Effect of Timiperone, a New Antipsychotic Drug, on the Sleep-Wakefulness Cycle in Cats

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Accepted August 22, 1985

Abstract—The effect of timiperone, a new antipsychotic drug, on the sleep-wakefulness cycle in cats was assessed by EEG, EMG and eye movement potential. Timiperone (0.03 to 0.3 mg/kg, i.p.) dose-dependently increased the slow wave sleep (SWS) time and decreased the paradoxical sleep (PS) time. Further, the onset of the first period of PS was delayed, and the number of PS phases tended to be decreased after the 0.3 mg/kg dose. These results suggest that the neurological control of the cerebral dopaminergic system might be at least in part attributable to the effect of timiperone on sleep mechanisms.

Timiperone, 4'-fluoro-4-[4-(2-thioxo-1-benzimidazolyl)piperidino]butyrophenone, possesses a potent antipsychotic activity with lesser liability to an extrapyramidal action in experimental animals (1, 2). We have previously shown that timiperone produced a moderate synchronization of spontaneous EEG in acute experiments (3) and that this action may be attributed to a suppression of the ascending reticular activating system (4). Based on these findings, the present study was undertaken to investigate the effect of timiperone on the sleep-wakefulness cycle using cats with chronically implanted electrodes in comparison with that of the other butyrophenone, haloperidol.

Six adult cats of either sex (2.3–3.1 kg) were used, and chronic implantation of electrodes was performed under pentobarbital anesthesia (30 mg/kg, i.p.). The screw electrode for the cortical EEG was placed over the somatosensory cortex, and the subcortical coaxial electrode was stereotaxically inserted into the hippocampus using the brain atlas of Reinoso-Suárez (5). Two silver wires were implanted deeply into the neck muscle for EMG recording, and eye movement potential was recorded from a dental screw in the left orbit. The recording electrodes and the indifferent electrode in the frontal bone were soldered to a miniature socket and fixed to the skull with dental cement.

The animals were allowed two weeks to recover from surgery and individually housed in the plastic observation box (40 x 40 x 60 cm) placed in the air conditioned and sound attenuated room with dim lighting. All recordings were made with an ink writing electroencephalograph (San-Ei, model la-52). Behavior of the cats was simultaneously monitored by a videocamera.

The sleep-wakefulness cycle of the cats was measured for 6 hours (9 a.m. to 4 p.m.). The records were visually scored in 1-min epochs into the following five categories: arousal, rest, slow wave light sleep (SWLS), slow wave deep sleep (SWDS) and paradoxical sleep (PS). After EEG recording, percentage of awaking (arousal+rest), SWS (SWLS+SWDS) and PS time were calculated.

At the start of recording, the animal received intraperitoneal injection of either saline or timiperone hydrochloride (Daiichi Seiyaku) and haloperidol hydrochloride (synthesized in our institute) which were dissolved in physiological saline. In an experimental period of two days, the first day was taken for the control recording (saline), and the second day was used for a recording under
Table 1. Effects of timiperone and haloperidol on several variables of sleep-wakefulness cycle in cats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg, i.p.)</th>
<th>A/TRT</th>
<th>TS/TRT</th>
<th>SWS/TRT</th>
<th>PS/TRT</th>
<th>PS latency (min)</th>
<th>No. of PS phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>43.7±7.9</td>
<td>56.3±7.9</td>
<td>35.7±6.2</td>
<td>20.6±3.1</td>
<td>41.0±8.5</td>
<td>10.0±2.7</td>
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<tr>
<td>Timiperone</td>
<td>0.03</td>
<td>42.3±5.7</td>
<td>57.7±5.7</td>
<td>40.7±3.2</td>
<td>17.0±3.0</td>
<td>41.8±7.8</td>
<td>7.0±0.8</td>
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<tr>
<td>Control</td>
<td></td>
<td>38.5±6.0</td>
<td>61.5±6.0</td>
<td>42.9±4.3</td>
<td>18.6±1.7</td>
<td>31.0±4.7</td>
<td>9.8±1.8</td>
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<tr>
<td>Timiperone</td>
<td>0.1</td>
<td>35.5±5.3</td>
<td>64.5±5.3</td>
<td>51.0±5.5</td>
<td>13.5±1.3</td>
<td>34.5±4.8</td>
<td>7.8±1.1</td>
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<tr>
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<td></td>
<td>37.5±2.4</td>
<td>62.5±2.4</td>
<td>44.5±1.3</td>
<td>18.0±1.8</td>
<td>34.6±3.1</td>
<td>11.7±2.6</td>
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<tr>
<td>Timiperone</td>
<td>0.3</td>
<td>34.9±4.2</td>
<td>66.1±4.2</td>
<td>57.5±7.7*</td>
<td>7.6±1.4**</td>
<td>71.8±14.7*</td>
<td>4.8±0.9</td>
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<tr>
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<td>38.6±8.0</td>
<td>61.4±8.0</td>
<td>43.9±3.9</td>
<td>17.5±2.4</td>
<td>32.8±3.5</td>
<td>9.5±1.9</td>
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<td>Haloperidol</td>
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<td>40.6±2.7</td>
<td>59.4±0.9</td>
<td>46.4±3.2</td>
<td>13.0±0.9</td>
<td>35.3±8.2</td>
<td>7.0±0.4</td>
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<tr>
<td>Control</td>
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<td>41.5±5.6</td>
<td>58.5±5.6</td>
<td>38.6±4.0</td>
<td>19.9±1.9</td>
<td>34.8±2.7</td>
<td>10.5±1.2</td>
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<tr>
<td>Haloperidol</td>
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<td>9.4±2.0**</td>
<td>59.5±24.8</td>
<td>7.8±0.8</td>
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</tbody>
</table>

