

Investigational agents in the treatment of Parkinson's disease: focus on safinamide

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Abstract: The authors review management issues in Parkinson's disease (PD) and provide an overview of the current pharmacological management strategies, with a specific focus on safinamide. Current therapeutic management of PD largely involves strategies to optimize the replacement of deficient dopamine, using levodopa, dopamine agonists, and inhibitors of dopamine-metabolizing enzymes. Currently under investigation for use in the treatment of PD, safinamide has multiple modes of action including monoamine oxidase B inhibition. It is well absorbed orally, has a long plasma half-life, and does not have liver enzyme-inducing or liver enzyme-inhibiting activity. Peak plasma concentration occurs 2–4 hours after single oral doses. Safinamide as monotherapy and as an adjunct to dopamine agonists improves Unified Parkinson's Disease Rating Scale motor scores. One randomized, placebo-controlled trial involving 168 patients given a median safinamide dose of 70 mg/day (range 40–90 mg/day) significantly increased the proportion of responders – defined as patients improving their Unified Parkinson's Disease Rating Scale motor scores by 30% or more from baseline – after 3 months (37.5% for safinamide versus 21.4% for placebo; $P < 0.05$). Safinamide increased “on” time with no or minor dyskinesia compared with the placebo in another trial, but dyskinesia severity was not reduced. Safinamide was well tolerated, with an adverse effect profile similar to that of the placebo. Further Phase III trial data for safinamide efficacy is awaited, and will be of interest in a comparison with other developments in PD therapeutics: modified formulations of available compounds, new drug classes such as adenosine receptor antagonists, and gene-based therapies.

Keywords: monoamine oxidase B inhibitors, dyskinesia, Unified Parkinson's Disease Rating Scale, antiparkinsonian drug

Introduction to the management issues in Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by a deficiency of dopamine in the nigrostriatal pathway. It is recognized by the core motor symptoms of bradykinesia, rigidity, tremor, and postural instability that help to make the clinical diagnosis of PD (according, for example, to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria¹), but nonmotor symptoms such as sleep disturbances, olfactory dysfunction, and behavioral and cognitive problems can also cause considerable functional disability. Management initially involves a discussion of the diagnosis and nature of the condition with the patient, followed by a combined approach to ameliorate

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the motor and nonmotor symptoms, with pharmacotherapy and physical, occupational, and speech therapy.

Overview of current pharmacological management strategies

Since the discovery of levodopa as a treatment for PD, additional treatments, with fewer long-term side effects such as dyskinesia and with a better pharmacokinetic profile than the short half-life of levodopa (1–2 hours), have been developed.² Over the last decade this search has been further motivated by discoveries in the understanding of the pathological mechanisms underlying PD. Available PD treatment options largely improve motor symptoms rather than being neuroprotective, although there is an indication that some agents may fulfill both objectives.³ Current pharmacological management of the motor symptoms of PD relies mainly on dopamine precursors (levodopa), dopamine agonists (DAs), enzyme inhibitors of monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT), and amantadine, which is an N-methyl-D-aspartate antagonist.

Levodopa was first introduced in the 1960s for the treatment of PD and remains the gold standard. It is an amino acid precursor of dopamine and acts by replenishing striatal dopamine. Levodopa is combined with an extracerebral dopa decarboxylase inhibitor (DDI), either benserazide or carbidopa, to inhibit peripheral breakdown and enhance central delivery. Levodopa-based treatment may cause nausea, vomiting, and postural hypotension in the early stages, and it is linked to the development of dyskinesia in the later stages when response fluctuations emerge. It causes fewer neuropsychiatric side effects than other antiparkinsonian drugs and is, therefore, a common first choice for older patients and those with comorbidities.

DAs bind directly to the postsynaptic dopamine receptors and are effective in improving function in patients with PD, both as monotherapy and as adjuncts to levodopa. The ergot-derived DAs (bromocriptine, cabergoline, and pergolide) have fallen out of favor because of their fibrogenic potential. Non-ergot DAs including pramipexole, ropinirole, and rotigotine are often first-line agents in younger-onset PD patients, where the risk of longer-term motor complications is higher. Side effects include nausea, hypotension, peripheral edema, tiredness, and impulse control disorders.

Monoamine oxidase (MAO) is one of the enzymes that catalyze the breakdown of dopamine. Selective MAO-B inhibitors selegiline and rasagiline are effective as monotherapy and as adjuncts to levodopa or other agents, without having the dietary restrictions of nonselective MAO inhibitors. When used with levodopa, selegiline may accentuate

postural hypotension. Rasagiline is contraindicated in severe hepatic impairment.

