Amantadine hydrochloride is a stable white or nearly white crystalline powder, freely soluble in water and soluble in alcohol and in chloroform.

Amantadine hydrochloride has pharmacological actions as both an anti-Parkinson and an antiviral drug.

Amantadine hydrochloride oral solution contains 50 mg of amantadine hydrochloride per 5 mL and has the following inactive ingredients: artificial raspberry flavor, citric acid, methylparaben, propylparaben, purified water, and sorbitol.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action: Antiviral**

The mechanism by which amantadine exerts its antiviral activity is not clearly understood. It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the 

**Pharmacodynamics**

**Mechanism of Action: Parkinson’s Disease**

The mechanism of action of amantadine in the treatment of Parkinson’s disease is not clearly understood. It is known that amantadine reduces the release of dopamine into the synapse, thereby decreasing the symptoms of Parkinson’s disease.

**Drug Resistance**

Influenza A virus strains other than those caused by influenza A virus are not known to be resistant to amantadine. Therefore, it is not recommended to use amantadine as a prophylaxis against these viruses.

**Mechanism of Action: Anti-Parkinsonism**

Amantadine is known to slow the progression of Parkinson’s disease, although the exact mechanism of action is not fully understood.

**Pharmacokinetics**

Amantadine hydrochloride is well absorbed orally. Maximum plasma concentrations are directly related to dose for doses up to 200 mg/day. Doses above 200 mg/day may result in a decrease in the half-life and plasma concentrations.

**Drug Interactions**

Amantadine may increase the effectiveness of other antiviral drugs by inhibiting viral RNA polymerase.

**Adverse Effects**

The most common adverse effects of amantadine are nausea, vomiting, and headache. Other adverse effects include dizziness, drowsiness, and hallucinations.

**Overdosage**

Overdosage with amantadine hydrochloride may result in an increased risk of side effects, including nausea, vomiting, diarrhea, and dizziness. In severe cases, it may lead to seizures and respiratory arrest.

**CONTRAINDICATIONS**

Amantadine hydrochloride is contraindicated in patients with known hypersensitivity to amantadine hydrochloride or to any of the other ingredients in amantadine hydrochloride.

**WARNINGS**

Deaths have been reported from overdose with amantadine hydrochloride. The lowest reported acute lethal dose was 1 gram. Acute toxicity may be attributable to the anticholinergic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension. (see DOSAGE AND ADMINISTRATION; Dosage of Implantation and OVERDOSE).

**Suicide Attempts**

Suicide attempts, some of which have been fatal, have been reported in patients treated with amantadine hydrochloride. Many of whom received short courses for influenza treatment or prophylaxis. The incidence of suicide attempts is not known to be different in patients with Parkinson’s disease treated with amantadine hydrochloride than in the general population. Suicide attempts and suicidal ideation have been reported in patients with and without prior history of psychiatric illness. Amantadine hydrochloride can exacerbate mental problems in patients with a history of psychotic disorders or substance abuse. Patients who attempt suicide may exhibit abnormal mental states which include disorientation, confusion, delusions, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, somnolence or insomnia. Because of the possibility of serious adverse effects, caution should be observed when prescribing responses to natural disease or vaccination and may be protected when later exposed to antigenically related viruses. Following vaccination during an influenza A outbreak, amantadine hydrochloride prophylaxis should be considered for the 2- to 4-week period required to develop an antibody response.

**Drug Resistance**

Amantadine hydrochloride is also indicated in the treatment of uncomplicated respiratory tract illness caused by influenza B virus strains especially when administered early in the course of illness. There are no well-controlled clinical studies demonstrating that treatment with amantadine hydrochloride will result in a more rapid resolution of illness compared to placebo. The following points should be considered before initiating treatment or prophylaxis with amantadine hydrochloride:

- Amantadine hydrochloride is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention (CDC) in the Prevention of Influenza in Health Care Workers, 2007. (see DOSAGE AND ADMINISTRATION; Dosage of Implantation and OVERDOSE).

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amantadine hydrochloride to patients being treated with drugs having CNS effects, or for whom the potential risks outweigh the benefit of treatment.

CNS Effects

Patients with a history of epilepsy or other “seizures” should be observed closely for possible increased seizure activity. Patients receiving amantadine hydrochloride who note central nervous system effects (e.g., clumsiness) should be cautioned against driving or working in situations where alertness and adequate motor coordination are important.

Other

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving amantadine hydrochloride.

Patients with Parkinson’s disease improving on amantadine hydrochloride should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebitis/bromhidrosis.

Because amantadine hydrochloride has anticholinergic effects and may cause mydriasis, it should not be given to patients with untreated angle closure glaucoma.

PRECAUTIONS

Amantadine hydrochloride should not be discontinued abruptly in patients with Parkinson’s disease since a few patients have experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration in the parkinsonian state that was suddenly stopped. The dose of anticholinergic drugs or of amantadine hydrochloride should be reduced if atropine-like effects appear when these drugs are used concurrently. Abrupt discontinuation may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and suicidal attempts.

