REL-1017 (esmethadone) DID NOT PRODUCE INITIAL OR CUMULATIVE NEUROTOXIC EFFECTS OR OTHER EVIDENCE OF DAMAGE TO CORTICAL NEURONS

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BACKGROUND

Olney’s lesions Definition

Olney’s lesions are characteristic vacuolations (feature of neurotoxicity and potentially irreversible damage in the CNS), which can be seen by light microscopy in neurons of rats, mainly in posterior cingulate and retrosplenial cortices, after administration of select NMDAR channel blockers, like MK-801, ketamine and dextromethorphan.

REL-1017 (esmethadone) is a promising NMDAR channel blocker

<table>
<thead>
<tr>
<th>Test item</th>
<th>IC50 (µM)</th>
<th>NMDAR Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>REL-1017</td>
<td>64</td>
<td>NMDA-1</td>
</tr>
<tr>
<td>Esmethadone</td>
<td>35</td>
<td>NMDA-1</td>
</tr>
<tr>
<td>Ketamine</td>
<td>27</td>
<td>NMDA-1</td>
</tr>
<tr>
<td>(-)-Ketamine</td>
<td>0.26</td>
<td>NMDA-1</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>51</td>
<td>NMDA-1</td>
</tr>
</tbody>
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REL-1017 (esmethadone) is the d-opioid isomer of the racemic mixture d,l-methadone. REL-1017 has been shown to have robust, rapid and sustained antidepressant effects in humans (Relmada data on file). Esmethadone is free from clinically relevant opiate side effects and free from dissociative effects seen with other NMDAR channel blockers. Esmethadone has been shown to exert antidepressant-like effects in all tested murine models of depression. Esmethadone’s estimated potency at NMDAR subtypes in relation to FDA approved NMDAR channel blockers and MK-801 is shown in the table above (Relmada data on file).

REL-1017 (esmethadone) is a promising low affinity, low potency NMDAR channel blocker, presently undergoing Phase 3 clinical trials for the treatment of major depressive disorder (MDD).

OBJECTIVES

To determine if the novel NMDAR antagonist REL-1017 administered once daily at three different doses for 4 days would cause cumulative neurotoxic effect and potential progression to irreversible damage (Olney’s lesions) in the rat brain.

STUDY DESIGN

Group randomization

1) vehicle

2) REL-1017

3) Racemic methadone 31.25/50 mg/kg/day

4) MK-801 5/2 mg/kg/day

Brain of animal treated either with REL-1017 or with racemic methadone did not show the microscopic features of Olney’s lesions

In this experiment, the administration of the novel NMDAR channel blocker REL-1017 (esmethadone) did not produce initial or cumulative neurotoxic effects or other evidence of damage to cortical neurons in normal rats.

RESULTS

The brain of animals treated with REL-1017 or with racemic methadone did not show the microscopic features of Olney’s lesions. In contrast, the animals treated with MK-801 (positive control) showed, as expected, neuronal vacuolation and necrosis (hallmarks of Olney’s lesions) (Fic, 1996). In particular, daily administration via oral gavage of REL-1017 for up to 4 days at all tested doses to both male and female SD rats did not produce Olney’s lesions. Compared to REL-1017 at any dose and vehicle, the effects of MK-801 on cortical neurons were statistically significant (p<0.01). Furthermore, the oral administration of methadone racemate to both male and female SD rats did not produce Olney’s lesions.

CONCLUSIONS

In this experiment, the administration of the novel NMDAR channel blocker REL-1017 (esmethadone) did not produce initial or cumulative neurotoxic effects or other evidence of damage to cortical neurons in normal rats.

REFERENCES


DISCLOSURES

This research was sponsored by Relmada Therapeutics, Inc. Drs. Manfredi and Pappagallo are paid consultants of Relmada Therapeutics, Inc. Dr. Manfredi is an inventor on esmethadone patents and other patents and patent applications.