EFFECT OF ARIPIPRAZOLE COMBINED WITH OLANZAPINE ON THE CLINICAL EFFICACY OF SCHIZOPHRENIA

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Abstract

In this study, the clinical efficacy of aripiprazole combined with olanzapine in the treatment of schizophrenia was analysed. Sixty-eight schizophrenic patients were included in the study and randomly divided into a control group (34 cases) and an experimental group (34 cases) and underwent treatment for 8 weeks. The patients from the control group received olanzapine started with 10-20 mg/day and adjusted according to clinical evolution for 8 weeks. The patients from the experimental group received olanzapine in the same dose associated with aripiprazole starting with 10 mg/day and adjusted according to clinical evolution for 8 weeks. The results showed that the clinical total effective rate of the control group was significantly reduced compared with the experimental group. The addition of aripiprazole to the olanzapine significantly decreases the positive and negative syndrome scale (PANSS) score, total cholesterol, triglycerides, blood glucose levels, free thyroxine (FT4), triiodothyronine (T3), thyroxine (T4) levels, level of neuron-specific enolase (NSE) and the incidence of adverse reactions compared with the control group, and significantly increase the Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) score, thyroid-stimulating hormone (TSH) level, brain-derived neurotrophic factor (BDNF) levels compared with the control group. In conclusion, aripiprazole combined with olanzapine has a significant clinical effect on schizophrenic patients, can improve glucose and fat metabolism and cognitive function, and decrease neurological dysfunction, with minor adverse reactions and good medication safety.

Rezumat

În acest studiu, a fost analizată eficacitatea clinică a aripiprazolului combinat cu olanzapină în tratamentul schizofreniei. Șaizeci și opt de pacienți schizofrenici au fost incluși în studiu și împărțiți aleatoriu într-un grup control (34 de cazuri) și un grup experimental (34 de cazuri) și au fost tratați timp de 8 săptămâni. Pacienții din grupul control au primit olanzapină 10-20 mg/zi, doză ajustată în funcție de evoluția clinică. Pacienții din grupul experimental au primit olanzapină în aceeași doză, asociată cu aripiprazol 10 mg/zi, doză ajustată în funcție de evoluția clinică. Rezultatele au arătat că eficacitatea clinică în grupul control a fost semnificativ redusă comparativ cu grupul experimental. Adăugarea aripiprazolului la olanzapină a scăzut semnificativ scorul sindromului pozitiv și negativ (PANSS), colesterolul total, trigliceridele, nivelurile de glucoză, tiroxină liberă (FT4), triiodotironina (T3), tiroxină (T4), enolaza neuronală (NSE) și incidența reacțiilor adverse în comparație cu grupul control și a crescut semnificativ scorul Loewenstein (LOTCA), nivelurile hormonului de stimulare a tiroidei (TSH) și factorului neurotrofic derivat din creier (BDNF) în comparație cu grupul control. În concluzie, aripiprazolul combinat cu olanzapină are un efect clinic semnificativ asupra pacienților schizofrenici, poate îmbunătăți metabolismul glucozei, grăsimilor și funcția cognitivă și poate reduce disfuncția neurologică, cu reacții adverse minime.

Keywords: aripiprazole, olanzapine, schizophrenia, neurological function, thyroid hormones

Introduction

Schizophrenia is a common mental disorder, and the specific cause is not clearly identified. Its clinical characteristics are mainly behavioural, emotional and mental incompatibility and disengagement from reality [1, 2]. In recent years, the incidence of schizophrenia has been increasing. Once it is developed, the symptoms gradually deteriorate, resulting in a decline in social function and mental deterioration, which seriously affects the life quality of patients [3, 4]. Antipsychotic drugs play a huge role in the treatment of schizophrenia, but they cannot prevent the appearance of the disease that affects the life quality of the patients [5].

Olanzapine is one of the main drugs used to treat schizophrenia, but has a high incidence of side effects such as increased blood glucose, increased blood fat and increased body weight [6]. Aripiprazole is an oral atypical antipsychotic drug which can relieve positive symptoms, negative symptoms and cognitive function degradation [7]. Compared with other atypical antipsychotics, aripiprazole has no significant effect on body weight and blood glucose, making it a new choice for the treatment of mental illness [8]. This study aims to observe the effect of olanzapine combined with aripiprazole in the treatment of schizophrenia and to explore the improvement of adverse reactions caused by the two drugs.

