SUMMARY

Positron emission tomography (PET) scan with $^{18}$F-6-fluoro-dihydroxyphenylalanine (FDOPA) is currently the imaging "gold standard" for diagnosing Parkinson’s disease (PD), but this procedure is available at only a limited number of facilities. PET cameras are expensive, they require proximity to a cyclotron, and tests are nonreimbursable. A less costly and more available test, such as a single photon emission computed tomography (SPECT), may thus be helpful in the diagnosis of early or atypical PD, if its sensitivity is comparable with a PET scan. Altropane is an iodinated form of the N-allyl analog of WIN 35,428, which acts as a dopamine transport inhibitor. When radiolabeled with the $\gamma$-emitting isotope $^{123}$I, altropane serves as a SPECT ligand with high affinity and selectivity for the dopamine transporter. It is a good marker for dopamine neurons and is useful in detecting PD. There have now been reported cases that suggest altropane SPECT is comparable, if not possibly superior, to FDOPA PET scans in detecting early cases of PD.

Key Words: Altropane; dopamine transporter ligand; SPECT; PET; Parkinson.

1. MEASURING DOPAMINERGIC ACTIVITY IN EARLY PARKINSON’S DISEASE (PD): ITS CHALLENGES AND SIGNIFICANCE

Early PD can be a difficult diagnosis to be certain of given the spectrum of clinical symptoms and signs with which a patient can present. The diagnostic challenges faced by clinicians are illustrated by estimates that as many as 25% of patients diagnosed with idiopathic PD do not have the characteristic Lewy bodies at autopsy, many years further into the course of disease (1,2). A fraction of these patients have other parkinsonian disorders such as progressive supranuclear palsy (PSP), cortico-basal ganglionic degeneration, and multiple systems atrophy. The clinical presentation of parkinsonism can include symptoms of fatigue, for example, dragging one leg or stiffness in an arm, and can be misconstrued as age-related or, more commonly, as the result of arthritic conditions. A paucity of facial expression and decreased spontaneity of speech or withdrawal from social events, features that often accompany parkinsonism, may be misinterpreted as depression. The occurrence of unilateral “pill-rolling” tremor at rest, although pathognomonic of parkinsonism, is observed in only 40% of patients with idiopathic PD and fewer still with Parkinson’s variants such as multiple systems atrophy and PSP (3). Not uncommonly, the action and intention tremor that may appear in parkinsonism can lead to a false diagnosis of benign essential tremor—the most prevalent nonparkinsonian movement disorder. The characteristic pathology all these parkinsonian disorders have in common is the loss of dopaminergic neurons whose presynaptic axons end in the caudate and putamen. A surrogate marker of early disease would ideally measure the loss of dopaminergic neurons and not be influenced by treatment status, age or sex of the patient.

The accurate and early diagnosis of PD and other parkinsonian syndromes have become even more critical as clinical trials in PD have now entered the era of neuroprotection. Soon, it will be critical that PD patients be identified at the earliest possible stage, not only for proper inclusion in neuroprotective clinical trials but also to give the prospective disease-modifying agent the best chance of slowing or stopping PD progression.

At present the diagnosis of parkinsonian disorders during life is based on a careful exclusion of structural disorders in the basal ganglia, clinical observation during a period of time (usually 2 to 5 yr), and a sustained, robust response to dopamine-replacement therapy. Although Rajput et al. (3) and Hughes et al. (4) have shown that the accuracy of the clinical diagnosis of idiopathic PD improves between the initial diagnosis (65–74%) and the final diagnosis; still, only 76–82% of patients with the final (5–12 yr) diagnosis of PD are found to have substantia nigra loss and Lewy-body type pathology on autopsy. Rajput et al. suggested that response to levodopa may not be
specific to the underlying pathology of PD and concluded “there were no clues to distinguish neurofibrillary tangle parkinsonism or profound substantia nigra loss without neuronal inclusions from idiopathic PD” (3). In a community-based retrospective population study of 402 cases of diagnosed parkinsonism published by Meara et al. (5), 74% of cases were “confirmed” as having parkinsonism and 53% as “clinically probable idiopathic PD” when re-evaluated by neurologists following formal diagnostic criteria. This type of inaccuracy has been seen both in movement-disorders specialty clinics and general brain pathology registries.

Several in vivo imaging modalities have been evaluated in patients with parkinsonian disorders. Routine “anatomic” or structural imaging techniques, including magnetic resonance imaging, are generally not useful in distinguishing PD from other neurodegenerative conditions (6). In contrast, “functional” imaging techniques, including positron emission tomography (PET) using a variety of radioligand agents such as $^{18}$F-6-fluoro-dihydroxyphenylalanine (FDOPA) and $^{18}$F-deoxyglucose ($^{18}$FDG), have been used with varying degrees of success to differentiate PD from other movement disorders (7,8). Agents evaluated using PET imaging include radiolabeled phenyltropane analogs that have a binding affinity for the dopamine transporter, normally found in high concentrations in the striatal region of the brain. Clinical studies using PET imaging have demonstrated that striatal uptake of several phenyltropane analogs is markedly reduced in patients with PD. However, because of the limited availability and economic costs, the routine use of PET imaging has not been adopted widely.

