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Effect of escitalopram combined with zolpidem on sleep structure, sleep process and neurotransmitter in elderly patients with chronic insomnia

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ABSTRACT

Objective: To analyze the effect of escitalopram combined with zolpidem on sleep structure, sleep process and neurotransmitter in elderly patients with chronic insomnia. **Methods:** A total of 112 elderly patients with chronic insomnia treated in our hospital were included in the study and randomly divided into observation group and control group (n=56). Control group received zolpidem therapy alone, observation group received escitalopram combined with zolpidem therapy, and then differences in sleep structure and process, neurotransmitter, stress hormones, hypothalamus-pituitary-thyroid axis indexes and so on were compared between two groups of patients. **Results:** The sleep structure and sleep process parameters SL, RL and S2 levels of observation group after treatment were significantly lower than those of control group while TST, S3 and REM levels were significantly higher than those of control group; Orexin, ACTH, 5-HT, NE, CRH, E, Ang Ⅱ, Cor, ALD, DA and TGA content in serum were significantly lower than those of control group while T3, T4, TSH and TRH content were significantly higher than those of control group. **Conclusions:** Escitalopram combined with zolpidem can optimize the sleep structure and process in elderly patients with chronic insomnia, and also plays a prominent role in regulating the body's homeostasis.

1. Introduction

The incidence of chronic insomnia in the elderly is extremely high, which is mainly related to the neural function degradation, mood disorders as well as heart disease, chronic obstructive pulmonary disease and other primary diseases. Chronic insomnia has become the primary factor that reduces the elderly life quality, zolpidem is an imidazopyridine hypnotic drug similar to benzodiazepine, and it is mostly used in the treatment of senile chronic insomnia and can exert significant sedative hypnotic effect[1,2]. But many patients state that there is much nightmare after taking zolpidem and the sleep quality hasn′t been improved, which may be because that it cannot regulate sleep structure and process. Escitalopram belongs to first-line antidepressant, has the effect on inhibiting 5-hydroxytryptamine (5-HT) reuptake, and can not only improve patients′ anxiety caused by insomnia, but also increase 5-HT levels in synaptic cleft to optimize the insomnia and sleep quality in patients[3]. In order to define the improvement of escitalopram combined with zolpidem for elderly patients with chronic insomnia, 112 patients in our hospital were included in the study, and the changes in patients' sleep structure, sleep process, neurotransmitter levels and other aspects were mainly elaborated.

2. Materials and methods

2.1. General information

A total of 112 elderly patients with chronic insomnia treated in our hospital between August 2012 and August 2015 were included, and they were without cerebral organic disease and mental disorder. All

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patients were randomly divided into observation group and control group (n=56). Control group included 26 male cases and 30 female cases, they were 62-78 years old and (69.28±7.14) years old in average, and the course of insomnia was 1-9 years and (4.38±0.79) years in average; observation group included 25 male cases and 31 female cases, they were 63-77 years old and (69.63±7.55) years old in average, and the course of insomnia was 1-8 years and (4.79±0.81) years in average. The two groups of patients showed no statistically significant difference in the distribution of gender, age and course of insomnia (P>0.05) and could be subsequently compared.

2.2. Treatment methods

Observation group received escitalopram combined with zolpidem therapy, specifically as follows: Escitalopram tablets [10 mg/tablet, Jewim Pharmaceutical (Shandong) Co., LTD., approved by H20103327] 5 mg/d were taken after breakfast, the dosage was gradually adjusted according to the condition, and the maximum was 20 mg/d; Zolpidem Tartrate Tablets (10 mg/tablet, Hunan Yada Pharmaceutical Co., LTD., approved by H20031147) 5 mg/d were taken before sleep, the dosage was gradually adjusted according to the condition, and the maximum was 10 mg/d. The above two drugs were continuously taken for 8 weeks. Control group received zolpidem therapy alone, and the usage and dosage were the same as those of observation group, and the drug was continuously taken for 8 weeks.

2.3. Sleep process and structure

After 8 weeks of treatment, the two groups of patients received the following test: they slept in the laboratory for three nights, adapted to the laboratory environment in the first two nights and received formal test on the third night. The laboratory temperature was adjusted to 15 ℃-26 ℃, the room was kept quiet, P&D-9600 sleep breath recorder was used to detect and analyze patients' sleep process and sleep structure. Sleep process: sleep latency (SL), the actual total sleep time (TST) and rapid-eye-movement sleep latency (RL); sleep structure: sleep stage 1 (S1), S2, S3 as well as the ratio of rapid-eye-movement sleep (REM) to sleep.

