Effects of dexzopiclone and estazolam on neurotransmitters, nerve cytokines and stress states in patients with insomnia after stroke

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ABSTRACT

Objective: To study the effects of dexzopiclone and estazolam on neurotransmitters, nerve cytokines and stress states in patients with insomnia after stroke. Methods: The patients with insomnia after stroke who were treated in Linyi Rongjun Hospital between March 2015 and October 2017 were chosen and randomly divided into dexzopiclone group and estazolam group. The levels of neurotransmitters, nerve cytokines and stress indexes in serum were measured before treatment as well as 14 days and 28 days after treatment. Results: Compared with those before treatment, serum Glu, \( \gamma \)-GABA, 5-HT, 5-HIAA, BDNF and NGF levels of both groups significantly increased whereas NE, TNF-\( \alpha \), IL-6, ATCH, Cor, CRP, SOD and GSH levels significantly decreased after treatment, and serum Glu, \( \gamma \)-GABA, 5-HT, 5-HIAA, BDNF and NGF levels of dexzopiclone group after treatment were higher than those of estazolam group whereas NE, TNF-\( \alpha \), IL-6, ATCH, Cor, CRP, SOD and GSH levels were lower than those of estazolam group. Conclusion: Dexzopiclone is more effective than estazolam to regulate the secretion of neurotransmitters and nerve cytokines and reduce the stress state in patients with insomnia after stroke.

1. Introduction

Stoke is a common clinical cardiovascular and cerebrovascular disease and includes hemorrhagic stroke and ischemic stroke, which can cause neurological impairment and corresponding clinical symptoms. Sensory and motor dysfunction are the common clinical symptoms after stroke, and there are also mental symptoms, such as anxiety, depression and sleep disorders in some patients, which will not only cause adverse effect to daily life, but also hinder the exercise and reconstruction sensory and motor function[1,2]. The occurrence of insomnia after stroke is closely related to the structure and function damage of 5-hydroxytryptamine neurons and norepinephrine neurons, and the change in the secretion of corresponding neurotransmitters and nerve cytokines will directly affect the brain function to affect the normal sleep structure and lead to insomnia. Estazolam and dexzopiclone are common psychiatric drugs for clinical treatment of insomnia, the former belongs to benzodiazepines, the latter belongs to non-benzodiazepines, and they exert sedative and dormitive effect through different mechanisms[3,4]. In the following studies, we compared the effects of dexzopiclone and estazolam on neurotransmitters, nerve cytokines and stress states in patients with insomnia after stroke.

2. Case information and research methods

2.1 Case inclusion and information

The patients with insomnia after stroke who were treated in the three wards of Geriatrics Department in Linyi Rongjun Hospital between March 2015 and October 2017 were chosen for study, all patients had history of stroke and conformed to the diagnostic criteria for insomnia, and the patients combined with alcohol or drug dependence, those combined with sleep apnea syndrome and those combined with anxiety or depression were eliminated. A total of 78 cases were enrolled and divided into two groups by random number table method, each with 39 cases. There were 22 males and 17 females in dexzopiclone group, they were 45-69 years old, and PSQI score was (14.85±1.84) points; there were 23 males and
2.2 Clinical therapy

After inclusion, the patients with insomnia after stroke started 1 week of washout, all sedative drugs were stopped and the patients received basic health education, and then drug treatment was started. Dexzopiclone group took initial dose 1.5 mg of dexzopiclone tablets orally 30 min before sleep every night, the dosage was adjusted according to the sleep condition after 3 d, and the maximum dose should not exceed 3 mg/d. Estazolam group took initial dose 0.4 mg of estazolam tablets before sleep every night, the dosage was adjusted according to the sleep condition after 3 d, and the maximum dose should not exceed 1.2 mg/d.

2.3 Laboratory detection methods

Before treatment as well as 14 d and 28 d after treatment, serum BDNF, NGF, TNF-α levels were determined according to the radioimmunoprecipitation kit instructions. 3-5 mL of morning fasting peripheral venous blood was collected and centrifuged to separate serum, the Elisa kit instructions were referred to determine Glu, γ-GABA, 5-HT, 5-HIAA, NE, BDNF, NGF, TNF-α, IL-6, ATCH, Cor and CRP levels, and the levels of SOD and GSH were determined according to the radioimmunoprecipitation kit instructions.

2.4 Statistical methods

Software SPSS 19.0 was adopted to input data, the data between two groups were analyzed by t test and the difference was statistically significant with \( P < 0.05 \).