Problems that arise with using agents that bind to the dopamine transporter protein (DAT) to measure early parkinsonism include uncertainty about the rate of progression of presynaptic dopaminergic cell loss and latency to onset of clinical disease (9). Longitudinal PET and single-photon emission computed tomography (SPECT) studies suggest a relatively rapid or exponential decline of dopaminergic function in early PD, followed by slowing of the degeneration process in the later stages of the disease (10–12). In a SPECT study using $^{[12]}$I-β-CIT, a significant reduction of striatal binding over the course of 2 yr was found in the PD group who had symptoms for fewer than 5 years compared with the PD group who had a longer duration of symptoms (12). However, recent reports using β-CIT show a slower, more linear decline of striatal binding in the first 3 yr of the disease (13). Furthermore, variability on test/retest protocols, such as the one study published using a 3- to 6-wk interval between scans with β-FP-CIT, also demonstrated a 7.4–7.9% fluctuation in measurements within subjects (14). The published multicenter trials for many of the radioligands report poor negative predictive values for both quantitative and qualitative methods of interpreting scans (15). In this regard, alatropane SPECT imaging may be more sensitive than FDOPA PET for detecting early PD. A report of two patients with clinically defined early PD, summarized later in this chapter, supports this statement (15). Finally, the influence of dopaminergic therapy on DAT homeostasis is not yet clearly understood and potentially confounds interpretation of both PET and SPECT scans in early parkinsonism. Whether drugs under current study are “neuroprotective” or simply “levodopa sparing” may require imaging of individuals “at risk” for PD during a period of 5–10 yr without drug therapy. However, the feasibility of such study and the ethical implications of withholding putative neuroprotective agents from this control group once abnormal DAT images are perceived makes such a study unlikely to occur.

2. ALTROPA: ITS NOVEL PROPERTIES

Recently, radiolabeled phenyltropane analogs have been modified for SPECT imaging, a technology that is widely available in nuclear medicine departments and much less costly than PET. The first analog in the United States to be studied extensively in vivo was β-CIT, but its equilibrium properties require a 24-h delay between injection and measurement of DAT in the striatum. Furthermore, β-CIT has an equal affinity for the serotonin transporter, which may affect the background counts and tracer distribution (16). Alatropane is a new phenyltropane analog ($^{[12]}$I-2β-carbomethoxy-3β-nortropane or $^{[12]}$I-E-IACT) with pharmacologic properties that make it more practical for clinical application (Fig. 1). It is rapidly and widely distributed after administration and the majority of the drug is cleared in urine during the next 24 to 48 h as iodinated metabolites. It does not significantly bind to human plasma proteins and requires only 5 to 8 mCi to obtain clearly defined uptake in the brain. Image acquisition is optimal at 1 h after injection because of its high binding affinity ($K_d$, 5.33 nM) preferential of 28:1 for dopamine over serotonin and relatively low nonspecific binding (17). Images are obtained at 10-min intervals for 1 h after injection and radioactivity approaches baseline at less than 2 h. No differences in binding have been noted in healthy subjects older than age 50 of either gender. Adverse reactions in preliminary studies have been frequent but clinically insignificant (e.g., mild headache, slight elevation in blood pressure, bowel frequency).

Phase I trials conducted by Boston Life Sciences, Inc (BLSI) established age-related binding potentials, safety, and radiation dosimetry in a total of 39 healthy subjects (BLSI report to FDA April 9, 1999). The Phase II multi-center trial involved nine study sites, with 12 normal and 25 PD subjects. There was also a post-hoc blinded qualitative assessment of the images to determine the sensitivity and specificity of alatropane for diagnosis of PD. Results showed a sensitivity of 95.8%, specificity 100%, positive predictive value 100%, and negative predictive value of 91.7% compared with the standard of a movement disorders specialist (MDS) diagnosis (BLSI report to FDA August 2, 2000). The final study reviewed to date, a Phase III multicenter trial involving 50% parkinsonian and 50% nonparkinsonian movement disorders, was expanded to include 15 sites and a total of 165 patients. The technical variability of different readers and different cameras for data acquisition was reflected in an overall accuracy of blinded interpretation of SPECT images of 79.5% (BLSI report to FDA March 26, 2001). This still represents a meaningful improvement over the non-MDS experience of 30–50% false-positive diagnoses of PD reported in the literature. Another Phase III trial is being launched soon to assess sensitivity and specificity for distinguishing parkinsonian from nonparkinsonian tremor disorders (IND in process). This trial will compare the diagnostic accu-