ± 2.54
	T value	3.78	3.65	2.85	0.98	3.22	2.794
	P value	<0.01	<0.01	<0.01	>0.05	<0.01	<0.01

Table 3
Comparison of side effects between groups A and B.

Index	Group A (n)	Group B (n)	X^2 value	P value
ECG	3	4	0.00	>0.05
EEG	2	3	0.00	>0.05
Granulocytes	2	1	0.00	>0.05
EPS	4	3	0.00	>0.05
Headache	2	3	0.00	>0.05
Dizziness	3	4	0.00	>0.05
Nausea	1	1	0.00	>0.05
Vomit	0	2	0.00	>0.05
Body weight gain	3	19	6.54	<0.01
Dyslipidemia	4	37	33.41	<0.01
Pathoglycemia	3	15	8.79	<0.01
Blood pressure	1	3	0.00	>0.05
Other	6	7	0.08	>0.05

ECG, electrocardiogram; EEG, electroencephalogrphy; EPS, effects of extrapyramidal system.

TC, LDL-C, HDL-C, body weight and blood glucose were normal, but after treatment, in both groups, except for HDL-C, the differences in TG, TC, LDL-C, body weight and blood glucose had statistically and significantly changed, and the differences in the levels of blood glucose, blood lipids and body weight between the two groups were highly statistically significant. Additionally, in the treatment group, the differences in TG, TC, LDL-C, HDL-C, body weight and blood glucose levels before and after treatment were not statistically significant, while in the control group, except for HDL-C, the differences in TG, TC, LDL-C, body weight and blood glucose levels before and after treatment were statistically significant. The results revealed that low-dose bezafibrate had a significant preventive effect on increases in glucolipid levels and body weight when patients with schizophrenia were treated with antipsychotics. With the exception of changes in body weight, blood lipid and blood glucose levels, the differences in side effects between the two groups were not statistically significant, and the incidence of side effects in the treatment group did not increase after patients were treated with low-dose bezafibrate. Nevertheless, the inclusion of a placebo control group was not considered in this study, because it was intended to explore the preliminary efficacy of bezafibrate — and a placebo group will be used in a future in-depth study of its efficacy. Our present study only discusses the efficacy of bezafibrate plus risperidone. Moreover, further studies should be performed to evaluate if comparable or even greater benefits would be seen in combining the fibrate with other antipsychotics, such as quetiapine, olanzapine, or clozapine. In conclusion, our study shows that it is safe to use low doses of bezafibrate in the treatment of schizophrenia with antipsychotics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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