COMT is another enzyme that catabolizes dopamine, both peripherally and in the central nervous system. Inhibition of COMT in the periphery allows for increased bioavailability and longer duration of action of levodopa. Entacapone and tolcapone are used as adjuncts to levodopa for PD patients who experience “end of dose” deterioration. Because of the hepatotoxic potential of tolcapone, entacapone is the preferred COMT inhibitor. Entacapone is contraindicated in those with pheochromocytoma, a history of neuroleptic malignant syndrome, or nontraumatic rhabdomyolysis. Side effects include diarrhea, nausea, dry mouth, and sweating. It is available as a triple combination tablet with levodopa and a DDI, marketed as Stalevo® (Novartis International AG, Basel, Switzerland).

Amantadine is an N-methyl-D-aspartate antagonist and a weak DA with modest antiparkinsonian effects. It is used as an antidyskinetic agent in PD. It is contraindicated in epilepsy and in those with a history of gastric ulceration. Tolerance to its effects may develop, and confusion and hallucinations occasionally occur.

Anticholinergic drugs (orphenadrine, procyclidine, and trihexyphenidyl) exert their antiparkinsonian action by reducing the effects of relative central cholinergic excess that occurs as result of dopamine deficiency. However, the use of anticholinergic drugs has declined significantly because of adverse cognitive effects; other side effects include dry mouth, constipation, and urinary retention.

In the early stages of the disease, DAs, MAO-B inhibitors, and levodopa with a DDI are the main choices for the symptomatic treatment of the motor symptoms of PD. There is no single drug of choice. Physician and patient preference, considering the adverse effect profile of individual drug classes, and comorbidities influence the choice and sequence of drug therapy. Current approaches favoring DAs initially for many young-onset patients who are otherwise well and levodopa as the first choice for older patients (often with comorbidity) may change with results of the Parkinson's Disease Medicines (PD MED) trial, although full results are not yet reported.⁴ The management of later stages of PD often involves combinations of dopamine replacement therapies, such as levodopa with a DDI, DAs, MAO-B inhibitors, and COMT inhibitors. However, motor and nonmotor complications may limit drug choices and require individualization of drug therapy. Parenteral routes of drug delivery (apomorphine, levodopa plus carbidopa intestinal gel) are utilized when motor complications become more troublesome, providing a more physiologic nonpulsatile delivery of dopamine.

Safinamide

MAO plays a major role in the *in vivo* inactivation of biogenic and diet-derived amines, in both the central nervous system and the peripheral body tissues. MAO isoenzyme A (MAO-A) is mainly responsible for the deamination of serotonin and noradrenaline in the intestine. The MAO-B isoenzyme predominates in the striatum.⁵

Dopamine is a substrate for both MAO-A and MAO-B. Selective inhibitors of MAO-B reduce the catabolism of dopamine and thereby increase the presynaptic levels of this neurotransmitter in the basal ganglia, without affecting the metabolism of other amines that are catabolized by MAO-A.

Safinamide mesylate was first synthesized in 1989 in the medicinal chemistry program at Farmitalia Carlo Erba (Milan, Italy). Initial investigation of safinamide was for its use as a potential antiepileptic drug, following the observation that milacemide, from which safinamide is derived, had some anticonvulsant activity.⁶ Safinamide mesylate is an alpha-aminoamide (chemical formula $C_{17}H_{19}FN_2O_2 \cdot CH_4O_3S$) with multiple mechanisms of action.

Mechanism of action

Sodium channel- and calcium channel-blocking properties led to initial trials of safinamide as an antiepileptic drug, but its selective and reversible MAO-B inhibitor activity drew attention toward its potential use in PD.^{7–10} The selectivity of safinamide for the B isoform of the human enzyme versus the A isoform is about 1000:1, compared with selegiline at 3400:1 and rasagiline at 2500:1.^{6,11,12}

Safinamide also inhibits dopamine reuptake and glutamate release, the latter action being shared with amantadine, which has some efficacy in reducing dyskinesia in PD.^{13–16} The main safinamide mechanism of action is inhibition of the sigma-1 receptor, where the half maximal inhibitory concentration (IC₅₀) is 19 nM.⁸ The potency of safinamide is less at other sites, being in the micromolar range for sodium channel blockade (IC₅₀, 8.2 μM) and the high micromolar range for calcium channel blockade (IC₅₀, 31.5 μM) and glutamate release (IC₅₀, >56.4 μM). Its potency in blocking MAO-B is in the submicromolar range (IC₅₀, 450 nM).^{8,17,18} Sigma-1 receptors are unique chaperone proteins that reside in the endoplasmic reticulum of cells. Initially considered a subtype of the opioid receptor subfamily, sigma-1 receptors are now thought to be multifunctional regulatory proteins with a role in central nervous system development, plasticity, and neurodegenerative disorders.¹⁹ Other drugs that inhibit sigma-1 receptors