Materials and Methods

Patients

From May 2018 to January 2020, sixty-eight first-episode schizophrenic patients in the hospital were selected as the research subjects and randomly divided into control group and experimental group, with 34 cases in each group. There were 19 men and 15 women in the control group, with the age of 29-63 years old and a course of 3 - 38 months of disease. There were 18 men and 16 women in the experimental group, aged 32 - 65 years old, and the course of the disease was 3 - 36 months. The study was approved by the Medical Ethics Committee of the Jiande Fourth People's Hospital, Jiande, Zhejiang, China.

Inclusion criteria: (1) in line with the diagnostic criteria for schizophrenia in the Guidelines for Clinical Diagnosis and Treatment - Psychiatry Sub Volume of Chinese Medical Association; (2) first onset, course of disease ≤ 36 months; (3) no previous history of antipsychotic drug use; (4) Positive and Negative Syndrome Scale (PANSS) score ≥ 60 points; (5) no contraindications for the research drugs; (6) with the informed consent of patients and their families.

Exclusion criteria: (1) severe heart, liver, kidney and other organic diseases; (2) generalized developmental disorders and mental retardation; (3) history of alcohol and drug dependence; (4) pregnant and lactating women; (5) haematological, neurological and infectious diseases; (6) combined with malignant tumour; (7) thyroid disease, diabetes and other endocrine and metabolic diseases; (8) application of drugs affecting thyroid hormone level in recent 3 months; (9) giving up treatment halfway.

Treatment plan

The patients from the control group received olanzapine (national medicine permission number H20052688, Jiangsu Hansoh Pharmaceutical Co., Ltd). The starting dose was set at 10 - 20 mg, once a day. The treatment was carried out for 8 weeks. The patients from the experimental group received the same doses of olanzapine as the control group and aripiprazole (national medicine permission number H20140121, Jiangsu Nhwa Pharma. Corporation) based on basic drug treatment. The starting dose was set at 10 mg once a day, and the dosage was adjusted according to the actual condition of the patients. The treatment was carried out for 8 weeks. According to the current state of the patients, the dosage should be adjusted strictly according to the instructions, and the dosage should be strictly controlled to avoid adverse reactions; During the treatment, the two groups of patients were not allowed to use other antidepressants and antipsychotics. Electroconvulsive therapy was not allowed. An ordinary diet was required. High shock and high protein food were not allowed.

Observation indicator

Before and after the treatment, 3 mL of peripheral venous blood was collected from each patient in the morning after 8 hours of starvation. The blood samples were centrifuged at 3000 rotations/min for 10 minutes in order to separate the serum. After separation, the serum was stored at -70°C till further analysis.

The levels of total cholesterol (TC), triglyceride (TG) and blood glucose (GLU) in patients were determined using the Hitachi 7600 automatic biochemical analyser.

The PANSS score and Loewenstein Occupational Therapy Cognitive Assessment (LOTCA) were observed before and after treatment. The lower the PANSS score was, the better the patient's mental state was, and the higher the LOTCA score was, the better the cognitive function was.

The levels of thyroid hormone levels in the two groups before and after treatment, including free triiodothyronine (FT3), free thyroxine (FT4), triiodo-thyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH), were determined using a Chemi-luminescence Immunoassay Analyzer, Guangdong Maikang Medical Co., Ltd, Guangdong, China.

The changes in nerve function indicators before and after treatment were observed, including brain-derived neurotrophic factor (BDNF) (enzyme linked immuno-sorbent assay), neuron-specific enolase (NSE) (enzyme linked immunosorbent assay), and Hcy (immune scattering turbidimetric method) were detected. The kits and reagents used for these determinations were purchased from Beijing Jingmei Bioengineering Co., Ltd., China.

During the treatment, all the adverse reactions induced by the treatment were observed in the two groups.

Evaluation of clinical efficacy

The clinical efficacy of the treatment was evaluated as follows: Cure: if the patient's mental symptoms disappear or stop the attack, the patient's insight completely recovers, and the patients adapt to the environment well; Remarkable effect: the patient's mental symptoms basically disappear, or attack reduces by 50% ~ 75%, the patient's insight is basically restored, and the patients adapt to the environment well; Effective: patients' mental symptoms improve, or attack reduces by 25 ~ 49%, and patients' insight improves significantly; Ineffective: patients' mental symptoms and insight do not improve.

Statistical methods

SPSS22.0 statistical software was used to process the data. The counting data were expressed as rate and compared using the chi-square test (χ^2), while the measurement data were expressed as mean ± standard deviation. The differences between the groups were evaluated by the Students't-test. The difference was statistically significant if $p < 0.05$.

Results and Discussion

Clinical efficacy

The total effective rate of the experimental group is higher than that of the control group ($p < 0.05$) (Table I).

