

Investigational Pharmacological Treatments for Parkinson's Disease

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Effective therapy for Parkinson's disease (PD) has existed for 40 years. Currently, levodopa, the precursor to dopamine, remains the most consistently effective medication. Most other pharmacologic treatments, such as dopamine agonists, augment and replace the endogenous dopamine loss that causes PD symptoms. Other treatments such as anticholinergic medications and amantadine often help symptoms through nondopaminergic mechanisms. Numerous other medications such as antidepressants and antipsychotics are used to treat specific symptoms in PD.

Conceptually, there are two major shortcomings to our current pharmacological armamentarium: loss of effect and lack of effect. Dopaminergic medications often initially improve symptoms, but as the disease progresses, patients develop motor fluctuations. Initially, the duration of medication action shortens. The subsequent development of dyskinesia and on/off phenomenon complicates dosing and markedly worsens quality of life. This is particularly problematic in younger patients. Certain aspects of PD never respond well to dopaminergic drugs, such as cognition, mood, balance, gait freezing, gastroenterological and urological symptoms, and bulbar symptoms. Finally, no available medication can

definitely claim to offer anything other than symptomatic benefit. Therefore, despite a recent increase in available medications and the tremendous advances in surgical treatments, the overall treatment of PD remains wanting.

New medications can be broadly classified into three categories: 1) improved versions of drugs that employ similar mechanisms of action as currently available medications, 2) drugs with novel mechanisms of action, and 3) drugs designed to treat only a particular aspect of the disease (psychosis, dementia, etc.). In this chapter we will only discuss new drugs designed to treat the motor features of PD.

NEW DOPAMINERGIC AGENTS

The general goals of new dopaminergic therapies are to maximize the therapeutic effect while minimizing typical adverse events (AEs), including sedation, nausea, hallucinations, edema, and hypotension. Clinically, a rapid onset to action is also desirable. Furthermore, there is increasing evidence that continuous dopaminergic stimulation may delay the appearance of fluctuations and potentially retard neuronal degeneration. The new dopaminergics generally achieve one of these goals.

Ropinirole (Requip[®]) controlled-release (CR) capsules (Glaxo-SmithKline) are currently undergoing Phase II/III trials for PD. The dopamine agonist component (ropinirole) is identical to the currently available drug. The CR tablet employs a Geomatrix[®] technology involving altering layers of active drug and erodible hydroxypropyl methylcellulose polymers, which slow absorption of the drug. This formulation is already used in medications marketed in the United States including diltiazem hydrochloride (Dilacor XR[®]) and paroxetine hydrochloride (Paxil CR[®]). The ropinirole Geomatrix system differs slightly from previous systems in that it employs a carboxymethylcellulose sodium. Pharmacokinetic studies show that this safely slows absorption without any dose dumping. Two Phase II trials are ongoing with doses ranging from 0.75 to 3.0 mg tablets. No unexpected AEs have been reported to date.

Rotigotine CDS[®] (constant delivery system), (-)-5,6,7,8-tetrahydro-6-[propyl]-[2-(2-thienyl-ethyl) amino]-1-naphthalenolis (Schwarz Pharma, Mannheim, Germany) is a silicone-based lipophilic D2 agonist patch designed to deliver constant drug levels over a 24-hour period (1). Detectable serum levels are achieved 2–3 hours after initial application and a serum steady state is achieved after approximately 24 hours. In the current formulation, the 9 mg (20 cm²) patch delivered approximately 5 mg of drug over a 24-hour period. Increased dermal sizes appear to proportionally increase serum drug levels. Pharmacokinetic studies demon-

strate that the drug (N-0923) has a half-life ($T_{1/2}$) of about 5 hours but maintains steady-state levels while the patch is worn. There were no measurable metabolites.

Phase I and II studies have shown efficacy and a similar adverse event profile to that of other dopamine agonists (DAs) (2,3). The most common AEs included nausea, hypotension, drowsiness, and dizziness. AEs were generally dose dependent. Many patients also reported some skin irritation after repetitive administration to the same location. Between 1.4 and 3.6% withdrew from studies due to skin irritation. Subsequent studies allowing for placement on different skin areas have reduced this problem.