(eg, Anavex 2-73, Anavex Life Sciences Corporation, Vancouver, Canada) have, like safinamide, been investigated as antiepileptic drugs. The role of sigma-1 receptor inhibition in PD is unclear; this mode of action may not be relevant to safinamide's antiparkinsonian effect.²⁰

Dopamine metabolism produces free radicals and these are believed to contribute to oxidative stress in nigral cells. In blocking the first step of dopamine metabolism by inactivating MAO-B, safinamide may reduce the production of free radicals, but this is expected to be a class effect.²¹

The multiple pharmacodynamic actions of safinamide make it a suitable candidate for evaluation as a neuroprotective agent against excitotoxicity and oxidative damage leading to neuronal cell death in PD.

Pharmacokinetics

Marzo et al²² administered safinamide orally to eight healthy human volunteers in the dose range of 0.025–10 mg/kg in single doses and 1.25–5 mg/kg in a repeat-dose regimen. It was well absorbed systemically, with peak plasma concentrations reached at 2–4 hours after single doses and 5–6 hours after repeat dosing. The maximum concentration at steady state was 1.5–1.7 times higher than the maximum concentration after single dosing, suggesting no significant safinamide accumulation in subjects with normal excretory function. The clearance half-life was about 22 hours and 89% was bound to plasma proteins.

Both dose linearity and dose proportionality were demonstrated after enteral absorption. The ingestion of food heavy in fat prior to oral dosing of safinamide resulted in a more sustained rate of absorption, without affecting the extent of absorption.²² Approximately 70% of an ingested dose is metabolized to a major inactive Phase I metabolite in plasma and is conjugated to a second major Phase II metabolite in urine.²³

Pharmacodynamics

In human studies, the MAO-B enzyme was partially and dose-proportionally inhibited in the dose range 25–150 μg/kg of oral safinamide. Safinamide plasma levels of about 200 ng/mL, reached with a 600 μg/kg oral dose, caused 91% MAO-B inhibition, suggesting that doses greater than 300–600 μg/kg at steady state would totally inhibit MAO-B. The median effective dose for MAO-B inhibition was 87.5 μg/kg.²⁰

Safinamide potentiates levodopa-mediated increases in dopamine levels in dopamine-depleted mice and reverses the waning motor response after prolonged levodopa treatment in rats with 6-hydroxydopamine lesions.¹⁴

Safinamide has been reported to have neuroprotective effects and to be able to counteract excitotoxin-induced hippocampal neuronal death in animal models.^{9,24}

In the mouse model, safinamide has been reported to fully prevent forebrain dopamine depletion and neuronal cell death in the substantia nigra if given prior to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a toxin known to produce parkinsonism. This preventive effect is shared with the other MAO-B inhibitors selegiline and rasagiline.^{24,25}

Safety and tolerability

Safinamide was well tolerated in human studies. Safinamide was not found to be genotoxic in the Ames and DNA repair tests. Negative in vitro results for mutagenicity studies in mouse lymphoma cells and the in vivo micronucleus test have been reported.⁷

Drug formulation

Safinamide is water-soluble and has been formulated as 5, 10, 50, and 200 mg oral tablets for use in clinical trials.

Drug interactions

In vitro studies show that safinamide has no inhibiting activity on various cytochrome P450 isoenzymes (CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) involved in the metabolism of drugs, except CYP1A1/2, but this is at a negligible level at therapeutic doses.²²

Enzyme-inducing antiepileptic drugs (eg, phenobarbital and carbamazepine) decrease plasma concentration of safinamide by approximately 30% and shorten the half-life of safinamide, but safinamide does not affect plasma concentrations of carbamazepine, phenobarbital, valproic acid, or lamotrigine.⁷

In one open-label, single-dose, placebo-controlled trial there was no synergistic action of safinamide with tyramine in raising blood pressure; similar results were reported in another study.^{26,27}

Clinical trials

In an open-label pilot study, doses of safinamide (100, 150, and 200 mg) administered along with a DA (n = 13) led to an improvement in motor performance over a 6-week period, with a significant improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (measured by part III of the UPDRS) (4.2 points, $P < 0.001$). In association with levodopa, the same doses of safinamide in eleven patients induced a significant decrease in motor fluctuations (UPDRS part IV, 2.1 points, $P < 0.001$),

accompanied by a dose-proportional increase of the area under the plasma concentration-time curve for levodopa, ranging from 56% at the dose of 100 mg/day to 88% at the dose of 200 mg/day.²⁸

