P17: Safety, Tolerability and Cerebral Blood Flow After Single Doses of the β_2 Adrenoceptor agonist, Clenbuterol, in Patients with MCI or Parkinson's Disease

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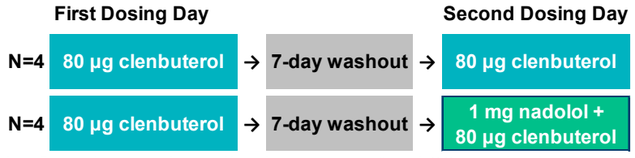
Introduction

Early-stage deficiency in the noradrenergic system of the brain is a common pathogenic mechanism in multiple neurodegenerative disorders including Alzheimer's and Parkinson's disease (PD) (Braak et al., J Neuropathol Exp Neurol 2011). Depletion in noradrenergic signaling, originating largely from neurons in the locus coeruleus, may lead to reduced neuronal activity in key cortical and limbic areas including the prefrontal cortex, thalamus, hippocampus and amygdala. This can have a significant impact on associated functions including attention, learning and working memory. Activation of excitatory receptors of the ascending noradrenergic system, and β_2-adrenoceptors (β_2-AR) in particular, could therefore be promising therapeutic targets in neurodegenerative disorders. As long-term daily exposure to β_2-agonists will impart undesirable peripheral effects (including tachycardia, hyperglycemia and hypokalemia), co-administration of a peripherally restricted β-blocker may be beneficial to control the cardiovascular and metabolic effects of chronic treatment.

Objectives

- Primary: evaluate safety and cerebral blood flow effects (CBF) of the β_2-adrenoceptor agonist, clenbuterol, in patients with MCI or PD.
- Secondary: evaluate the effects of pre-administration of 1 mg nadolol, a β-blocker with minimal brain penetration, on the CNS and peripheral effects of clenbuterol.

Methods



- On the first dosing day, all subjects received 80 µg clenbuterol.
- On the second dosing day, all subjects received 80 µg clenbuterol again as monotherapy (N=4) or 2.5 hours after a dose of 1 mg nadolol (N=4).
- Safety and tolerability were evaluated by AEs, ECGs, vital signs, and labs.
- CBF was measured by single-delay pseudo-continuous arterial spin labeling magnetic resonance imaging (pCASL MRI, 3T; GE Signa PET/MR) prior to (baseline), and 3 hours after administration of clenbuterol.
- CBF changes from baseline to post-dose were calculated and expressed as the Mean Relative Difference (MRD, %) in perfusion.

Figures

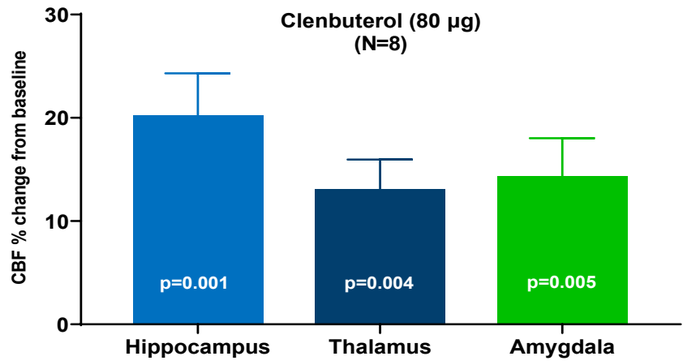


***Figure 1**. Administration of 80 µg clenbuterol significantly increased regional cerebral blood flow. Data are plotted as mean ± SEM CBF % change from pre-dose on Day 1.*