2.4. Serum indexes

After 8 weeks of treatment, peripheral blood was collected from two groups of patients and centrifuged to get serum and cryopreserve it in -80 ℃ refrigerator for test. Specific detected indexes were as follows: (1) neurotransmitter: the instructions of enzyme-linked immunosorbent assay kit were followed to determine the serum levels of neurotransmitters such as Orexin, adrenocorticotropic hormone (ACTH), 5-hydroxytryptamine (5-HT), norepinephrine (NE) and corticotropin releasing hormone (CRH). (2) Stress hormones: ELISA method was used to determine epinephrine (E), angiotensin (Ang Ⅱ), cortisol (Cor), aldosterone (ALD) and dopamine (DA). (3) Hypothalamus-pituitary-thyroid axis indexes: radioimmunoassay method was used to detect triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH) and anti-thyroglobulin antibody (TGA).

2.5. Statistical methods

SPSS23.0 was used to input and analyze the data obtained in the

Table 1
Comparison of sleep process and structure parameters between two groups after treatment.

Groups	Case No.	SL (min)	TST (min)	RL (min)	S1	S2	S3	REM
Observation group	56	12.94±1.73	429.37±51.94	81.26±9.34	0.21±0.02	0.40±0.05	0.17±0.02	0.27±0.03
Control group	56	15.42±1.76	391.55±42.38	94.52±9.71	0.22±0.03	0.45±0.06	0.12±0.01	0.20±0.02
t		5.934	6.182	7.291	0.324	5.483	6.102	6.382
P		<0.05	<0.05	<0.05	>0.05	<0.05	<0.05	<0.05

Table 2
Comparison of neurotransmitter content in serum between two groups after treatment.

Groups	Case No.	Orexin (pg/mL)	ACTH (pg/mL)	5-HT (ng/mL)	NE (pg/mL)	CRH (ng/mL)
Observation group	56	453.28±50.23	38.29±4.11	71.23±8.15	101.27±10.85	32.18±4.12
Control group	56	612.83±71.29	47.61±5.08	95.18±10.23	124.38±15.11	50.53±5.76
t		11.293	7.283	8.251	8.475	7.293
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 3
Comparison of stress hormone content in serum between two groups after treatment.

Groups	Case No.	E (ng/L)	Ang Ⅱ (ng/L)	Cor (μg/L)	ALD (ng/L)	DA (ng/L)
Observation group	56	178.53±20.27	220.63±25.17	193.26±20.18	20.17±2.58	130.55±15.76
Control group	56	213.67±25.48	261.74±30.68	271.54±30.69	31.64±3.49	182.64±20.17
t		6.948	7.293	8.192	7.394	9.273
P		<0.05	<0.05	<0.05	<0.05	<0.05

study, measurement data was in terms of mean±sd, comparison between groups was performed by t test and $P<0.05$ was set as the standard of statistical significant difference.

3. Results

3.1. Sleep process and structure

SL, RL and S2 levels of observation group after treatment were significantly lower than those of control group while TST, S3 and REM levels were significantly higher than those of control group. Differences in sleep process and structure parameters SL, TST, RL, S2, S3 and REM levels were statistically significant between two groups after 8 weeks of treatment ($P<0.05$) and differences in S1 levels were not statistically significant ($P>0.05$), shown in Table 1.

3.2. Neurotransmitters

Orexin, ACTH, 5-HT, NE and CRH content in serum of observation group were significantly lower than those of control group ($P<0.05$), shown in Table 2.

3.3. Stress hormones

E, Ang Ⅱ, Cor, ALD and DA content in serum of observation group were significantly lower than those of control group ($P<0.05$), shown in Table 3.

3.4. Hypothalamus-pituitary-thyroid axis indexes

T3, T4, TSH and TRH content in serum of observation group were significantly higher than those of control group while TGA content was significantly lower than that of control group ($P<0.05$), shown in Table 4.

4. Discussion

The incidence of chronic insomnia in the elderly is as high as above 50%, the incidence in the female is slightly higher (about 60%), and it is associated with growing age-related degenerative changes in nervous system, which are mostly manifested as fragmentary sleep at night and increased daytime sleepiness. Related research has confirmed that chronic insomnia has severely reduce the life quality in the elderly, and the elderly sleep electroencephalogram is mostly shown as increased ratio of non-rapid-eye-movement sleep (NREM) Ⅰ and Ⅱ stages as well as decreased the slow-wave sleep and REM[4]. How to optimize the sleep quality in elderly patients with chronic insomnia and reduce or even reverse the abnormal change is the focus of current geriatric study. Diagnosis and treatment guide for insomnia in China in 2012 has pointed out that the combined use of antidepressants in patients with primary insomnia is expected to improve the patients' prognosis[5,6]. Given the poor effect of zolpidem and other hypnotics on elderly patients with chronic insomnia at present, antidepressants escitalopram was added in the treatment system of the study, and the effect of combined drug use on patients' sleep state, neurotransmitter secretion and so on was mainly elaborated.