PANSS score and LOTCA score

There is no significant difference in the PANSS score and LOTCA scores between the two groups before treatment ($p > 0.05$). After treatment, the PANSS score decreases while the LOTCA score increases in both groups ($p < 0.05$). After the treatment, the combined treatment significantly decreased the PANSS score and increased the LOTCA score compared with the control group ($p < 0.05$) (Figure 1).

Blood fat and blood glucose levels

There is no significant difference in TC, TG and GLU levels between the two groups ($p > 0.05$) before treatment. After 8 weeks of treatment, the levels of TC, TH and GLU in the control group significantly increased compared with the values before treatment ($p < 0.05$), while in the experimental group slightly decreased compared with the values before treatment without reaching statistical significance ($p > 0.05$) (Figure 2).

Table I

Clinical efficacy

Group name	Cure (n)	Remarkable effect (n)	Effective (n)	Ineffective (n)	Total effective rate (%)
Control group	3	11	8	12	64.71
Experimental group	7	15	9	3	91.18[#]

Compared with the control group, [#] $p < 0.05$.
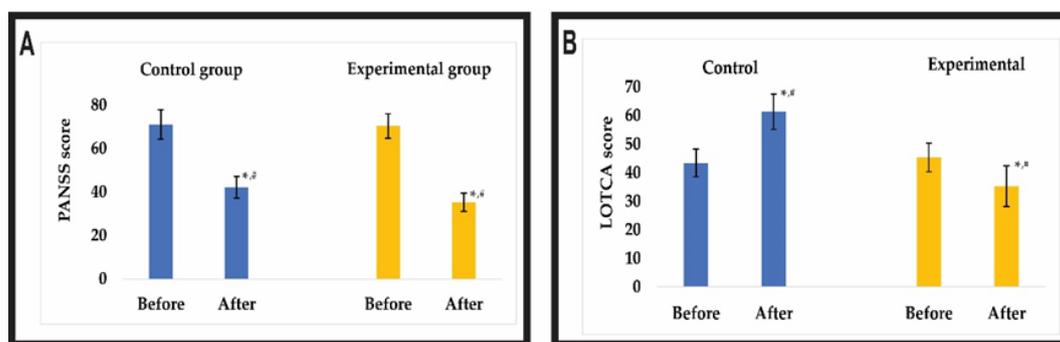
Figure 1.

PANSS score and LOTCA score.

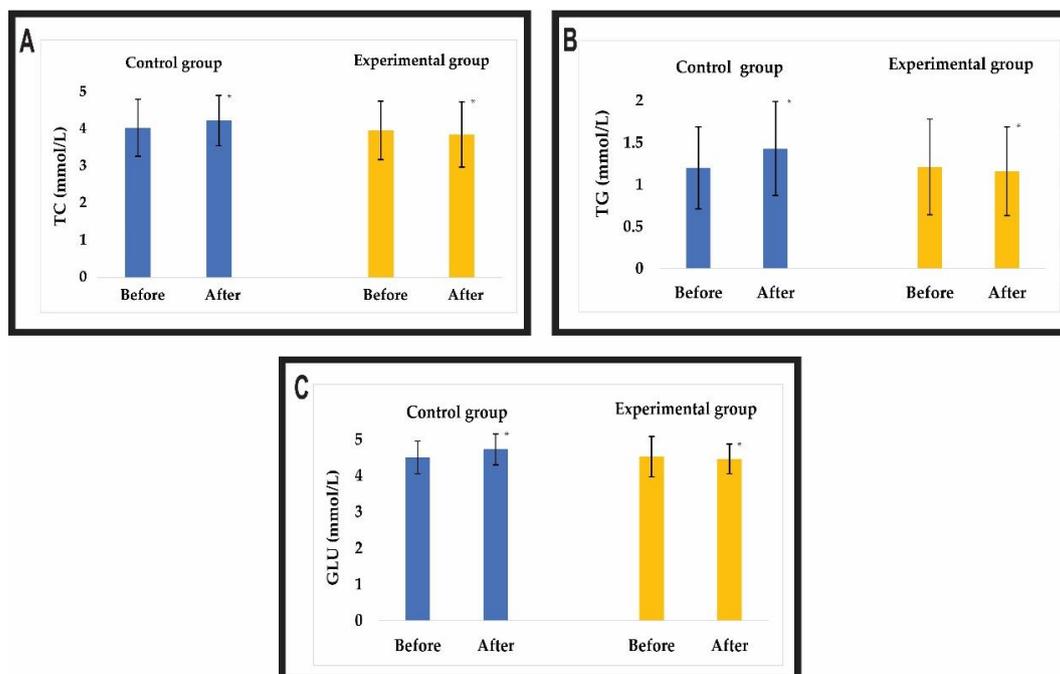* $p < 0.05$ compared with the group before treatment; [#] $p < 0.05$ compared with the control group after treatment

Figure 2.

