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Amantadine in Parkinson's Disease

An expert Opinion



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CHAPTER

3

Role of Amantadine in Parkinson's Disease

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INTRODUCTION AND BASIC CHEMISTRY

In 1966, amantadine was first approved as an antiviral compound by the Food and Drug Administration (FDA). Later in 1968, a 58-year-old woman with moderately severe Parkinson's disease had remarkable remission in her symptoms of rigidity, tremor, and akinesia when initiated on amantadine.

The drug is hydrophilic in nature and penetrates the blood–brain barrier (due to active transport probably via a proton-coupled organic cation antiporter). Amantadine is a symmetrical C10 primary amine with a remarkable cyclic structure belonging to the class of aminoadamantanes (see **Fig. 1**).[1,2]

- Amantadine is a synthetic tricyclic amine that belongs to the class of aminoadamantanes
- It is an antiparkinsonian agent and anti-influenzal virostatic drug

PHARMACODYNAMIC

Amantadine is an oral N-methyl-D-aspartate (NMDA) receptor antagonist, which was originally approved as an antiviral and was later

- Amantadine is an oral NMDA receptor antagonist
- Amantadine improves bradykinesia, rigidity, and tremor
- Amantadine has antidyskinetic effects

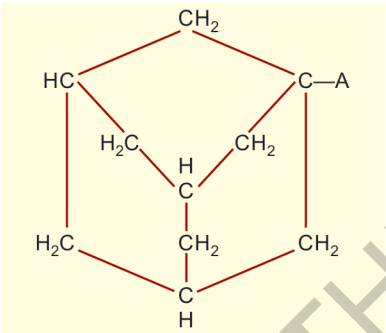

FIG. 1: Structure of amantadine.

discovered to exert an antiparkinsonian effect with remissions in rigidity, bradykinesia, and tremor.[3]

MECHANISM OF ACTION OF AMANTADINE

Amantadine, a tricyclic amine, exhibits both dopaminergic and nondopaminergic actions, owing to its well absorption and is largely excreted unchanged in the urine.[3,4] Amantadine has several proposed mechanisms of action (see **Fig. 2**).[4]

General Pharmacodynamics of Amantadine:[5]

- *Dopaminergic system*: Amantadine inhibiting dopamine reuptake in synaptic cleft and increases dopamine level in the brain. These effects are observed at clinically high doses in humans. Though exact effect on dopaminergic transmission are still unknown, some results show that amantadine exhibits direct effects on D2 receptors. However, in one of the studies among patients, being treated with amantadine 200 mg/day and were suspended L-DOPA treatment a night before, showed an increase in ^{11}C raclopride binding in the caudate and putamen. Thereby, suggesting that amantadine increased neosynthesis of D2 receptors.[5]

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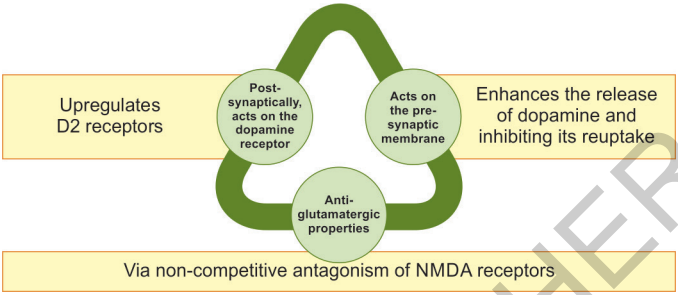

FIG. 2: Amantadine mechanism of action. (NMDA: N-methyl-D-aspartate)

- *Noradrenergic system*: The drug exerts similar pharmacodynamic actions to that of tricyclic antidepressants, thereby causing a significant increase in the levels of norepinephrine.[5]
- *Glutamatergic system*: Amantadine also has noncompetitive NMDA receptor antagonist. It inhibits NMDA receptor activation through the stabilization of ion channels and more rapid channel closure.[5] The mechanism of action is owing to its NMDA blockade action (see **Fig. 3**).[6]

- Amantadine is indicated in the treatment of Parkinson's disease both as a monotherapy as well as in combination with levodopa
- In addition, the drug is used for other indications which include drug-induced extrapyramidal side effects, attention deficit disorder, L-DOPA-induced motor fluctuations, traumatic brain injury, and autistic spectrum disorders

