**POSTER NUMBER**

19

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**ABSTRACT CATEGORY**

Basic Research

**ABSTRACT TITLE**

Effects of ATH434, a Clinical Phase Small Molecule Drug Candidate with Moderate Affinity for Iron, in Hemiparkinsonian Macaques

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OBJECTIVE

(1) Determine whether orally dosed ATH434 improves motor performance in a non-human primate hemiparkinasonian model. (2) Relate clinical observations to changes in brain iron, striatal integrity, and tyrosine hydroxylase positive (TH+) neurons in the substantia nigra (SN).

BACKGROUND

ATH434 is a novel small molecule drug candidate currently in phase 2 for Multiple System Atrophy based on efficacy in multiple murine parkinsonian models. ATH434 is postulated to redistribute excess labile cellular iron by restoring impaired cellular export. In contrast to high-affinity iron binding drugs tested in Parkinson’s disease, ATH434’s moderate iron affinity precludes it from interfering with endogenous dopamine synthesis or iron trafficking proteins such as transferrin.

METHODS

Macaques received a single right carotid infusion of MPTP, a model of acute oxidative injury (Day 0), followed by daily oral doses of vehicle or ATH434 (3, or 10 mg/kg/day) from Day 3 to
Weeks 12-14 (final n=2-3/group). Neurologic Deficit Scores (NDS) were recorded prior to MPTP infusion and on Day 2 and Weeks 4, 8, and 12. Terminal endpoints included SN iron (mass spectrometry), dopamine transporter (DAT) density (PET and immunocytochemistry), synaptophysin (western blot), and total TH+ SN neurons number (stereology).

RESULTS

Day 2 left side-specific and generalized NDS indicated significant parkinsonian effects in all macaques. At study-end, all ATH434-treated and 1 vehicle-treated macaque had improved or stabilized NDS; the remaining 2 vehicle-treated macaques demonstrated worsening symptoms. Reduced NDS correlated with increased right-side striatal synaptophysin and reduced right-side SN iron. Striatal DAT confirmed similar lesions across groups (approximate 50% reduction in DAT). Neuroprotection of SN neurons was not evident.

CONCLUSION

This first-in-primate study suggests that ATH434 may improve motor scores by reducing excess iron in areas of pathology and enhancing synaptic connectivity in the nigrostriatal pathway. The severity of oxidative injury may have limited the ability of the treatment to preserve neurons.