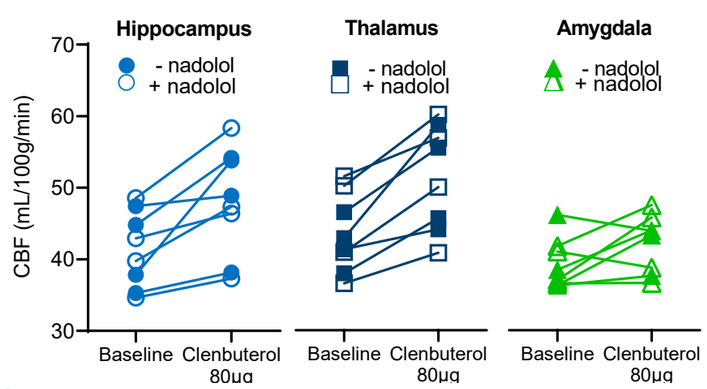


***Figure 2**. Administration of nadolol had no effect on the clenbuterol induced regional changes in CBF (individual CBF observations).*

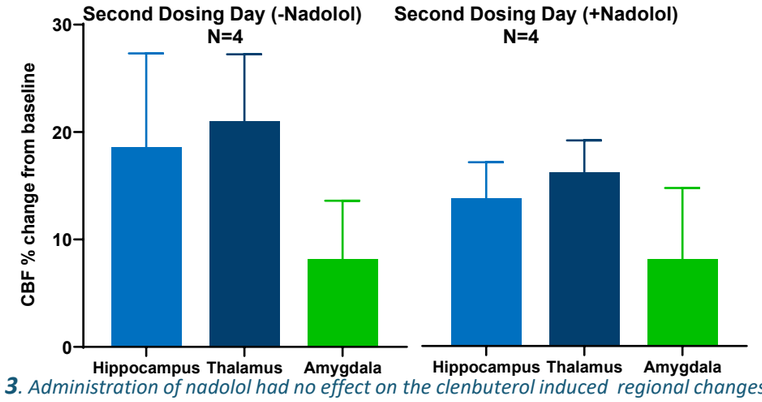


***Figure 3**. Administration of nadolol had no effect on the clenbuterol induced regional changes in CBF (mean ± SEM CBF % change from pre-dose).*

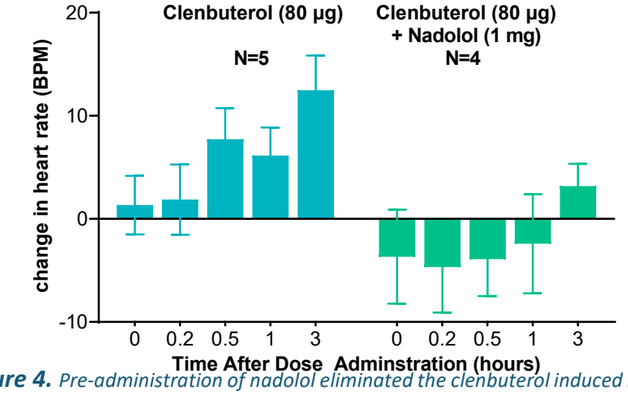


***Figure 4.** Pre-administration of nadolol eliminated the clenbuterol induced increase in heart rate. Data are plotted as mean ± SEM heart rate change from pre-dose on Day 1*

Results

- Eight patients with neurodegenerative disorders (7 MCI, 1 PD) between the ages of 58 and 71 years were enrolled in the study.
- Significant increases in CBF from pre-dose were observed following treatment with 80 µg clenbuterol (Figure 1).
- These effects were generally reproducible when clenbuterol was administered again on the second dosing day (Figure 2) as monotherapy (N=4, Figure 3A) or with 1 mg nadolol (N=4, Figure 3B).
- Single doses of 80µg clenbuterol were safe and well tolerated. The most common effects were known side effects of β_2-agonists including increases in heart rate (mean[SD] = 12.9 [8.2] bpm, Figure 4), tremor (4/8 subjects), and palpitations (1/8 subjects). These effects were mostly eliminated by pre-treatment with 1mg of nadolol.

Conclusions

Increases in CBF are expected under conditions of increased neuronal activity. This phenomenon of neurovascular coupling arises from integrated responses from multiple cell types, many of which are known to express β_2-AR, including neurons, microglia, oligodendrocytes and astrocytes. The observed increases in CBF may therefore suggest that the deficiency in the noradrenergic system that arises early in neurodegenerative disease progression may be at least partially restored by direct β_2-AR activation with clenbuterol.