Phase IIa dose finding studies showed a linear dose-response curve, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS), from 4.5 to 54 mg/day. A Phase IIb study of early PD patients found significant improvement compared to placebo at doses from 9 to 40 mg (4).

Sumanitrole maleate (PNU-95666E; Pharmacia) is a novel oral D2 agonist, which differs from existing dopamine agonists secondary to its low affinity for the D3 receptor. In PD, the positive motor features elicited by DAs appear to be modulated primarily by D2 receptors. The role of D3 receptors in PD is not clear, but in animal models, pure D3 agonists may actually slow movement (5). All existing DAs have strong affinity for both receptors, so it is impossible to segregate the contributions of each receptor type in human disease. Nevertheless, 6-OHDA rat models of PD treated with sumanitrole improved more robustly than those treated with traditional DAs.

Sumanitrole has a relatively short $T_{1/2}$, but several preparations, including an extended release and a combination extended release/immediate release, have also been tested in Phase II trials. Therefore, dosing varies from two to four times daily depending on the preparation.

Phase II trials in early and advanced PD patients have generally reported efficacy similar to that of other DAs at doses ranging from 2 to 48 mg/day. No unexpected serious AEs have been reported. Sedation and hallucinations may occur less frequently than what is historically reported in DA trials, but this awaits head-to-head confirmation. The drug is also being tested for restless legs syndrome, hyperprolactinemia, and sexual dysfunction.

Etilevodopa (TV-1203/carbidopa), TEVA Pharmaceuticals, is an ethyl ester derivative of levodopa. The prodrug is designed to be absorbed more rapidly and reliably in the gut than levodopa, primarily because it is more soluble in aqueous solutions. It is rapidly and almost completely hydrolyzed to levodopa by pancreatic enzymes in the gastric tract, and only negligible amounts of etilevodopa are detected in serum. Several animal and human pharmacokinetic studies have confirmed that peak plasma levels of

levodopa are achieved more rapidly after ingestion of etilevodopa compared to equimolar amounts of levodopa. Some of these have also demonstrated slightly higher peak levels than seen with equimolar concentrations of oral levodopa, without any difference in the total levodopa absorbed.

To date, Phase I and Phase II trials of etilevodopa, in combination with a decarboxylase inhibitor have demonstrated good efficacy and AEs comparable to levodopa compounds. No meaningful unexpected AEs have been reported. Phase III trials are ongoing to test etilevodopa in patients with fluctuating PD.

MONOAMINE OXIDASE INHIBITORS

Rasagiline (*N*-propargyl-1R-aminoindan) mesylate (TEVA Pharmaceuticals) is a potent irreversible inhibitor of monoamine oxidase B (MAO-B). In addition to improving motor symptoms in animal models of PD, rasagiline improved cognitive impairment in animals resulting from hypoxia (6) and trauma (7) and improved cell survival in a variety of *in vitro* and *in vivo* models of cell death (7,8). Rasagiline has several potential advantages over oral selegiline, including its superior ability to inhibit MAO-B, better penetration into the central nervous system (CNS), and lack of potentially pro-oxidant and amphetamine-like metabolites.

Several Phase I and II trials have reported good efficacy and excellent tolerability in early- and late-stage PD patients (9). A 404-patient, 26-week, double-blind Phase III study showed that both 1 and 2 mg/day of rasagiline improved UPDRS scores compared to placebo in subjects with early PD (10). AEs were similar to those of placebo. Over the subsequent 6 months, all subjects received rasagiline. At the end of 12 months, subjects who were originally assigned to rasagiline maintained relatively better UPDRS scores (11). Given the potential interaction between tyramine and MAO inhibition, a subset of patients also underwent uneventful tyramine challenge tests (12). Blood pressures were generally unchanged after a 75 mg tyramine ingestion. Phase III trials in fluctuating PD are ongoing.

