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OPICAPONE: A NOVEL THIRD GENERATION COMT ADJUNCTFOR WEARING OFF IN PARKINSON'S DISEASE

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ABSTRACT

Opicapone is a potent, reversible, and peripherally-acting third-generation inhibitor of catechol-o-methyltransferase (COMT), an enzyme involved in the breakdown of variouscatecholamines including dopamine. In June 2016, the European Commission granted a marketing authorization valid throughout the European Union for OPC, indicated as adjunct therapy to levodopa and decarboxylase inhibitors in adult patients with Parkinson's disease and end-of-dose motor fluctuations. In April 2020, the FDA approved the use of Opicapone as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD)experiencing "off" episodes. Opicapone is marketed as, under the brand name Ongentys as once-daily oral capsules. Almost all individuals with Parkinson's disease whom are treated with levodopa plus a dopa decarboxylase (DDC) inhibitor (e.g. carbidopa) will develop motorcomplications in time. The initial step in the management is changing the levodopa/DDC inhibitor dosage and the use of adjunct drugs. Various options include supplementing with a dopamine agonist, a monoamine oxidase B inhibitor (Selegiline, Rasagiline), a catechol-O- methyl transferase (COMT) inhibitor, or Amantadine, or using a modified-release formulation of levodopa. The newest adjunctive option is Opicapone. This drug is a peripherally selective reversible COMT inhibitor that offers the benefit of a duration of action exceeding 24h, allowing for once-daily administration. Opicapone demonstrates the lowest risk for

cytotoxicity in comparison with other catechol-O-methyltransferase inhibitors. This review encompasses the clinical pharmacology, adverse effects, interactions and dosage of Opicapone- a future boon to PD.

KEYWORDS: Parkinson's disease, Opicapone, COMT inhibitor.

INTRODUCTION

Parkinson's disease (PD) is a progressive, chronic, neurodegenerative disease characterizedby rigidity, tremor, bradykinesia and postural instability secondary to dopaminergic deficit in the nigrostriatal system.[1–3] Currently, disease-modifying therapies are not available, and levodopa (LD) treatment remains the gold standard for controlling motor symptoms of the disease.[4–7] Nonmotor symptoms (eg, cognitive decline, psychiatric symptoms, autonomic and sleep disturbance, etc) also cause a marked decrease in the quality of life, but currently there is limited evidence that LD treatment can alleviate these symptoms. Furthermore, within 5 years of treatment, ~50% of patients develop motor fluctuations and dyskinesia.[1,2,8] The pathophysiology behind motor complications is that instead of physiologic, tonic stimulation, there is a reduced and pulsatile dopaminergic stimulation of striatal neurons.[9] This is due to fluctuations in the plasma concentration of LD and progressive neuronal cell death in the nigrostriatal system.[10]

Catechol O-methyltransferase (COMT) inhibitors are an established treatment for motor fluctuations associated with levodopa therapy. Two COMT inhibitors are currently available for clinical use. Tolcapone was widely used, but owing to the risk for potentially fatal hepatictoxic effects, its clinical use now requires regular liver function monitoring and is only considered in patients who have failed to respond to entacapone.[11,12] Entacapone is considered safer, but gains in daily on-time (the state of adequate control of symptoms) are moderate (mean of 0.6 hours across randomized trials). Thus, a more effective COMTinhibitor that can be easily used in routine clinical practice is needed.[13] Opicapone was rationally designed to provide high COMT inhibitory potency and avoid toxic effects to cells.[14] Opicapone has a very high binding affinity that translates into a slow complex dissociation rate constant and a longduration of action that allows once-daily dosing.