### Table 1

Comparison of serum Glu, γ-GABA, 5-HT, 5-HIAA and NGF before treatment and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>Glu</th>
<th>γ-GABA</th>
<th>5-HT</th>
<th>5-HIAA</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexzopiclone</td>
<td>39</td>
<td>Before treatment</td>
<td>0.25±0.04</td>
<td>0.32±0.04</td>
<td>65.8±8.2</td>
<td>70.3±8.7</td>
<td>59.6±7.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d after treatment</td>
<td>0.52±0.07*</td>
<td>0.49±0.06*</td>
<td>98.4±11.3*</td>
<td>101.4±13.7*</td>
<td>27.5±5.2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 d after treatment</td>
<td>0.65±0.08*</td>
<td>0.58±0.08*</td>
<td>126.5±15.7*</td>
<td>131.5±17.8*</td>
<td>21.3±3.4*</td>
</tr>
<tr>
<td>Estazolam</td>
<td>39</td>
<td>Before treatment</td>
<td>0.23±0.03</td>
<td>0.30±0.03</td>
<td>66.4±8.9</td>
<td>71.1±9.3</td>
<td>60.8±8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d after treatment</td>
<td>0.38±0.06*</td>
<td>0.39±0.05*</td>
<td>79.3±9.4*</td>
<td>89.4±11.3*</td>
<td>38.6±5.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 d after treatment</td>
<td>0.49±0.06*</td>
<td>0.47±0.07*</td>
<td>93.5±11.2</td>
<td>104.6±14.8*</td>
<td>29.4±4.4*</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within two groups, \( P < 0.05 \); #: comparison between two groups after treatment, \( P < 0.05 \).

### Table 2

Comparison of serum BDNF, NGF, TNF-α and IL-6 before treatment and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>BDNF</th>
<th>NGF</th>
<th>TNF-α</th>
<th>IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexzopiclone</td>
<td>39</td>
<td>Before treatment</td>
<td>9.85±1.13</td>
<td>6.48±0.89</td>
<td>46.8±6.8</td>
<td>93.5±11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d after treatment</td>
<td>16.48±2.03*</td>
<td>12.67±1.57*</td>
<td>25.2±3.7*</td>
<td>68.7±8.9*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 d after treatment</td>
<td>20.33±2.89*</td>
<td>16.52±2.16*</td>
<td>20.1±3.2*</td>
<td>50.3±7.2*</td>
</tr>
<tr>
<td>Estazolam</td>
<td>39</td>
<td>Before treatment</td>
<td>9.91±1.05</td>
<td>6.62±0.89</td>
<td>47.4±7.2</td>
<td>95.1±10.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d after treatment</td>
<td>12.75±1.52*</td>
<td>9.12±1.14*</td>
<td>34.8±5.5*</td>
<td>79.3±9.3*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 d after treatment</td>
<td>15.03±1.88*</td>
<td>12.33±1.85*</td>
<td>28.9±4.2*</td>
<td>66.5±7.8*</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within two groups, \( P < 0.05 \); #: comparison between two groups after treatment, \( P < 0.05 \).
Comparison of serum ATCH, Cor, CRP, SOD and GSH before treatment and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>ACTH</th>
<th>Cor</th>
<th>CRP</th>
<th>SOD</th>
<th>GSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexzopiclone</td>
<td>39</td>
<td>Before</td>
<td>16.82±2.21</td>
<td>242.3±34.5</td>
<td>12.17±1.53</td>
<td>119.72±18.94</td>
<td>93.47±11.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d after</td>
<td>8.92±1.13*</td>
<td>207.6±26.2*</td>
<td>6.48±0.86*</td>
<td>83.51±10.35*</td>
<td>70.33±9.35*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td>7.38±0.93*</td>
<td>189.3±22.4*</td>
<td>4.52±0.62*</td>
<td>65.75±9.75*</td>
<td>62.31±8.35*</td>
</tr>
<tr>
<td>Estazolam</td>
<td>39</td>
<td>Before</td>
<td>17.02±2.14</td>
<td>241.8±31.8</td>
<td>12.24±1.44</td>
<td>120.22±15.24</td>
<td>95.12±9.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d after</td>
<td>12.15±1.58</td>
<td>226.5±30.5</td>
<td>9.39±1.15</td>
<td>98.21±11.52</td>
<td>81.73±9.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>treatment</td>
<td>9.39±1.05</td>
<td>201.3±27.8</td>
<td>7.86±0.93</td>
<td>79.35±8.36</td>
<td>73.33±9.39</td>
</tr>
</tbody>
</table>

*: comparison between before and after treatment within two groups, *P*<0.05; #: comparison between two groups after treatment, *P*<0.05.

### 3.3 Serum stress index levels

Before treatment as well as 14 d and 28 d after treatment, analysis of serum stress indexes ATCH (pmol/L), Cor (ng/mL), CRP (mg/L), SOD (U/L) and GSH (U/L) levels was as follows: compared with those before treatment, serum ATCH, Cor, CRP, SOD and GSH levels of both groups significantly decreased after treatment (*P*<0.05); serum ATCH, Cor, CRP, SOD and GSH levels were not significantly different between the two groups of patients before treatment (*P*>0.05) while serum ATCH, Cor, CRP, SOD and GSH levels were significantly different after treatment (*P*<0.05), and serum ATCH, Cor, CRP, SOD and GSH levels of dexzopiclone group were lower than those of estazolam group.

