CHAPTER 3: PHARMACOLOGY OF CENTRAL NERVOUS SYSTEM DRUGS AND CONSIDERATIONS IN POSTURAL CONTROL

Drugs Affecting Dopaminergic Neurotransmission

Pharmacology

As this discussion focuses on cholinergic contributions to PD, the pharmacology of dopaminergic drugs will be discussed only in brief. Levodopa is the "gold standard" treatment for motor symptoms of PD. Levodopa is a pro-drug that is capable of crossing the blood-brain barrier (BBB). Levodopa is decarboxylated to dopamine once it has entered the CNS via DOPA-decarboxylase. Because DOPA-decarboxylase is also present in the periphery, levodopa is commercially supplied in combination with carbidopa, which inhibits the peripheral conversion of levodopa to dopamine. Dopamine itself is unable to cross the BBB. Administration of levodopa thereby increases the amount of dopamine available for binding to dopamine receptors in the striatum. Levodopa and carbidopa are also available in combination with entacapone, an inhibitor of catechol-O-methyl transferase. This enzyme is also responsible for the peripheral and central breakdown of levodopa and monoamines such as dopamine. Other DRTs consist of dopamine agonists such as pramipexole and ropinirole that bind to and activate dopamine receptors in the striatum. Levels of dopamine may also be increased by inhibitors of monoamine oxidase, such as selegiline. Monoamine oxidases are a group of enzymes responsible for inactivating dopamine and other neurotransmitters in the CNS (Micromedex® Product Monographs for Sinemet®, Comtan®, Mirapex®, Requip®, Eldepryl®).

Efficacy

The introduction of DRT has drastically improved motor symptom control in PD. Postural and gait-related symptoms also tend to improve with DRT, however this is often limited to the early stages of the disease and these symptoms are significantly less

responsive to DRT than motor symptoms (Vu, Nutt, & Holford, 2012). These symptoms usually become refractory to DRT in later stages where it is likely that the disease has spread to involve non-dopaminergic pathways (Kim et al., 2013).

The study by Vu and colleagues (Vu et al., 2012) was a relatively large modeling study comprising a cohort of 795 initially untreated patients with PD. These patients were followed for nearly 8 years for the cardinal features of tremor, rigidity, bradykinesia, and postural instability and gait disorder (PIGD) derived from the total unified Parkinson's disease rating scale (total UPDRS), cognitive status as per the mini-mental status exam (MMSE) and depression from the Hamilton depression scale (HAM-D). The PIGD subscale was the sum of falling, freezing, walking, gait and postural stability. Using a quantitative prediction model, the authors found that levodopa had a relatively low potency for effect on PIGD (ED_{50} of 1237 mg/day compared to 7–24 mg/day for other motor and non-motor symptoms).

Clinical Trials

Bloem and colleagues (Bloem et al., 1996) conducted a study that compared 23 patients with idiopathic PD and 24 healthy controls. Patients stood on a forceplate and received 20 sequential 4-degree toes-up rotations. Patients with PD were tested in the OFF (i.e. no DRT for at least 12 hours) and ON state (i.e. 1 hour after DRT) and controls tested and re-tested after 1 hour. Destabilizing medium latency responses in the gastrocnemius muscles and long latency responses in the tibialis anterior muscles were recorded via EMG. Changes in CoP (foot) and CoG were also assessed. In the OFF state, increased ML amplitudes and decreased long latency amplitudes were observed in PD patients compared to controls (both ps <0.05). An increased posterior CoG displacement was observed and the initial forward (i.e. destabilizing) movement of the CoP increased, with a delayed posterior movement of the CoP (i.e. corrective action of long latency responses). In the ON state, medium latency amplitudes reduced, however they were still elevated compared to controls. The displacement of the CoP was only marginally improved in the ON state and no improvements were observed in the later postural

responses. Therefore, the increased posterior CoG displacement was also unimproved in the ON state. Because these postural responses appear to be relatively non-responsive to DRT. These observations provide evidence of non-dopaminergic pathways in postural instability.

