Amantadine (Symmetral®)

Class:
Amantadine is a semisynthetic petroleum hydrocarbon derivative.

Antiviral Activity:
Amantadine has activity against influenza A with little or no activity against influenza B.

Mechanism of Action:
Amantadine interferes with the release of infectious viral nucleic acid into the host cell through interaction with the transmembrane domain of the M2 protein of the virus. It also appears to prevent virus assembly during replication in some cases.

Mechanism of Resistance:
Resistance to amantadine occurs due to point mutations in the M gene that leads to single amino acid substitutions in the transmembrane domain of the M2 protein. This allows the virus to uncoat in the presence of amantadine. Resistant variants show cross-resistance to amantadine, rimantadine, and related compounds. Consequently, higher drug doses or alternative drugs with the same antiviral target are unable to overcome this resistance.

Pharmacokinetics:
Amantadine bioavailability ranges from 66 to 100%. The tablet and syrup formulations appear equally bioavailable. Plasma protein binding of amantadine is approximately 67%. Amantadine undergoes N-acetylation, N-methylation and formation of Schiff bases and N-formiates. N-acetylamantadine is the principal metabolite. Amantadine is eliminated by both glomerular filtration and renal tubular secretion.

Adverse Effects:
Common adverse events are nervousness, lightheadedness, difficulty concentrating, insomnia, fatigue, slurred speech, loss of appetite, and nausea. More serious CNS adverse effects include hyperexcitability, confusion, depression, tremors, mood disturbance, ataxia and gait disturbance, hallucinations, psychosis, and coma have been seen. Adverse effects are related with the dose of amantadine and are also influenced by renal function.

Dosage:
Tablet 100mg (100 and 500 tablet bottle)
Syrup 50mg/5ml (480ml bottle)

Children:
< 1 year old – no data available
1-9 years old – 5 mg/kg/day (max. 150 mg daily in two divided doses)
10-17 years old – 1.4 mg/kg (max. 100 mg twice daily)

Adults:
18-64 years old – 1.4 mg/kg (max. 100 mg twice daily)
≥ 65 – 1.4 mg/kg (max. 100 mg daily)
Disease state based dosing:
Children:
5 mg/kg/day (max. 150 mg/day in 2 divided doses)
   Reduce dose in proportion to reduction in CrCl:
      Normal CrCl
      1-2 years old = 90 mL/min
      > 2 years old = 115 mL/min
Adults:
CrCl ≥ 80 ml/min 1.4 mg/kg every 12 hours
CrCl 79-35 ml/min 1.4 mg/kg every 24 hours
CrCl 34-25 ml/min 1.4 mg/kg every 2 days
CrCl 24-15 ml/min 1.4 mg/kg every 3 days
CrCl < 15 ml/min 1.4 mg/kg every 7 days

Contraindications/Warnings/ Precautions:
Deaths have been reported in patients who overdose on amantadine. Amantadine can exacerbate mental illness in patients with history of psychiatric disorders or substance abuse. Patients with a history of seizures, congestive heart failure and peripheral edema should be followed closely while on amantadine.

Drug Interactions:
Antihistamines, antidepressants, and anticholinergic drugs increase the risk of CNS side effects when combined with amantadine. The combination of triamterene and hydrochlorothiazide increases CNS toxicity and trimethoprim-sulfamethoxazole has been shown to increase amantadine toxicity. Cases of neuroleptic malignant syndrome have been reported in patients who have abruptly discontinued or reduced their dose of amantadine.

Pregnancy:
Category C: Risk unknown. Human studies inadequate.

 Monitoring Requirements:
Renal function, blood pressure, neurologic exam

Brand names/Manufacturer:
Symmetral®/ Endo Pharmaceuticals Inc, Bristol Myers Squibb Pharma Co
Amantadine/ Sandoz Pharmaceuticals, Upsher-Smith Laboratories Inc, Silarx Pharmaceuticals Inc, Pharmaceutical Assoc Inc Div Beach Products, Bristol Myers Squibb Pharma Co, Qualitest Pharmaceuticals Inc, Hi Tech Pharmacal Co Inc, Morton Grove Pharmaceuticals Inc, Endo Pharmaceuticals Inc Dba Endo Generic Products, USL Pharma Inc
Amantadine Hydrochloride/Carolina Medical Products Co