Abbreviations are as follows: A, arousal; SWS, slow wave sleep; PS, paradoxical sleep; TRT, total recording time; TS, total sleep time. Recording was carried out for 6 hours, and the values are expressed as a mean percentage of total recording time and standard error (n=4). *P<0.05 and **P<0.01: significant difference from the control (saline treated).
the treatment of drug. The cats were used repeatedly at intervals of at least a week. The statistical significance of differences between the control and treated group was analyzed by Student’s t-test. At the end of each experiment, the stereotaxic placement of the subcortical electrode was verified histologically.

Timiperone and haloperidol at the doses used did not produce appreciable changes in the electroencephalographic pattern, but they altered the sleep-wakefulness cycle (Table 1 and Fig. 1). Following timiperone (0.03 to 0.3 mg/kg), no changes could be observed in the awaking time when compared to each saline treated animal. However, the PS time was dose-dependently decreased, while the SWS time was dose-dependently increased. There were significant changes in PS and in SWS after the 0.3 mg/kg dose of timiperone. In addition, the number of PS phases was reduced, and this reduction was in the range of 40–66% as compared with the control values at the highest dose. Moreover, the PS latency was significantly lengthened. Similarly, haloperidol (1 and 3 mg/kg) dose-dependently increased SWS time and decreased PS time. The increase in SWS and a decrease in PS were statistically significant.

It is well known that antipsychotic drugs could influence the sleep mechanisms (6, 7). In the present experiments, the effect of timiperone on the sleep-wakefulness cycle was qualitatively similar to that of haloperidol. This finding is in agreement with the observation of Monti (8) who described an increase in the SWS time and a decrease in the PS time after intraperitoneal haloperidol in cats. The suppressive effect of timiperone on PS was observed at a dose as low as 0.03 mg/kg and more markedly at 0.3 mg/kg. Its potency was approximately 10 times higher than that of haloperidol.

On the other hand, it was shown that timiperone significantly potentiated the caudate spindle evoked by electrical stimulation of the caudate nucleus (4). A recent report indicates that the caudate spindle is enhanced by dopamine receptor antagonists such as haloperidol and pimozide and that these enhancing actions are completely antagonized by the dopaminergic agonist, apomorphine (9). In our previous paper (4), timiperone suppressed apomorphine- and methamphetamine-induced stereotyped behavior in rats more strongly than did haloperidol, and its potency was approximately 8–10 times higher than that of haloperidol.

From these findings, it was considered that the central dopaminergic system might be partially involved in the effect of timiperone on sleep mechanisms in cats. However, according to Jouvet (10), sleep cycles are modulated by the other brain biogenic amines such as noradrenaline and serotonin. Therefore, further investigations are required with respect to the detailed mechanisms of the effect of timiperone on the sleep cycle.

References