- *Immunomodulation:* Additionally, the drug also has immunomodulatory effects. In patients with Parkinson's disease, the interleukin (IL)-2 is dysfunctional and amantadine restores the production of IL-2. Various clinical studies have shown that treatment with amantadine was an independent predictor of improved survival in Parkinson's disease.[5]

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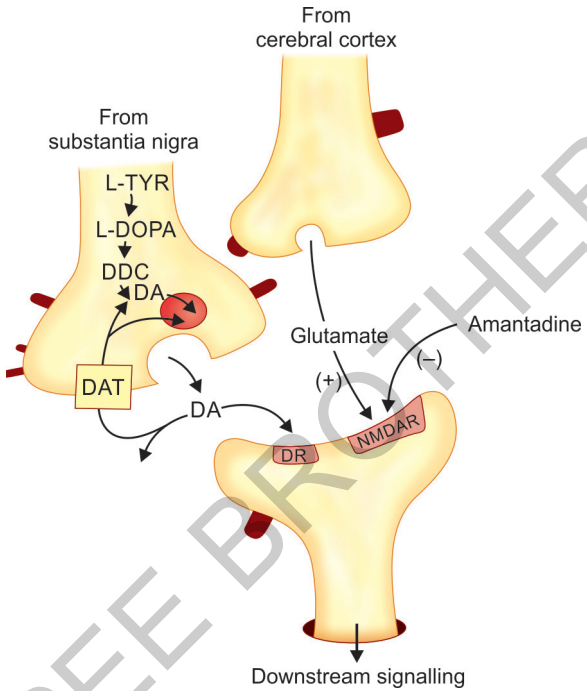

FIG. 3: Interface between a dopaminergic (DAergic) nigrostriatal nerve terminal in which dopamine (DA) is synthesized from L-tyrosine (L-Tyr) via L-DOPA to DA with a glutamatergic terminal of the corticostriatal tract and the postsynaptic neuron.[6]

Of all these proposed mechanisms of action, NMDA receptor blocking activity could be more relevant mechanism therapeutically for relevant doses of amantadine.[5]

CLINICAL INDICATIONS

Amantadine is indicated in the treatment of Parkinsonism and drug-induced extrapyramidal reactions, which include but not limited to:[7]

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- Idiopathic Parkinson's disease
- Postencephalitic Parkinsonism
- Symptomatic Parkinsonism followed by carbon monoxide intoxication, drugs, etc.
- Vascular Parkinsonism in association with cerebral arteriosclerosis
- Drug-induced Parkinsonism

PHARMACOKINETIC PROPERTIES

After oral administration, amantadine is well absorbed, and maximum plasma level is attained at approximately 3.3 hours after administration. The drug has a half-life of approximately 16 hours. Additionally, almost 90% of the drug is excreted unchanged in urine. The approved clinical dose is 100 mg twice daily, which based on the need can be increased up to 400 mg/day.[5]

In a clinical study, 24 healthy adult male volunteers were evaluated for amantadine pharmacokinetic profile. The volunteers were administered oral single dose of amantadine hydrochloride. Following findings were reported in the study:[7]

Maximum plasma concentration was 0.22 ± 0.03 µg/mL
Time to peak concentration was 3.3 ± 1.5 hours
Oral clearance was 0.28 ± 0.11 L/h/kg
Half-life was 17 ± 4 hours

However, in another study on six healthy volunteers and six elderly volunteers, single oral dose of amantadine 200 mg reported amantadine presence in nasal mucous after 4 and 6 hours of dosing with 67% bound to plasma proteins.[7]

Clearance of amantadine is significantly reduced in adults with renal insufficiency and elimination half-life increases >two- to threefold when creatinine clearance is <40 mL/min. Amantadine half-life may be 8 days in patients on chronic

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maintenance hemodialysis. Amantadine is nondialysable and maintains blood level even after dialysis.[7]

A detailed breakdown of amantadine pharmacokinetics has been depicted in **Table 1**.[3,8]

TABLE 1: Pharmacokinetic properties of amantadine.