The success of levodopa used together with other antiparkinsonian drug classes means that most patients living with Parkinson's disease (PD) enjoy a good quality of life for many years.[15,16] Nevertheless, the long-term therapeutic response is marred in many by the

emergence of disabling fluctuations and dyskinesias[17,18] that lead to a reduced quality of life and motor handicap.[16,19] Wearing-off results from levodopa's short duration response which reflects the amino acid's short half-life (~ 60–90 min).[20] Over time, patients will experience more and more hours per day in a disabling OFF-state and some will develop intrusive and adventitious involuntary movements.[21]

Current treatment guidelines consider adjunctive treatment with catechol-O-methyltransferase (COMT) inhibitors, dopamine agonists and monoamine oxidase type B (MAO-B) inhibitors, as efficacious to reduce OFF time in patients treated with levodopa/dopa decarboxylase inhibitor (DDCI) therapy.[22–24] In routine practice, many physicians will also consider various formulations of levodopa (e.g. controlled-release and extended-release preparations) as well as dosing manipulations to increase the dose and/ or dosing frequency of levodopa. COMT inhibitors have been an established first-line strategy to manage motor fluctuations for over 25 years[25–28], and are the only adjunct class to directly address the peak-trough variations in plasma levodopa levels that clinically manifest as wearing-off fluctuations.[25] The third generation COMT inhibitor – Opicapone (Ongentys®)– has been approved in Europe since 2016 as adjunct therapy to preparations of levodopa/DDCI for end-of-dose motor fluctuations. Based on rational drug design, Opicapone was specifically developed to reduce the risk of toxicity and improve peripheral tissue selectivity.[30] In one pharmacokinetic study, Opicapone (50 mg once daily) significantly increased levodopa bioavailability compared with both placebo and entacapone (200 mg TID) by increasing substantially the trough plasma levels and each dose systemic exposure time (half-life) by at least 1hr.[31] Phase III studies have established that treatment with Opicapone 50mg once daily reduces daily OFF-time, without significantly increasing ON-time with troublesome dyskinesia versus placebo, and most patients show an improvement in the Clinician's Global Impression of Change (CGI-C).[32,33] While placebo-controlled trials remain the gold standard in assessing response to a therapeutic intervention, alone they do not provide sufficient information of clinical effectiveness and safety. Many regulators and payers now encourage the supplementation of randomized controlled trials with other forms of evidence, such as 'real world' studies.[34, 35]

CHEMISTRY

ONGENTYS contains opicapone, a peripheral, selective and reversible catechol-O-methyltransferase (COMT) inhibitor. The chemical name of opicapone is 2,5-dichloro-3-(5-

(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol3-yl)-4,6-dimethylpyridine-1-oxide with the following structure in Fig. 1. The molecular formula of Opicapone is C15H10Cl2N4O6; and its molecular weight is 413.17. Opicapone is a yellow powder/crystalline solid with limited aqueous solubility.

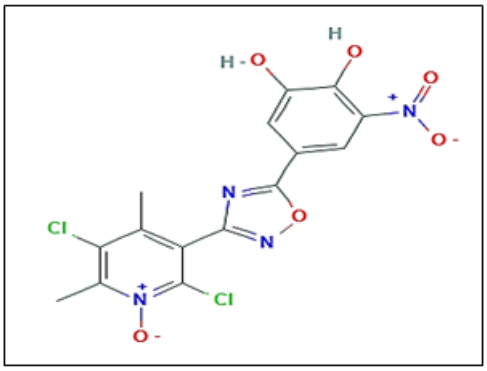

Fig 1: Chemical structure of Opicapone.

CLINICAL PHARMACOLOGY

Mechanism of action

Opicapone is a selective and reversible inhibitor of catechol-O-methyltransferase (COMT). COMT catalyzes the transfer of the methyl group of S-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include DOPA, catecholamines (dopamine, norepinephrine, and epinephrine), and their hydroxylated metabolites. When decarboxylation of levodopa is prevented by carbidopa, COMT becomes the major metabolizing enzyme for levodopa, catalyzing its metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).[34]

Pharmacokinetics

Opicapone demonstrates dose-proportional pharmacokinetics over a 25 mg (0.5 times the recommended dosage) to 50 mg dose range. The pharmacokinetics of Opicapone are similar in both PD patients and healthy subjects.

