ASSESSMENT OF A NEW TREATMENT (BN82451) AGAINST L-DOPA-INDUCED DYSKINESIA IN PARKINSONIAN MACAQUES

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L-DOPA pharmacotherapy alleviates parkinsonian symptoms but with time induces abnormal involuntary movements in most patients.

To evaluate the anti-dyskinetic effect of a novel multitargeting molecule, BN82451, on L-dopa-induced dyskinesia (LID) in a primate MPTP model of Parkinson’s disease.

Nine male Macaca fascicularis were intoxicated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; 0.2mg/kg i.m.). Six were treated with increasing daily L-dopa doses (100:25mg levodopa:benserazide) to induce LIDs. Acute and subchronic 5-day treatments with BN82451 (5mg/kg), Amantadine (5mg/kg) or their solvent poly ethylene glycol-400 were administered together with L-dopa. Animals were filmed on the 1st and 5th day of treatment. Ethovision® and The Observer® software were used to analyse locomotor behaviour and dyskinesia. Brains were extracted and post-fixed for histology while fresh biopsy punches were analyzed by qPCR and Western blotting.

Acute and sub-chronic treatments with BN82451 resulted in overall LID decreases of 43% and 34% respectively. These effects were not associated with a reduction in locomotion. In contrast, animals treated with Amantadine showed changes in LID that were directly related to alterations (decrease, increase) in total distance moved. ¹⁸F-fluoro-L-dopa positron emission tomography experiments were performed to rule out that BN82451 directly interferes with L-dopa metabolism. Histology indicates that all parkinsonian primates had similar nigro-striatal deafferentation levels. Preliminary data suggest that BN82451 anti-dyskinetic effect relates to changes in the expression of genes involved in the pathogenesis of LID.

BN82451 might be an interesting therapy for dyskinetic PD patients since it is more efficacious than Amantadine in decreasing total LIDs in our primate model without impairing spontaneous locomotor activity.