In a similar study, Horak and colleagues (F. Horak, Frank, & Nutt, 1996) showed that the main postural deficit in PD was a reduced capacity to rapidly generate EMG bursts and subsequent force against the support surface following external perturbations, which may be explained by bradykinesia and rigidity. Surprisingly, patients in the OFF state were able to scale postural responses to changes in displacement velocity and amplitude, however, they showed decreased torque responses overall. As above, these patients showed abnormally small agonist and excessive antagonist activity. Muscle EMG tone was also higher in the OFF state compared to controls. Little changed in the ON state except that levodopa decreased background EMG tone and passive stiffness following perturbations. In fact, worsened scaling abilities were observed in the ON state. DRT did not affect the latencies or order of postural responses to external perturbations. These observations led the authors to conclude that the role of dopamine may be relegated to the control of background muscular tone and the production of adequate EMG responses and their related forces for postural responses.

Drugs Affecting Noradrenergic Neurotransmission

Pharmacology

As this discussion focuses on cholinergic contributions to PD, the pharmacology of noradrenergic drugs will be discussed only in brief. Because of the observation that methylphenidate (MPH) is a central nervous system stimulant traditionally used for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults, it has gained attention in PD and PDD as a potential pharmacologic treatment for the cognitive and attention deficits characteristic of the disease. MPH inhibits the reuptake of dopamine and norepinephrine from the synapse via blockade of presynaptic

norepinephrine and dopamine transporters, thereby increasing post-synaptic receptor activation in the striatum and prefrontal cortex (Kimko, Cross, & Abernethy, 1999). Other drugs such as idazoxan and select stereoisomers of dihydroxyphenylserine have been studied in PD, however these drugs are considered experimental (Grimbergen et al., 2009).

Clinical Trials

It appears as if MPH may have some benefit in ameliorating freezing of gait in PD. A small double-blind crossover study has shown that single doses of MPH 20 mg may improve gait speed, timed-up-and-go test and stride-time variability in older adults (Ben‐Itzhak, Giladi, Gruendlinger, & Hausdorff, 2008). Similarly, freezing of gait improved in an open-label pilot study of 5 PD patients treated with single doses of MPH 10 mg (Auriel, Hausdorff, Herman, Simon, & Giladi, 2006).

MPH may represent a therapeutic option for freezing of gait in advanced PD refractory to DRT and DBS. In their randomized, placebo-controlled, double blind, multi-centre trial, Moreau and colleagues (Moreau et al., 2012) compared 90 days of MPH at a dose of 1mg/kg/day to placebo in PD patients younger than 80 years old with severe gait abnormalities and freezing of gait despite DRT and subthalamic DBS. The primary outcome of the number of steps taken in the stand-walk-sit test was measured under an acute levodopa challenge to control for the confounding effects of levodopa. In the 65 patients completing the study (n=69 randomized), patients in the methylphenidate group made fewer steps at 90 days compared to patients in the placebo group (median of 31 versus 33 steps; p=0·017). Adverse effects were more common in the MPH group with more patients experiencing heart rate elevations and weight loss.

The results of the above trial contradict an earlier double blind, placebo-controlled crossover trial showing no benefit of MPH at doses of up to 80 mg per day on gait as measured by stride length and velocity (Espay et al., 2011). However, this was a smaller trial with only 17 patients completing the study and a different outcome was assessed.

Therefore, the risks and benefits must be considered in each individual patient before treatment with MPH can be recommended. According to the literature, the study of MPH for postural instability has not been formally reported.

Drugs Affecting Cholinergic Neurotransmission

Pharmacology

The major target of drug therapy in AD and PDD is AChE, an enzyme responsible for the breakdown of ACh in the central nervous system via hydrolysis. Inhibitors of this enzyme serve to decrease the breakdown of ACh in the synaptic cleft, thereby increasing the levels of ACh available for binding to post-synaptic receptors (Pope, Karanth, & Liu, 2005). Currently available AChEIs include donepezil, galantamine and rivastigmine, with each having slightly different pharmacokinetic and pharmacologic properties. Of the three, rivastigmine is the only AChEI approved for the treatment of PDD in Canada.