Absorption	Bioavailability	Good GI absorption; Peak plasma in 2–4 h
	Onset	Within 48 h
	Plasma concentrations	• Peak plasma concentrations attained at 200 mg daily of <1,000 ng/mL • Dosage > 200 mg results in greater than proportional increase in peak plasma
	Special populations	Increased in renal impairment
Distribution		Distributed into nasal secretions, erythrocytes, CSF, and milk
	Plasma protein binding	67%
Elimination	Metabolism	Undergoes N-acetylation
	Elimination route	• Excreted unchanged in urine • 5–15% excreted in urine as acetylamantadine
	Half-life	16 h
	Renal impairment patients	18.5–81.3 h
	Chronic hemodialysis	8.3 days
	Geriatric adults	29 h

(CSF: cerebrospinal fluid; GI: gastrointestinal)

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Metabolism

Pharmacokinetic studies have revealed eight amantadine metabolites. One of the metabolites, an N-acetylated compound was accounted for 5–15% of the administered dose. In 5 of 12 healthy volunteers, plasma acetylamantadine accounted for up to 80% of the concurrent amantadine plasma concentration following ingestion of 200 mg dose of amantadine. However, in remaining seven volunteers, no acetylamantadine was detected in plasma. The contribution of this metabolite to efficacy or toxicity is not known.[9]

There exists a relationship between plasma amantadine concentration and its toxicity. As concentration increases, toxicity seems to be more prevalent; however, absolute values of amantadine concentrations associated with adverse effects have not been fully defined.[9]

Elimination

Amantadine is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion (**Table 2**).

A study on 19 health volunteers reported plasma half-life of 16 ± 6 hours (range: 9–31 h). In another study with 15 healthy volunteers, plasma amantadine clearance ranged from 0.2 to 0.3 L/h/kg after the administration of 5–25 mg intravenous doses. In six healthy volunteers, the ratio of amantadine renal clearance to apparent oral plasma clearance was 0.79 ± 0.17 (mean ± SD).[9]

TABLE 2: Amantadine clearance and half-life.

Parameters	Value
Oral clearance	0.28 ± 0.11 L/h/kg (range: 0.14–0.62 L/h/kg)
Half-life	17 ± 4 h (range: 10–25 h)

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The apparent oral plasma clearance of amantadine is reduced, and the plasma half-life and plasma concentrations are increased in healthy elderly individuals aged 60 years and older. In another study with seven healthy, elderly male volunteers, the apparent plasma clearance of amantadine was 0.10 ± 0.04 L/h/kg (range: 0.06–0.17 L/h/kg) and the half-life was 29 ± 7 hours (range: 20–41 h) with single amantadine dose administration of 25–75 mg. However, the reason for changes could be due to decline in renal function or could be age related which is not known. In a study of young healthy subjects (n = 20), mean renal clearance of amantadine, normalized for body mass index, was 1.5-fold higher in males compared to females ($p < 0.032$). Compared with otherwise healthy adult individuals, the clearance of amantadine is significantly reduced in adult patients with renal impairment. In patients on chronic maintenance hemodialysis, with creatinine clearance < 40 mL/min/1.73 m^2, there is an increase in the elimination half-life by two- to threefold. During hemodialysis, amantadine is removed in negligible amounts. Urine pH has an influence on excretion of amantadine; therefore, the excretion rate of amantadine increases when urine is acidic. Administration of urine-acidifying drugs may increase the elimination of the drug from the body.[9]

SUMMARY

- Amantadine is a synthetic tricyclic amine that belongs to the class of aminoadamantanes having an NMDA receptor antagonist activity.
- It is an antiparkinsonian agent and virostatic anti-influenza drug.
- Amantadine improves bradykinesia, rigidity, and tremor and has antidyskinetic effects.
- Amantadine increases norepinephrine levels and has pharmacological actions that are like those of tricyclic antidepressants.

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- Amantadine may also have immunomodulatory properties. It restored the production of interleukin (IL)-2, which is dysfunctional in patients with Parkinson's disease.
- Amantadine is well absorbed orally and attains maximum concentration at approximately 3.3 hours.
- Amantadine has half-life of approximately 16 hours and approximately 90% of amantadine is excreted unchanged in urine.
- The usual clinical dose of amantadine is 100 mg twice daily, which can be increased up to 400 mg/day.

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Salient Features

- Written by practicing key opinion leaders in neurology.
- Covers basic aspects of Parkinsonism with description of various symptoms, pathophysiology, and management approach.
- Describes in detail the role of amantadine in the management of parkinsonism highlighting its clinical and safety parameters.
- Illustrated and summarized with tables and figures to enhance reading experience.
- One-stop information for practising neurologists and clinical practitioners on parkinsonism and role of amantadine.

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