Neuroleptic Malignant Syndrome (NMS)

Sporadic cases of possible Neuroleptic Malignant Syndrome (NMS) have been reported in association with dose reduction or withdrawal of amantadine hydrochloride therapy. Therefore, patients should be observed carefully when the dosage of amantadine hydrochloride is being reduced or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia; neurologic findings including muscle rigidity, involuntary movements, altered consciousness; mental status changes; other disturbances such as acute autonomic dysfunction, tachycardia, tachypnea, hyperpyrexia, or hypotension; laboratory findings such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum creatine phosphokinase. The early diagnosis of this condition is important for the clinical management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal symptoms and signs (EPS). Other important considerations in the differential diagnosis includes central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring, and 2) treatment of any potential secondary medical condition that may cause or exacerbate the condition. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene are often used in the treatment of NMS, however, their effectiveness has not been demonstrated in controlled studies.

Renal Disease

Because amantadine hydrochloride is mainly excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine hydrochloride should be reduced in patients with renal impairment and in individuals who are 65 years of age or older (see DOSAGE AND ADMINISTRATION; Dosage for Impaired Renal Function).

Liver Disease

Care should be exercised when administering amantadine hydrochloride to patients with liver disease. Rare instances of reversible elevation of liver enzymes have been reported in patients receiving amantadine hydrochloride, though a specific relationship between the drug and such changes has not been established.

Impulse Control/Compulsive Behaviors

Postmarketing reports suggest that patients treated with anti-Parkinson medications can experience intense urges to gamble, increased sexual urges, intense urges to spend money uncontrollably, and other intense urges. Patients may be unable to control these urges while taking one or more of the medications that are generally used for the treatment of Parkinson’s disease and that increase central dopaminergic tone, including amantadine hydrochloride. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. The cause of these behaviors as abnormal it is important for prescribers to specifically ask patients or their caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with amantadine hydrochloride. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking amantadine hydrochloride.

Malignancy

Epidemiological studies have shown that patients with Parkinson’s disease have a higher risk (2- to approximately 6-fold higher) for malignancy than the general population. Whether the increased risk observed was due to Parkinson’s disease or other factors, such as drugs used to treat Parkinson’s disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for malignancies for the duration of amantadine hydrochloride treatment. Physicians should consider dose reduction or stopping the medication if a patient develops such malignancy while taking amantadine hydrochloride.

Pregnancy

The effect of amantadine on fertility has not been adequately established, that is, in studies conducted under Good Laboratory Practice (GLP) and according to current recommended methodology. In a three litter, non-GLP study conducted in rats, amantadine hydrochloride at a dose of 32 mg/kg/day (equal to the maximum recommended human dose on a mg/m² basis) administered to both males and females slightly impaired fertility. There were no effects on fertility at a dose level of 10 mg/kg/day (equal to the maximum recommended human dose on a mg/m² basis); intermediate doses were not tested.

Failing fertility has been reported during human in vitro fertility (IVF) when the sperm donor ingested amantadine 2 weeks prior to, and during the IVF cycle.

Tetracyclines

Induction of pharmacologic effects

Induction of pharmacologic effects

Pregnancy Category C

The effect of amantadine on embryotrophic and peri-postnatal development has not been adequately established, that is, in studies conducted under Good Laboratory Practice (GLP) and according to current recommended methodology. However, in two non-GLP studies in rats in which females were dosed from 5 days prior to mating to Day 6 of gestation or on Days 7 to 14 of gestation, amantadine hydrochloride produced increases in embryonic death at an oral dose of 100 mg/kg (or 3 times the maximum recommended human dose on a mg/m² basis) in the non-GLP rat study in which females were dosed on Days 7 to 14 of gestation, there was a marked increase in severe visceral and skeletal malformations at oral doses of 50 to 100 mg/kg (or 1.5 and 3 times, respectively, the maximum recommended human dose on a mg/m² basis). The no dose for teratogenicity was 37 mg/kg (equal to the maximum recommended human dose on a mg/m² basis). The safety margins reported may not accurately reflect the risk considering the questionable quality of the study on which they are based, nor did these results result in further controlled studies in pregnant women. Human data regarding teratogenicity after maternal use of amantadine is scarce. Tetracycline of Follat and Blial heminemia (normal karyotype) occurred in an infant exposed to amantadine during the first trimester of pregnancy (100 mg P.O. for 7 days during the 6th and 7th week of gestation). Cardiovascular maldevelopment (anomalies, including pulmonary atresia) was associated with maternal exposure to amantadine (100 mg/d) administered during the first 2 weeks of pregnancy. Amantadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

Nursing Mothers

Amantadine hydrochloride is excreted in human milk. Use is not recommended in nursing mothers.