In another randomized, placebo-controlled trial involving 168 patients, Stocchi et al²⁹ reported that a median safinamide dose of 70 mg/day (range 40–90 mg/day) significantly increased the percentage of parkinsonian patients improving their UPDRS motor scores by a third or more from baseline (labeled as “responders”) after 3 months from 21.4% (placebo) to 37.5% ($P < 0.05$). In a subgroup of 101 patients under stable treatment with a single DA, addition of safinamide significantly magnified the response compared with placebo (47.1% responders, mean UPDRS motor score [part III] improvement of 4.7 points, $P = 0.016$). No significant differences for adverse events were noted between safinamide and the placebo.²⁹

Stocchi et al³⁰ reported the findings of a second 24-week, randomized, double-blind study. Patients with early PD receiving a stable dose of a single DA were randomized to once-daily safinamide 100 mg (n = 90), 200 mg (n = 89), or a placebo (n = 90). Mean improvement from baseline to week 24 in the primary endpoint, the UPDRS motor score (part III), was significant for safinamide 100 mg (6.0 points difference; $P = 0.0419$, versus placebo) but not for 200 mg (3.9 points difference; $P = 0.6504$, versus placebo). No clinically significant differences between safinamide and the placebo were observed for any safety variables. The most common adverse events were nausea, headache, upper abdominal pain, vomiting, pyrexia, cough, hypertension, blurred vision, gastritis, peripheral edema, nasopharyngitis, dizziness, back pain, and tremor. The incidence of these adverse events was less than 10% in each group; however, 21.3% of patients discontinued the safinamide 200 mg dose, compared with 10.0% for the safinamide 100 mg dose and 10.0% for the placebo.³⁰

Anand et al³¹ reported two Phase III studies in PD patients with motor fluctuations using safinamide as add-on therapy. In the first study, involving 669 patients, treatment was safinamide 50 mg/day (n = 223), 100 mg/day (n = 224), or a placebo (n = 222). The primary endpoint was “on” time with no or minor dyskinesia. After 6 months, “on” time was significantly increased by 0.6 hours in both treatment groups compared with the placebo group. From the total of 669 patients in this study, 544 patients were then followed for another 18 months, with a primary endpoint of change from baseline to month 24 in dyskinesia rating scale score during “on” time. There was an improvement at 2 years in the dyskinesia rating scale score during “on” time, but this

was not significant (50 mg/day, $P = 0.21$, versus placebo; 100 mg/day, $P = 0.15$, versus placebo). The significant improvement in “on” time was maintained at month 24: safinamide 50 mg/day increased the average daily “on” time with no or minor dyskinesia by 0.67 hours, while 100 mg/day gave an increase of 0.83 hours. The three most common side effects were dyskinesia, dry mouth, and back pain.^{31,32}

Other drugs in the same class

Lazabemide, another reversible MAO-B inhibitor, showed symptomatic effects similar to those of selegiline in a double-blind, placebo-controlled trial but was withdrawn by the study sponsor.^{33–35}

Conclusion

Safinamide has been evaluated as an add-on to DA therapy in the early stages of PD, as an adjunct to levodopa in the middle stages of PD, and as an antidyskinetic agent, showing some efficacy on all counts. Safinamide is comparable with the two other MAO-B inhibitors licensed for treatment of PD, selegiline and rasagiline, in that it does not have dietary restrictions for food with high tyramine content and can be used once daily because of its relatively long half-life. It has been studied in a large number of PD patients at doses ranging between 50 and 200 mg/day without serious side effects. There have been no direct comparisons made with selegiline or rasagiline. Two further Phase III trials, MOTION (safinamide add-on to DAs for early idiopathic PD) and SETTLE (safinamide in idiopathic PD with motor fluctuations, as add-on to levodopa), have yet to report. Merck KGaA recently returned the rights to develop, manufacture, and commercialize safinamide for PD to Newron Pharmaceuticals SpA.

Future directions

Drugs that are the subject of current trials for treatment of PD include modified formulations of levodopa (IPX066), DAs (pardoprux), COMT inhibitors (necicapone), adenosine receptor antagonists (istradefylline, preladenant), neurotrophic factors (Cogane[®]), gene therapies utilizing an adeno-associated virus vector to deliver the glutamic acid decarboxylase gene, stem cell therapies, antidyskinetic agents (fipamezole), and drugs for treatment of excessive daytime sleepiness (pitolisant). Nondopaminergic mechanisms play a role in many of the nonmotor manifestations of PD and are therefore a key current focus of research. Dopaminergic therapies underpin current management strategies in treating PD, and their evolution continues with agents

such as safinamide. It is also anticipated that the scope of antiparkinsonian therapy will broaden, with new treatments that influence nondopaminergic mechanisms.

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