Absorption- After single-dose administration of Opicapone 50 mg, the median (range) plasma T max value was 2.0 (1.0-4.0 hours).

Effect of Food- Following a moderate fat/moderate calorie meal, the mean peak plasma concentration (C max) for Opicapone decreased 62%, the mean overall plasma exposure (AUC) decreased 31%, and the Tmax was delayed by 4 hours.'

Distribution- Opicapone is highly bound to plasma proteins (>99%), which is independent of concentration.

Elimination- The mean elimination half-life of Opicapone is 1 to 2 hours.

Metabolism- Sulphation is the primary metabolic pathway of Opicapone, based on clinical studies and in vitro assessments. Other metabolic pathways include glucuronidation, methylation (by COMT), reduction, and glutathione conjugation.

Excretion- After administration of a single dose of radiolabelled Opicapone 100 mg (2 times the recommended dosage) to healthy subjects, approximately 70% of the dose was recovered in feces (22% as unchanged), 20% in expired air, and 5% in urine (<1% as unchanged).

Renal Impairment

Based on population pharmacokinetic analyses, no clinically significant differences in the pharmacokinetics of Opicapone were observed in patients with mild or moderate renal impairment (CLcr 30-89 mL/min using the Cockcroft-Gault equation) relative to those with normal renal function (CLcr >90 mL/min). Patients with severe renal impairment or ESRD (CLcr <30 mL/min) have not been studied.

Hepatic Impairment

The single-dose pharmacokinetics of Opicapone was evaluated in subjects with mild (Child-Pugh: A) and moderate (Child-Pugh: B) hepatic impairment. In subjects with mild hepatic impairment, the mean overall Opicapone plasma exposure (AUC) increased by 35%, which is not expected to be clinically significant. In subjects with moderate hepatic impairment, the mean overall Opicapone plasma exposure (AUC) increased by 84%. Dosage adjustment for Opicapone is required in subjects with moderate hepatic impairment.[34]

Pharmacodynamics

COMT Activity- Once-daily administration of Opicapone 50 mg caused inhibition of COMT activity in erythrocytes; the maximal inhibition seen was 84% and was maintained >65% over a 24-hour dosing interval in patients with Parkinson's disease. Following termination of treatment, COMT inhibition slowly returns to baseline levels, with >35% inhibition still observed 5 days after the last dose.

Effects on Levodopa- Peak (Cmax) and overall levodopa exposure (AUC) increased by 43-

44% and 62-94%, respectively, in PD patients following once-daily administration of Opicapone at bedtime with levodopa/carbidopa administered every three or every four hours, as compared to after administration of levodopa/carbidopa alone.

Cardiac Electrophysiology- At a dose 16 times the recommended dosage, Opicapone does not prolong the QT interval to any clinically relevant extent.[34]

INTERACTIONS

Both Opicapone and non-selective MAO inhibitors (e.g., phenelzine, isocarboxazid, and tranylcypromine) inhibit catecholamine metabolism, leading to increased levels of catecholamines. Concomitant use may increase the risk of possible arrhythmias, increased heart rate, and excessive changes in blood pressure. Selective MAO-B inhibitors can be used concomitantly with Opicapone.

Concomitant use of Opicapone with drugs metabolized by COMT may affect the pharmacokinetics of those drugs, which may increase the risk of possible arrhythmias, increased heart rate, and excessive changes in blood pressure. Monitor for changes in heart rate, rhythm, and blood pressure in patients concomitantly treated with Opicapone and drugs metabolized by COMT.

WARNING AND PRECAUTIONS

Cardiovascular Effects with Concomitant Use of Drugs Metabolized by CatecholO-Methyltransferase (COMT) - Possible arrhythmias, increased heart rate, and excessive changes in blood pressure may occur with concomitant use of Opicapone and drugs metabolized by COMT (e.g., isoproterenol, epinephrine, norepinephrine, dopamine, and dobutamine), regardless of the route of administration (including inhalation).