Zydis[®] selegiline (Elan Pharmaceuticals) is formulated as a sublingually absorbed preparation. The Zydis preparation is a drug-impregnated, water-soluble polymer matrix that is rapidly absorbed through oral mucosa. Oral selegiline undergoes extensive first-pass hepatic metabolism to amphetamine compounds that could potentially counteract the theoretical reduction in oxidative stress and inhibit any neuroprotective effect of the parent drug. Mucosal absorption bypasses most of the metabolism such that much smaller doses equally inhibit CNS MAO-B without compromising systemic MAO-B specificity or accumulating amphetamine metabolites.

Phase I and II trials did not show any unexpected AEs. Pooled data from two identical placebo controlled trials (1.25 mg/day for 6 weeks followed by 2.5 mg/day for 6 weeks) in fluctuating PD showed that the drug reduced the percentage of “off” time and improved UPDRS motor “off” examinations (13). It was well tolerated. Specifically, stomatitis and ulcerations were not seen more than in placebo.

AGENTS WITH NOVEL MECHANISMS OF ACTION

KW-6002 [(E)-1,3-diethyl-8-(3,4-dimethoxystryl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione; Kyowa Pharmaceuticals, Princeton, NJ] is a novel adenosine 2A antagonist. Adenosine receptors are found throughout the CNS, but type 2A receptors are seen almost exclusively on gamma-aminobutyric acid (GABA), enkephalin, and cholinergic (ACh) spiny neurons in the striatum. These neurons receive inhibitory dopaminergic input from the substantia nigra and then project to inhibit pallidal neurons as part of the indirect pathway of the basal ganglia. Therefore, in PD, dopaminergic cell loss results in disinhibition of striatal spiny neurons that subsequently overly inhibit the globus pallidus externus (GPe), which in turn overly stimulate the subthalamic nucleus (STN) and globus pallidus internus (GPi).

Antagonism of the adenosine A₂ receptor appears to modulate GABA and ACh release in a manner that could counteract the deleterious effects of reduced dopaminergic stimulation. In fact, nonspecific adenosine antagonists such as caffeine have been known to counteract motor retardation caused by dopaminergic blockade (14). Specific affinity for the striatal A₂ receptors could significantly reduce the numerous other effects mediated by gross manipulation of adenosine systems.

Animal studies using KW-6002 with 6-OH-dopa rodents and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primates have consistently shown beneficial motor effects (15,16). A single dose typically improved locomotion for about 10 hours. Interestingly, motor hyperactivity (dyskinesia) did not develop with long-term administration of KW-6002. When used in combination with dopaminergic drugs in these models, KW-6002 potentiated the duration and also allowed for dose reduction and improved dyskinesia, while maintaining improved locomotion.

Several Phase I trials in humans have not identified any serious AEs. A completed Phase II trial using three doses of KW-6002 (10, 20, 40 mg) in fluctuating PD patients found that the drug group reported less “off” time without any increase in dyskinesia (17,18). AEs were minimal, and additional studies are ongoing.

CEP-1347 (Cephalon Inc.) is a 5,16-bis[(ethylthio)methyl] derivative of indolocarbazole, k252a, which is being tested for neurodegenerative disease including PD. The drug inhibits proteins in the mixed-lineage kinase family (MLK) (19–21). These proteins activate c-Jun N-terminal kinase (JNK), which is a key kinase in the stress-activated protein kinase (SAPK) pathway. Therefore, the drug is thought to inhibit programmed cell death. A variety of animal models, including MPTP primates, support this.

The terminal $T_{1/2}$ of CEP-1347 averages about 30 hours in humans. Metabolism is predominately oxidation and hydrolysis with biliary excretion. Phase I and IIa trials have not demonstrated any consistent AEs at doses ranging from 5 to 150 mg/day, although gastrointestinal irritation has been reported in some series. Two 28-day trials in PD did not show any symptomatic clinical effect or change on [123 I] B-CIT single photon emission computed tomography (SPECT). Longer studies designed to look at possible neuroprotective effects in PD are ongoing.