Rivastigmine is reversible inhibitor of the AChE and the butyrylcholinesterase enzyme. Inhibition of AChE results in the central effects of increased ACH, however the additional activity of rivastigmine at butyrylcholinesterase is responsible for its increased peripheral effects compared to donepezil, which is specific for the AChE enzyme (Weinstock, 1999). Like ACh, rivastigmine binds to the active site of AChE and undergoes hydrolysis. This hydrolysis reaction produces a phenolic compound and a carbamyl moiety that remains bound in the enzyme active site (Anand & Gharabawi, 1996). This benefit of rivastigmine lies in the fact that this carbamyl moiety remains bound, and thus inactivates the enzyme, for a relatively long period of time compared to the acetyl moiety produced by hydrolysis of ACh. The acetyl derivative of ACh dissociates within microseconds from the enzyme active site, allowing the enzyme to continue degrading ACh (Polinsky, 1998). Alternatively, a single-dose study has shown that 3 mg of rivastigmine induces inhibition of AChE in the cerebrospinal fluid for at least 10 hours (Enz, Meier, & Spiegel, 1994).

A more recent, yet small, PET study comparing AD patients on donepezil (n=6) to patients on rivastigmine (n=5) shows that rivastigmine reduced AChE activity by 37% in the frontal (p=0.003, Bonferroni corrected), 28% in the temporal (p = 0.03, uncorrected) and 28% in the parietal cortex (p = 0.05, corrected) (Kaasinen et al., 2002). The results were similar for donepezil. The authors attribute the observation that these agents were more active in the frontal cortex to that fact that temporoparietal AChE is diminished in AD.

Cholinesterase Inhibitors and Fall Risk

The observation that anticholinergic medications tend to increase the risk of falling has served as a springboard for the generation of cholinergic hypotheses in postural control. However, others argue that cholinesterase inhibitors may actually increase fall risk via their adverse cardiovascular effects. Because of their cholinergic effects, AChEIs may alter cardiovascular autonomic tone and indeed, heart rate variability, a measure reflecting cardiac autonomic function, is impaired in patients with dementia taking donepezil (McLaren, Allen, Murray, Ballard, & Kenny, 2003). In their population-based cohort study, Gill and colleagues reported that patients using AChEIs for dementia experience more hospital visits for symptomatic bradycardia, syncope, permanent pacemaker insertion and hip fractures than matched controls (Gill et al., 2009). These observations are important to consider, especially in a PD population where up to half of patients may experience orthostatic hypotension (Ziemssen & Reichmann, 2010).

Clinical Trials

Systematic review has confirmed that cholinesterase inhibitors are effective in improving cognitive function, behavioural disturbances and activities of daily living in patients with PDD (Rolinski, Fox, Maidment, & McShane, 2012). In particular, Wesnes and colleagues demonstrated that rivastigmine improves attention compared to placebo in their randomized, 24-week, double blind, multi-centre trial in 487 patients with PDD (Wesnes, McKeith, Edgar, Emre, & Lane, 2005).

With regards to executive dysfunction, Schmitt and colleagues analyzed the secondary outcomes of the landmark EXPRESS trial (Emre et al., 2004), which initially established the efficacy of rivastigmine for PDD (Schmitt, Farlow, Meng, Tekin, & Olin, 2010). Of the 541patients in the EXPRESS trial, only a portion had data for Letter Fluency (n=402), Card Sorting (n=71) and Color-Word Interference subtests (n=97), and the Symbol Digit Modalities Test (n=65). These are all components included in the Delis-Kaplan Executive Function System (D-KEFS) measures of executive function. For Letter Fluency, rivastigmine improved the number of correct responses, set loss errors, and responses made (all $p < 0.05$), but not repetition errors. Improvements in Card Sorting ($p= 0.03$), and more correct substitutions on the Symbol Digit Modalities Test ($p= 0.02$) were also observed. Therefore, along with improving cognitive and behavioural function, rivastigmine also appears to improve attention, executive functions, problem solving and planning, which may have implications for postural control and balance.

With regards to gait velocity and variability, both are hypothesized to be measures of fall-risk (Montero-Odasso et al., 2005; Sheridan, Solomont, Kowall, & Hausdorff, 2003). In this instance, donepezil has been studied in a small open-label trial comparing donepezil (5 mg/day for one month then 10 mg/day) treated AD patients (n=6) with untreated elderly patients with mild cognitive impairment (n=8) (Montero-Odasso, Wells, & Borrie, 2009). After both 1 and 4 months of treatment, patients on donepezil showed significant improvements in gait velocity (under both single and dual-task conditions) from baseline. When compared to controls, donepezil-treated patients also exhibited less gait variability. Building on this study, the authors completed a phase II trial of donepezil in 43 patients with mild AD (Montero-Odasso et al., 2015). After 4 months of treatment, both normal and dual-task gait velocity were improved (108.4 ± 18.6 to 113.3 ± 19.5 cm/s, $p = 0.010$; and 80.6 ± 23.0 to 85.3 ± 22.3 cm/s, $p = 0.028$, respectively). Step time variability did not change significantly.