### 4. Discussion

Insomnia after stroke is a common mental symptom in patients with stroke, which will not only adversely affects daily life, but also hinder the exercise and reconstruction of sensory and motor functions[5]. In addition, the persistent insomnia state can lead to persistent stress in patients, and thus increase the risk of recurrent stroke[6,7]. In clinical practice, drug therapy should be actively conducted for insomnia after stroke on the basis of lifestyle intervention and healthy education[8]. Dexzopiclone and estazolam are two kinds of sedatives and hypnotics with different mechanisms, the former belongs to the non-benzodiazepines and can act on the GABA complex coupled with benzodiazepine receptor to exert sedative and hypnotic effect, and the latter belongs to benzodiazepines and can directly act on the benzodiazepine receptor and block the transition of the limbic system impulse to the cerebral cortex so as to exert sedative and hypnotic effects[9,10]. The two different kinds of sedative drugs can obtain the exact therapeutic effect in the treatment of patients with sleep disorder alone. But in patients with insomnia after stroke, the benzodiazepines will produce a hangover effect and affect cognitive and motor function to varying degrees, which is not conducive to the reconstruction of neural function; however, non-benzodiazepines have the advantages of quick effect and weak hangover effect, and have been proven to be more prominent in clinical treatment.

After 5-hydroxytryptamine neuron and norepinephrine neuron damage and destruction in the central nervous system of patients with stroke, the change in corresponding neurotransmitters 5-HT and NE secretion is an important pathological link that causes the changes of sleep structure. 5-HT plays a sedative and hypnotic role by acting on the 5-HT1A receptor and 5-HT2 receptor of the postsynaptic membrane. 5-HIAA is the metabolite of 5-HT, which can reflect the production of 5-HT in a certain degree[11]; NE acts on adrenergic neurons to maintain the excitability of the nervous system, and can obstruct the production of sleep. Glu and γ-GABA are amino acid neurotransmitters, which reduce the excitability of central nervous system, inhibit the transmission of impulses and promote sedation and sleep[12,13]. The analysis of the difference in above neurotransmitters before and after dexzopiclone and estazolam treatment showed that compared with those before treatment, serum Glu, γ-GABA, 5-HT and 5-HIAA levels of both groups significantly increased whereas NE levels significantly decreased after treatment, and serum Glu, γ-GABA, 5-HT and 5-HIAA levels of dexzopiclone group after treatment were higher than those of estazolam group. It means that both dexzopiclone and estazolam can adjust the neurotransmitter secretion in patients with insomnia after stroke to a certain extent, but dexzopiclone is better than estazolam in regulating the secretion of neurotransmitters.

The occurrence of insomnia after stroke is not only related to the changes in neurotransmitter secretion, but also closely related to the changes in secretion of various nerve cytokines[14]. BDNF and NGF are cytokines with neurotrophic function, which can act on neurons and promote their regeneration, and can also promote the growth of axons and the reconstruction of nerve function; in the occurrence of stroke, neuron damage can cause the reduction of BDNF and NGF secretion, thus weaken the neurotrophic state and lead to the corresponding mental symptoms, such as insomnia, anxiety, depression, etc[15]. TNF-α and IL-6 are pro-inflammatory cytokines that can cause inflammatory cell infiltration and inflammatory response activation in the stroke lesions, then affect the secretion of a variety of neurotransmitters and cause the occurrence of insomnia[16,17]. The analysis of the difference in above cytokines before and after dexzopiclone and estazolam treatment showed that compared with those before treatment, serum BDNF and NGF levels of both groups significantly increased whereas TNF-α and IL-6 levels significantly decreased after treatment, and serum
BDNF and NGF levels of dexzopiclone group after treatment were higher than those of estazolam group whereas TNF-α and IL-6 levels were lower than those of estazolam group. This means that although both dexzopiclone and estazolam can regulate the secretion of cytokines in patients with insomnia after stroke to a certain extent, dexzopiclone is better than estazolam in regulating cytokine secretion.

Persistent insomnia is a strong stressor for patients with stroke, which can activate the stress response in the body and cause disturbance in the internal environment.[18] Adrenal cortex is the endocrine gland that plays an important role in the process of stress, and constant stimulation from the stressors can make the pituitary gland secrete more ACTH and act on adrenal cortex to promote the secretion of Cor. CRP is a kind of acute phase protein, and the hepatocytes synthesize and secrete a lot of CRP when the body is in the acute event of stress. SOD and GSH are metabolic enzymes with anti-oxidative stress effect. During the over-activation of the stress response, the above two antioxidant enzymes show a tendency of compensatory high expression and secretion. The analysis of the difference in above stress indexes before and after dexzopiclone and estazolam treatment showed that compared with those before treatment, serum ATCH, Cor, CRP, SOD and GSH levels of both groups significantly decreased after treatment, and serum ATCH, Cor, CRP, SOD and GSH levels of dexzopiclone group after treatment were lower than those of estazolam group. This means that although both dexzopiclone and estazolam can relieve the stress rate and reduce the generation of stress products in the patients with insomnia after stroke to a certain extent, the dexzopiclone has more significant inhibiting effect on stress reaction than estazolam.

Thus, the dexzopiclone can better regulate the secretion of neurotransmitters and nerve cytokines and relieve the stress state in patients with insomnia after stroke.

References