Falling Asleep During Activities of Daily Living and Somnolence- Patients treated with dopaminergic medications and medications that increase levodopa exposure, including Opicapone, have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes has resulted in accidents. Before initiating treatment with Opicapone, advise patients of the potential to develop drowsiness and specifically ask about factors that may increase the risk for somnolence with dopaminergic therapy, such as concomitant sedating medications or the presence of a sleep disorder.

Hypotension/Syncope- Hypotension (orthostatic and non-orthostatic), syncope, and presyncope occurred in 5% of patients treated with Opicapone 50 mg compared to 1% of patients who received placebo. Monitor patients for hypotension (orthostatic and non-orthostatic) and advise patients about the risk for syncope and presyncope.

Dyskinesia- Opicapone potentiates the effects of levodopa and may cause dyskinesia or exacerbate pre-existing dyskinesia. It occurred in 20% of patients treated with Opicapone 50 mg compared to 6% of patients who received placebo in clinical trials.

Hallucinations and Psychosis- Auditory hallucinations, visual hallucinations, mixed hallucinations) occurred in 3% of patients treated with ONGENTYS 50 mg compared to 1% of patients who received placebo. Delusions, agitation, or aggressive behaviour occurred in 1% of patients treated with Opicapone 50 mg. Patients with a major psychotic disorder should ordinarily not be treated with Opicapone because of the risk of exacerbating the psychosis with an increase in central dopaminergic tone.

Impulse Control/Compulsive Disorders- Patients treated with Opicapone can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges while taking one or more dopaminergic therapies that increase central dopaminergic tone. In some cases, these urges were reported to have stopped when the dose was reduced, or the medication was discontinued.

Withdrawal-Emergent Hyperpyrexia and Confusion- A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone.[34]

CONTRAINDICATIONS

Opicapone is contraindicated in patients with.

- Concomitant use of non-selective monoamine oxidase (MAO) inhibitors.
- Pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms.

DOSAGE AND ADMINISTRATION

The recommended dosage of Opicapone is 50 mg or 25mg administered orally once daily at

bedtime. Patients should not eat food for 1 hour before and for at least 1 hour after intake of the drug.[34]

ADVERSE REACTIONS

The clinically significant adverse reactions were cardiovascular effects with concomitant use of drugs metabolized by catechol-o-methyltransferase (COMT), falling asleep during activities of daily living and somnolence, hypotension/syncope, dyskinesia, hallucinations and psychosis, impulse control/compulsive disorders and withdrawal-emergent hyperpyrexia and confusion.

Table 1: Adverse Reactions reported in clinicaltrials.[34]

Adverse Reactions	Opicapone 50 mg, N=265(%)	Placebo N=257(%)
Nervous system disorders		
Dyskinesia	20	6
Dizziness	3	1
Gastrointestinal disorders		
Constipation	6	2
Dry mouth	3	1
Psychiatric disorders		
Hallucination	3	1
Insomnia	3	2
Investigations		
Blood creatine kinase increased	5	2
Weight decreased	4	0
Vascular disorders		
Hypotension/syncope	5	1
Hypertension	3	2

CONCLUSION

Opicapone is a promising new peripheral COMT inhibitor that has been approved for adjunctive therapy to levodopa/carbidopa in PD patients showing motor fluctuations. Preclinical and clinical studies have shown that Opicapone, compared to the previous two COMT inhibitors, is more efficacious, has a significantly longer effect and is less toxic.

Opicapone therapy is thus far only recommended for patients who have been taking LD therapy for years and are inevitably showing signs of motor fluctuations. In the future, it would be interesting to see the effects of Opicapone treatment before the occurrence of motor fluctuations. Still, Opicapone promises a possibility that, Opicapone can delay the onset of the adverse effects of LD therapy by providing steadier and continuous plasma LD concentrations.

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