Amantadine hydrochloride is a weak, non-competitive NMDA receptor antagonist (K1 = 25.0 μg/mL) depending upon the assay protocol used, size of cell type used. Host cells in tissue culture readily tolerated amantadine and the clinical response to therapy has not been established in man. Sensitivity test results, expressed as the susceptibility of influenza A virus to amantadine, are generally unhelpful when used during virus replication. It does not appear to interfere with the immunogenicity of inactivated influenza A virus vaccine.

**Clinical Pharmacology**

**Mechanism of Action**

Amantadine inhibits the replication of influenza A virus isolates of type A/PR/8/34 (H2N2), H1N1, and H3N2. Its mode of action is to prevent virus assembly during virus replication. It does not appear to interfere with the immunogenicity of inactivated influenza A virus vaccine.

**Antiviral Activity**

Amantadine inhibits the replication of influenza A virus isolates of type A/PR/8/34 (H2N2), H1N1, and H3N2. Its mode of action is to prevent virus assembly during virus replication. It does not appear to interfere with the immunogenicity of inactivated influenza A virus vaccine.

**Dose-Response**

Studies in patients with reduced in vitro sensitivity to amantadine have been isolated from epidemic strains in areas where amantadine-resistant strains are being used. Influenza viruses with reduced in vitro sensitivity to amantadine have been isolated in patients with Parkinson’s disease and drug-induced extrapyramidal reactions is not known. Doses of 100 mg three times daily are recommended to suppress symptoms caused by influenza A virus infection. Amantadine hydrochloride capsules are also indicated in the treatment ofparkinsonism and drug-induced extrapyramidal reactions.

**Pharmacokinetics**

Amantadine is well absorbed orally. Maximum plasma concentrations are reached 1-3 hours after oral administration. Amantadine is removed from the circulation by metabolicosynthesis and by glomerular filtration and tubular secretion. Eight metabolites of amantadine have been identified in human urine. One metabolite, an N-acetylated compound, was quantified in human urine and accounted for 5% to 15% of the administered dose. Plasma acetylamantadine accounted for up to 80% of the concurrent amantadine concentration in 5 of 12 healthy volunteers following the ingestion of a 200 mg dose of amantadine. Acetylamantadine was not detected in the plasma of the remaining seven volunteers. The contribution of this metabolite to efficacy or toxicity is not known.

There appears to be a relationship between plasma amantadine concentrations and toxicity. As concentration increases, toxicity appears to increase. As concentration increases, toxicity appears to increase. As concentration increases, toxicity appears to increase.

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Cardiovascular maldevelopment (single ventricle with pulmonary stenosis in newborn infants and infants below the age of 1 year have not been established.

Usage in the Elderly

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

Adverse Reactions

The adverse reactions most frequently at the recommended dose of amantadine hydrochloride capsules are nausea, dizziness (lightheadedness), and insomnia. Less frequently (1 to 5%) reported adverse reactions are: vomiting, altered mental and behavioral changes, paresthesia, hallucinations, confusion, depression, anxiety, disorientation, agitation, delirium, ataxia, tremor, akathisia, and akinesia. Rare (less than 0.1%) occurring adverse reactions are: instances of convulsion, leukopenia, neutropenia, esematous dermatitis, oculogyric crises, suicidal attempt, suicide, and suicidal ideation.

Other adverse reactions reported during postmarketing experience with amantadine use include:

Nervous System/Psychoactive

- Coma, stupor, delirium, hypokinesia, hypertonia, delusions, aggressive behavior, paranoid reaction, mania, reaction, involuntary muscle contractions, gait abnormalities, paresthesia, EEG changes, and tremor. Abrupt discontinuation may also contribute to the observation or if related drugs produce a similar response.

Cardiovascular

- Cardiac arrest, arrhythmias including malignant arrhythmias, hypotension, and tachycardia.

Respiratory

- Acute respiratory failure, pulmonary edema, and tachypnea.

Gastrointestinal

- Diaphoresis.

Hematologic

- Leukopenia, agranulocytosis.

Special Senses

- Headache and visual disturbances.

Skin and Appendages

- Pruritus and diaphoresis.

Adverse effects on fertility at a dose level of 10 mg/kg/day (or 0.3 times the maximum recommended human dose on a mg/m² basis); administration to both males and females slightly impaired fertility. There were no effects on fertility at a dose level of 10 mg/kg/day (or 0.3 times the maximum recommended human dose on a mg/m² basis); intermediate doses were not tested.

Fertility

The effects of amantadine on fertility have not been adequately tested, 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 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 and 100 mg/kg (or 1.5 and 3 times, respectively), 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 and 100 mg/kg (or 1.5 and 3 times, respectively), the maximum recommended human dose on a mg/m² basis. The no-effect levels for teratogenicity were 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. There are no adequate and well-controlled studies in pregnant women. Human data regarding teratogenicity is insufficient and the risk cannot be disregarded. Data are insufficient to permit the detection of teratogenic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity. Cardiac dysfunction includes arrhythmia, tachycardia and hypertension. Pulmonary edema and respiratory distress (including adult respiratory distress syndrome) have been reported; renal dysfunction (including increased BUN, decreased creatinine clearance and renal insufficiency) may occur. The effects that have been reported include insulin, anxiety, agitation, aggression, hyperventilation, tachycardia, gait abnormality, tremor, confusion, disorientation, depression, disorientation, fear, delirium, hallucinations, psychotic reactions, delirium, somnolence and coma. Seizures may be observed in patients in whom the plasma concentration of amantadine may be increased by rapid administration.

The recommended dosage for patients on hemodialysis is 200 mg every 12 hours. Occasionally, patients whose responses are not optimal with amantadine hydrochloride capsules at 200 mg daily may benefit from an 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 capsules may decrease the dose or discontinue therapy after several weeks. If the drug is continued, the dose may be increased to 100 mg twice daily, if necessary.