However, there are marked differences between PDD and AD as previously mentioned. Particular to falls in PD, Chung and colleagues have embarked on a study of

cholinesterase inhibitor for falls in PD (Chung et al., 2010). As outlined in previous sections, the authors also rationalize the use of donepezil for falls based on the observation that (1) anticholinergic medications increase falls in the elderly, (2) there is evidence of cholinergic cell loss in the PPN in patients with PD and (3) that ACh plays a critical role in cognition and dementia is associated with an increased risk of falls. In their randomized, placebo-controlled crossover trial of 23 patients with PD without dementia and frequent falls, patients were given donepezil 5-10 mg daily or placebo for 6 weeks, with a 3-week washout between treatments. Daily fall frequency was significantly decreased with donepezil versus placebo (0.13 ±0.03 versus 0.25 ± 0.08; $p<0.05$). Those with the highest initial fall frequency benefited the most. While promising, this data must be replicated in larger trials and in patients with PDD.

In the most significant trial to date, Henderson and colleagues (E. J. Henderson et al., 2016) examined the effect of oral rivastigmine on step time variability in PD patients without dementia. In their randomized, double-blind, placebo-controlled study, patients were randomized in a 1:1 ratio to either oral rivastigmine (3-12 mg daily) or placebo for 32 weeks. Patients must have fallen at least once within the previous year, been able to walk 18 m without assistance and had no prior use of an AchEI. A total of 130 patients were enrolled; 59 were assessed in the placebo group and 55 in the rivastigmine group. At 32 weeks, patients assigned to rivastigmine had improved step-time variability for both normal walking (ratio of geometric means 0·72, 95% CI 0·58–0·88; p=0·002) and under a dual-task condition (0·79; 0·62–0·99; p=0·045). As a secondary outcome, the authors analyzed the number of falls per month; patients on rivastigmine experienced a significant reduction in monthly falls. Gastrointestinal side-effects were more common in the treatment group.

Consequently, the available literature suggests a cholinergic etiology for postural instability in PD and subsequently, PDD. Notably, patients with PDD experience attention deficits as well as visuospatial and executive dysfunction, which has been related to cholinergic degeneration in the nBM and PPN and to an increased risk of falling (Yarnall et al., 2011). Treatment with AChEIs in PD populations has shown

promise in reducing fall-risk (Chung et al., 2010) and surrogate measures of fall-risk (E. J. Henderson et al., 2016). Therefore, it is not unreasonable to believe that these agents may have benefit in PDD where the cholinergic deficit may be even greater. Owing to the lack of published data characterizing the neuropathology, clinical presentation and treatment of postural instability specific to PDD, the studies found in the succeeding chapters are an attempt to fill this gap in the literature.

The case study presented in Chapter 4 outlines a case of PSP, a rare Parkinsonian illness characterized by frequent falls. There is little to no literature to guide pharmacologic treatment of the disease and there exists no established standard of care. Patients are usually managed on a case-by-case basis and for this reason a case report of successful medication therapy contributes a great deal to the body of literature. As the PPN, among other structures, is thought to be heavily involved in the pathogenesis of PSP, the objective of treatment was to increase central cholinergic tone, as well as dopamine and noradrenaline, in a "multiple neurotransmitter" strategy using donepezil and selegiline, a monoamine oxidase inhibitor (MAOI). It was hypothesized that balance control, quantified using the CoP and measured using dynamic posturography, would improve with donepezil and even more so with the addition of selegiline.

In Chapter 5, the main article of this thesis is presented. The objective of this study was to compare the efficacy and safety of oral and transdermal rivastigmine for postural instability in patients with PDD who were candidates for an AChEI. The primary outcome was the change in mean velocity of the centre of pressure (CoP) after 6 months. It was hypothesized that treatment with rivastigmine would result in postural improvements at 6 months, rather than the expected deterioration associated with the natural history of the disease, and that those in the transdermal group would display similar benefits compared to the oral group.