MedicalXpress

Deuterated sigma-1 agonist showed anti-seizure activity in traumatic brain injury models

March 23 2015

Research results published in the *Journal of Neurotrauma* and conducted by the Walter Reed Army Institute of Research (WRAIR) as part of a collaboration with Concert Pharmaceuticals, Inc. showed that a novel deuterium-containing sigma-1 agonist invented at Concert, called C-10068, demonstrated anti-seizure and anti-inflammatory effects in a preclinical model of traumatic brain injury (TBI). C-10068, a novel metabolically-stabilized morphinan derivative, is based on a compound first identified at WRAIR in the 1990s as possessing anticonvulsant properties. In the current study C-10068 demonstrated a statistically significant reduction in frequency and duration of seizures following TBI in a preclinical model developed at the WRAIR. C-10068 affects multiple neurochemical pathways, including sigma-1 receptors which have a widespread modulatory role in the central nervous system (CNS).1 The C-10068 study was conducted under a Cooperative Research and Development Agreement (CRADA) granted to Concert in collaboration with the WRAIR.

"We are highly encouraged by the results with C-10068 in this study. The compound previously demonstrated anti-seizure activity in multiple non-TBI animal models, and our preclinical testing with C-10068 similarly showed significant seizure protection in our unique model of refractory, TBI-induced brain seizure activity," said Dr. Frank Tortella, whose team conducted the studies for this CRADA in his lab at WRAIR, and who serves as Chief of the Brain Trauma Neuroprotection and

Neuroplasticity Branch in the Center for Military Psychiatry and Neuroscience at the WRAIR.

"C-10068 represents an opportunity in our R&D pipeline that may be considered for advancement into the clinic in the future based on additional preclinical studies," said Nancy Stuart, Chief Operating Officer of Concert Pharmaceuticals. "C-10068 is another example of how applying deuterium chemistry can enhance the pharmacologic properties of novel therapeutics for CNS diseases, and builds on our pipeline of drug candidates for a range of CNS diseases including spasticity, narcolepsy, Alzheimer's agitation and major depressive disorder."

The purpose of the study published in the *Journal of Neurotrauma* was to evaluate the anti-seizure dose-response of C?10068 in a novel rat model of nonconvulsive seizures (NCS) induced by penetrating ballistic-like brain injury (PBBI). C-10068 was administered by continuous intravenous infusion in a saline vehicle, and the control group received vehicle alone. The results showed:

- Reduction in NCS incidence: While 75% of vehicle-treated PBBI animals experienced NCS which occurred spontaneously during the 72 hour recording period, those treated with C-10068 had a 40-50% reduced NCS incidence independent of dose.
- Reduction in NCS frequency and duration: On average, vehicle-treated animals had 8.3 NCS events per animal with total seizure duration of 379 seconds per animal. C-10068 treatments dose-dependently (low-to-high dose) reduced NCS frequency by 20%, 42%, and 70% (p