Pediatric Use

The safety and efficacy of amantadine hydrochloride in new-born infants and infants below the age of 1 year have not been established.

Use in the Elderly

Because amantadine hydrochloride is primarily excreted in the urine, it accumulates in the plasma and in the body when renal function declines. Thus, the dose of amantadine hydrochloride should be reduced in patients with renal impairment and in individuals who are 65 years of age or older. The dose of amantadine hydrochloride may need reduction in patients with severe congestive heart failure, peripheral edema, or orthostatic hypotension (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

To report SUSPECTED ADVERSE REACTIONS, contact Hi-Tech Pharmacal Co., Inc., at 1-900-262-9010 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
The adverse reactions reported most frequently at the recommended dose of amantadine hydrochloride (5 to 10%) are: nausea, dizziness, (lightheadedness), and insomnia. Less frequently (1 to 5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anxiety, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue.

Infrequently (0.1 to 1%) occurring adverse reactions are: congestive heart failure, psychosis, urinary retention, dyspepsia, skin rash, vomiting, weakness, slurred speech, euphoria, thrombocytopenia, anemia, hyperkinesia, hypotension, decreased libido, and visual disturbance, including punctate subepithelial or other corneal opacities, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palsy. Rare (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, eosinophilic, amylase, lipase, cholesterol, suicidal attempt, suicide, and suicidal ideation (see WARNINGS). Other adverse reactions reported during postmarketing experience with amantadine hydrochloride usage include:

Nervous System/Psychiatric
coma, stupor, delirium, hypokinnesia, hyperkinesia, delusions, aggressive behavior, paranoid reaction, manic reaction, involuntary muscle contractions, gait abnormalities, paresthesia, EEG changes, and tremor. Abrupt discontinuation may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and slurred speech;

Cardiovascular
cardiac arrest, arrhythmias including malignant arrhythmias, hypotension, and tachycardia;

Respiratory
acute respiratory failure, pulmonary edema, and tachypnea;

Gastrointestinal
diaphoria;

Hematologic
leukocytosis, agranulocytosis;

Special Senses
keratitis and mydriasis;

Skin and Appendages
pruritus and diaphoresis;

Miscellaneous
neuroleptic malignant syndrome (see WARNINGS), allergic reactions including anaphylactic reactions, edema and fever;

Laboratory Test
elevated: CPK, BUN, serum creatinine, alkaline phosphatase, LDH, bilirubin, GGT, SGOT, and SGPT.

OVERDOSAGE
Deaths have been reported from overdose with amantadine hydrochloride. The lowest reported acute lethal dose was 1 g, because some patients have attempted suicide by swallowing with amantadine, prescriptions should be written for the smallest quantity consistent with good patient management.

Acute toxicity may be attributable to the anticholinergic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, gastrointestinal, and central nervous system effects that have been reported include amantadine hydrochloride increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians. Patients initially deriving benefit from amantadine hydrochloride not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of amantadine hydrochloride for several weeks, followed by reinstitution of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy
Some patients who do not respond to anticholinergic antiparkinson drugs may respond to amantadine hydrochloride.

When amantadine hydrochloride or anticholinergic antiparkinson drugs are used with marginal benefit, concomitant use may produce additional benefit.

When amantadine hydrochloride and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. Amantadine hydrochloride should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.

When amantadine hydrochloride is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of development of side effects may possibly regain lost benefit with the addition of amantadine hydrochloride.

Dosage for Drug-Induced Extrapyramidal Reactions
Adult
The usual dose of amantadine hydrochloride is 100 mg twice a day. Occasionally, patients whose responses are not optimal with amantadine hydrochloride at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses.

Dosage for Impaired Renal Function
Depending upon creatinine clearance, the following dosage adjustments are recommended:

<table>
<thead>
<tr>
<th>CREATININE CLEARANCE (mL/min/1.73 m²)</th>
<th>AMANTADINE HYDROCHLORIDE DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 to 50</td>
<td>200 mg 1st day and 100 mg each day thereafter</td>
</tr>
<tr>
<td>15 to 29</td>
<td>200 mg 1st day followed by 100 mg on alternate days</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>200 mg every 7 days</td>
</tr>
</tbody>
</table>

The recommended dosage for patients on hemodialysis is 200 mg every 7 days.

HOW SUPPLIED
Amantadine Hydrochloride Oral Solution USP, 50 mg per 5 ml (1 teaspoonful) is supplied as a clear raspberry flavored oral solution supplied in a 16 fl oz (473 ml) container, and in 10 ml unit dose cups, packaged in trays of 10. Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature].

Dispense in original container or in a tight container as defined in USP, with a child-resistant closure (as required).

REFERENCES

Dyazide is a registered trademark of GlaxoSmithKline.

Manufactured by: HI-TECH PHARMACAL CO., INC., Amityville, NY 11701
Made in USA
Rev. 807.03 6’11
MG # 8847