THC346 (dibenzo[b,f]oxepin-10-ylmethyl-prop-2-ynyl-amine, hydrogen maleate salt; Novartis Pharmaceuticals) is a novel compound being studied for the treatment of neurodegenerative diseases such as PD. The drug is structurally similar to selegiline but has only a negligible effect on MAO. The mechanism of action is not entirely known, but the drug appears to interact with the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which is involved with programmed cell death. Furthermore, the drug maintains mitochondrial membrane potential, which may reduce oxidative damage.

Pharmacokinetic studies have demonstrated variable oral bioavailability and extensive first-pass metabolism that results in multiple metabolites of uncertain significance, which are predominately excreted in the urine. To date, multiple Phase I trials and a single Phase II trial in PD patients have not demonstrated any consistent meaningful AEs. Efficacy trials are ongoing.

Sarizotan (Merck KGaA, Darmstadt, Germany) is a novel compound belonging to the aminomethyl chromane chemical group, which was initially developed as an atypical antipsychotic, but is now being evaluated to treat dopaminergic-induced dyskinesia in PD. The drug has affinity for 5HT $_{1A}$, D2, D3, and D4 receptors. After oral ingestion, it is rapidly absorbed and highly protein bound, but readily crosses the blood-brain barrier. The terminal serum $T_{1/2}$ is approximately 7 hours, and the drug is extensively metabolized by *N*-dealkylation and hydroxylation.

In animal models of PD, including MPTP primates, sarizotan improved drug-induced dyskinesia without worsening motor function (22). In a Phase IIa open-label trial of 64 dyskinetic PD subjects, the drug, at doses ranging from 2 to 10 mg BID, prolonged the amount of “on” time

without dyskinesia. PD symptoms were not worsened, as assessed by “off” time or UPDRS examinations, although some patients did list “worsening of parkinsonism” as an AE. Additional AEs reported in tolerability studies included sedation and nausea. Higher doses have been associated with suppression of the cortisol response to adrenocorticotrophic hormone (ACTH) challenge, but this was not seen in PD.

Glial-derived neurotrophic factor (GDNF) (Amgen Inc., Thousand Oaks, CA) is a recombinant neuropeptide, which may promote survival of or regenerate dopaminergic neurons. When delivered directly into the CNS of animal PD models, GDNF improved pathological dopaminergic systems and clinical signs. Determining the best CNS delivery system in humans has been problematic. A single large controlled trial delivered between 25 and 4000 μg in monthly doses directly into the cerebral spinal fluid via intraventricular catheter (23). Overall, those receiving drug did not improve clinically compared to placebo. Furthermore, GDNF infusion was often complicated by nausea and headache. Some subjects also suffered from an infusion-associated chemical meningitis. Other AEs included weight loss and hyponatremia. It was postulated that the lack of symptom improvement might have resulted from failure of the drug to reach target tissues. In contrast, a recent five-subject, open-label trial that directly delivered GDNF to the putamen reported robust improvement in UPDRS scores, improved “on” time, and reduced dyskinesia (24). Alternative methods of delivery, including viral vector delivery systems, are also under development (25).

AMG-474-00 (aka GP-1046) (Amgen, Thousand Oaks, CA) is a synthetic drug that binds to intracellular neuro-immunophilin receptor proteins. Neuro-immunophilin drugs, through unknown mechanisms, possess neurotrophic properties, which may restore cell viability. Chemically, the drug is related to immunological drugs such as cyclosporine and FK-506, but lacks any immunosuppressive actions. AMG-474-00 is highly orally bioavailable and readily crosses the blood-brain barrier. When administered after MPTP lesioning in animal models of PD, oral AMG-474-00 resulted in robust reinnervation by dopaminergic terminals at doses ranging from 0.01 to 50 mg/kg/day. Clinically, motor function also improved.

CONCLUSION

The past 10 years have seen a marked acceleration in therapeutic research for PD. In addition to novel pharmacological agents, novel surgical approaches and drug-delivery systems are under development to address the unmet needs of PD management. Continued research into disease pathogenesis and continued integration of governmental, academic, and

pharmaceutical industrial resources will no doubt continue to foster innovative treatment strategies and hopefully cure PD altogether.

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