Comparison of blood fat and blood glucose before and after treatment.

* $p < 0.05$ compared with the group before treatment

Thyroid hormones levels
Before treatment, there was no significant difference in thyroid hormone levels between the two groups ($p > 0.05$). After treatment, in the control group, the T4 level decreased ($p < 0.05$), and the TSH level increased significantly ($p < 0.05$). At the same time, other indicators show a downward trend without reaching statistical significance ($p > 0.05$) compared with the levels before treatment. FT4, T3 and T4 levels in the experimental group significantly decreased ($p < 0.05$), and TSH levels significantly increased ($p < 0.05$) after treatment compared with the levels before treatment. Compared with the control group, the levels of FT4, T3 and T4 in the experimental group significantly decreased ($p < 0.05$) (Table II).

Table II

Comparison of thyroid hormone levels

Indicators		Control group	Experimental group
FT3 (pg/mL)	**Before**	2.81 ± 0.37	2.80 ± 0.41
	After	2.71 ± 0.39	2.67 ± 0.35
FT4 (ng/dL)	**Before**	0.82 ± 0.25	0.83 ± 0.21
	After	0.79 ± 0.26	0.68 ± 0.19*#
T3 (ng/mL)	**Before**	0.83 ± 0.23	0.82 ± 0.23
	After	0.80 ± 0.20	0.71 ± 0.18*#
T4 (µg/dL)	**Before**	9.09 ± 1.16	9.10 ± 0.61
	After	8.14 ± 1.04*	7.34 ± 0.96*#
TSH (µIU/mL)	**Before**	1.97 ± 0.77	2.03 ± 0.86
	After	3.14 ± 0.68*	3.27 ± 0.63*

* $p < 0.05$ compared with the group before treatment, # $p < 0.05$ compared with the control group after treatment.

Neurological function
There is no significant difference in serum BDNF, Hcy and NSE levels between the two groups before treatment ($p > 0.05$). After treatment, serum BDNF level increases, while Hcy and NSE levels decrease ($p < 0.05$) in each group compared with the values before treatment. Comparing the levels after treatment in the two groups, it was observed that serum BDNF levels significantly increased. In contrast, NSE levels significantly decreased in the experimental group compared with the control group ($p < 0.05$) (Table III).

Adverse reactions
The incidence of adverse reactions in the experimental group (8.82%) is significantly decreased compared with the control group (38.24%) ($p < 0.05$) (Table IV).

Table III

Comparison of nerve function

Indicators		Control group	Experimental group
BDNF (pg/mL)	**Before**	19.25 ± 6.66	18.94 ± 6.51
	After	32.46 ± 8.23*	38.15 ± 6.5*#
Hcy (µmol/L)	**Before**	20.76 ± 7.36	20.58 ± 7.15
	After	13.44 ± 2.87*	12.73 ± 3.52*
NSE (µg/L)	**Before**	26.84 ± 3.16	29.08 ± 3.28
	After	22.11 ± 2.91*	18.63 ± 2.80*#

* $p < 0.05$ compared with the group before treatment, # $p < 0.05$ compared with the control group after treatment.

Table IV

The incidence of adverse reactions in the two groups

Indicators	Control group	Experimental group
Gastrointestinal reactions (n)	3	1
Dizziness (n)	4	1
Nausea (n)	3	1
Sleepiness (n)	2	0
Thirst (n)	1	0
Incidence rate (%)	38.24	8.82#

# $p < 0.05$ compared with the control group

The specific biochemical mechanism and pathogenesis of schizophrenia have not been clearly defined [9]. Olanzapine is a common antipsychotic drug which is widely used in clinical practice and can effectively control negative and positive symptoms. However, its adverse reactions are obvious, limiting its clinical application [10, 11]. Aripiprazole and olanzapine are both effective and safe atypical antipsychotics [12].