Escitalopram is 5-hydroxytryptamine reuptake inhibitor, is the first-line drug for treatment of depression, and has been confirmed in many studies to be able to improve the patients′ anxiety and cognitive status. Research of Mao *et al*[7] believes that the combination of antidepressants and hypnotics can quickly improve the sleep state in patients with primary insomnia, but also puts forward the hidden trouble of increased drug tolerance during the treatment. Escitalopram has been pharmacologically confirmed to be without tolerance increase, and it elevates the 5-HT levels in synaptic cleft to shorten the sleep latency and increase patients' slow-wave sleep[8,9]. In order to define the improvement of escitalopram combined with zolpidem on patients' sleep state, the sleep breath recorder was used to record and analyze the sleep structure and process of the two groups of patients after treatment, and the results showed that in the aspect of sleep process: SL and RL value of observation group were lower while TST value were higher after treatment; in the aspect of sleep structure: S2 value was low while S3 and REM value were higher. Normal sleep is composed of REM and non-REM, and the above results indicate that escitalopram combined with zolpidem treatment can prolong the patients' total sleep time, maintain stable sleep, reduce daytime sleepiness, optimize the sleep structure and increase REM and Ⅱ stage sleep ratio. It can be found adding antidepressants plays a substantive role in optimizing patients' overall sleep quality, but the realization mechanism of the effect has not been confirmed by clear study, and most scholars speculate that it is associated with the changes in the levels of neurotransmitters[10,11].

Insomnia is mostly associated with the change of emotion and mood, and a variety of neurotransmitters are involved in its occurrence and development. Orexin, ACTH, 5-HT, NE, CRH and so on are the commonly studied neurotransmitters that play an important role in depression, mania and other abnormal mental and emotional diseases, and many scholars believe that they also play a key role in the senile chronic insomnia[12,13]. It has been confirmed in rat models that Orexin can extend the awakening time and reduce the slow-wave sleep and REM sleep, and Orexin can activate the NE, 5-HT and so on, and improve and maintain awakening degree. Foreign study has shown that monoamine neurotransmitters ACTH and CRH can improve the excitability of cerebral cortex and are the key links in sleep-wake regulatory mechanism. In the study, the neurotransmitter levels in peripheral blood were detected, and it was found that the neurotransmitters such as Orexin, ACTH, 5-HT, NE and CRH of observation group were lower after treatment, it indicates that escitalopram combined with zolpidem treatment has

adjusted the patients' sleep-wake mechanism, it shortens patients' awakening time and prolongs their sleeping time from the level of neurotransmitters, and this is consistent with the previously mentioned optimization of sleep structure and process, and explains that escitalopram combined with zolpidem adjusts the levels of neurotransmitters to affect the sleep state[14,15].

Patients with chronic insomnia can be associated with bad mood and rage, and studies have found that these patients are mostly accompanied by the changes in stress hormone content in the body, which further lead to aggravated insomnia and form a vicious circle[16,17]. Escitalopram helps change the mode in patients with chronic insomnia, so the stress hormone levels of the two groups were detected in the study after treatment, and the results showed that E, Ang Ⅱ, Cor, ALD and DA content of observation group were lower after treatment. A number of studies have confirmed that when human beings are in the stress state caused by emotional or pathological conditions, the above hormones will be massively secreted, and so the above results show that adding escitalopram helps to significantly improve the patients' stress state and prompt patients to return to normal mood and fall asleep. The hypothalamus-pituitary-thyroid axis is also confirmed to be involved in the occurrence of chronic insomnia, and due to the reduced central nervous sensitivity, elderly patients are mostly accompanied by the decrease of TSH and TRH, which directly results in the further decrease of T3 and thyroxine T4. The increase of anti- TGA content can be directly against thyroid tissue and affect its normal function, which results in decreased T3 and T4 secretion and further aggravates insomnia. It was found in the study that the T3, T4, TSH and TRH content in serum of observation group increased while TGA content decreased after treatment, indicating that combined treatment can optimize the central nervous function in elderly patients and increase the effect of TSH and TRH on promoting T3 and T4.

To sum up, it is concluded as follows: escitalopram combined with zolpidem can optimize the sleep structure and process in elderly patients with chronic insomnia, also plays a prominent role in regulating the body's homeostasis, and is worth popularization and application in clinical practice in the future.

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