Aripiprazole and olanzapine are effective drugs for treating schizophrenia and can effectively reduce symptoms [13]. In this study, we add aripiprazole to standard olanzapine treatment for newly initiated patients with schizophrenia. The effective clinical rate of aripiprazole combined with olanzapine in the experimental group is significantly higher than in the control group. Olanzapine antagonizes 5-HT2A and D2 receptors to exert the antipsychotic effect [7, 14]. Aripiprazole works through bidirectional regulation of the DA serotonergic nervous system [15]. The efficacy and safety of the two drugs are similar [8], but aripiprazole can improve some adverse reactions caused by olanzapine [9, 16]. In the comparison of adverse reactions, the adverse reaction rate of the control group is significantly higher than that of the experimental group. Aripiprazole, a quinoline derivative, is a partial agonist and antagonist of 5-HTIA and D2 receptors and has a blocking effect on the M receptor and H1 receptor [17, 18]. In treating schizophrenia by olanzapine combined with aripiprazole, antagonizing the D2 receptor is related to the treatment of positive symptoms of schizophrenia [19], reducing the discharge of dopaminergic neurons and improving the clinical effect. Moreover, the improvement of the life quality in the experimental group before and after treatment is significantly increased compared with the control group, indicating that the combined treatment can effectively improve the clinical effects and life quality of patients, which is similar to previous studies.

Schizophrenic patients are prone to metabolic diseases, such as increased body weight, increased blood fat, and abnormal blood glucose regulation, and antipsychotics can increase these risks [20]. Olanzapine can control mental symptoms by inhibiting the secretion of dopamine, but at the same time, it can promote food intake [21]. Aripiprazole is a partial agonist of the dopamine D2 receptor. Previous studies show that dopamine D2 receptor agonists may reduce food intake by acting on certain hypothalamus areas [22]. Previous studies reveal that aripiprazole can significantly reduce the increase of body weight and blood fat level in schizophrenia patients induced by olanzapine [6, 7, 23]. The results of this study show that the blood glucose and fat metabolism indicators of the control group are significantly higher than those before treatment. In contrast, no significant changes in blood glucose and fat metabolism indicators before and after treatment were observed in the experimental group, indicating that aripiprazole combined with olanzapine can improve the glucose and fat metabolism disorder caused by olanzapine.

Thyroid hormones are associated with the function of the central nervous system [10, 11, 24]. Previous studies suggest that olanzapine can regulate thyroid hormone levels [25, 26]. We found that after treatment with olanzapine alone, the T4 level significantly decreases, and the TSH level significantly increases.

After combined treatment with olanzapine and aripiprazole, the levels of FT4, T3 and T4 significantly decrease, and TSH levels significantly increase. The comparison between the groups after treatment reveals that the levels of FT4, T3 and T4 in the experimental group are significantly reduced compared with the control group. There are two possible reasons for these effects. First, olanzapine, as a multi receptor blocker, mainly antagonizes 5-HT and DA receptors [27]. Moreover, the function of T3 and T4 is associated with the 5-HT levels. More precisely, the expression of T3 and T4 can decrease with the decrease of the 5-HT level. The block of the D2 receptor by olanzapine determines the inhibition of the hypothalamus-pituitary thyroid axis and promotes the decrease of T4 level. Data show that thyroid hormones regulate the DA receptor level, and DA can inhibit TSH expression [28]. Therefore, DA blocker treatment combined with feedback regulation can cause an increase in TSH levels. The second explanation is related to the 5-HT serotonergic neurons that can stimulate the thyroid axis, and aripiprazole, as a 5-HT receptor antagonist, can inhibit the thyroid axis and block the expression of DA in the postsynaptic membrane, which leads to the decrease of FT4 level. Aripiprazole, as a DA transmitter stabilizer, has no significant effect on DA related TSH levels [16, 29].

BDNF is an essential nutrient factor for neurons and plays an important role in maintaining neuronal differentiation, survival, growth and normal physiological functions (30). In many studies [31, 32], it is reported that the decrease in serum BDNF level can cause severe damage to the repair and remodelling of neurons, cause neuronal apoptosis, and promote the occurrence of schizophrenia. NSE is an enzyme involved in glycolysis, which mainly exists in neuroendocrine cells and neurons and has been used as a marker for the determination of neuronal degeneration or injury [33]. The results of the current study show that the serum BDNF levels significantly increased in the experimental group compared with the control group after treatment. In contrast, the NSE level significantly decreased, indicating that the combination of drugs can improve the neurological function of patients.

Conclusions

In conclusion, aripiprazole combined with olanzapine has a clear clinical effect on schizophrenic patients, improves glucose and fat metabolism, limits neurological dysfunction, has few adverse reactions, and can improve the life quality of these patients compared with olanzapine alone. However, it still can influence the thyroid hormone levels, so clinical monitoring and medication should be considered according to patients' individual situations.

Conflict of interest

The authors declare no conflict of interest.

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