Pentamidine

Brand Name: Nebupent
Drug Class: Opportunistic Infection and Other Drugs

Drug Description

Pentamidine isethionate is an aromatic, diamidine-derivative antiprotozoal agent. It is structurally and pharmacologically similar to stilbamidine. The presence of a benzenecarboximidamide (aromatic amidine, benzamidine) group is associated with pentamidine's trypanosomicidal activity, and the presence of both benzenecarboximidamide groups is necessary for this activity. [1]

HIV/AIDS-Related Uses

Pentamidine isethionate was approved by the FDA on June 15, 1989, for use in the treatment of Pneumocystic jiroveci (formerly Pneumocystis carinii) pneumonia (PCP) in AIDS patients. Although pentamidine may be administered intramuscularly (IM) or intravenously (IV) for the treatment of PCP, only the IV route is currently recommended. Cotrimoxazole (sulfamethoxazole-trimethoprim) is considered the primary agent for PCP in patients who can tolerate it.[2]

Pentamidine isethionate is also available in an orally inhaled form via nebulization.[3] Aerosolized pentamidine is indicated in both primary prophylaxis (HIV infected patients with a CD4 lymphocyte count less than or equal to 200 cells/mm3) and secondary prophylaxis (people who have already had at least one episode) of PCP.[4]

Non-HIV/AIDS-Related Uses

Pentamidine isethionate is indicated as secondary prophylaxis in the treatment of PCP in patients who have already had at least one episode of the illness and in immunocompromised patients.[5] Pentamidine is one of several alternative agents that can be used for the treatment of patients whose infection does not respond to cotrimoxazole or who cannot tolerate cotrimoxazole, or for the treatment of patients with a history of severe allergic reactions to either component of cotrimoxazole.[6]

Pharmacology

Limited information is available on the pharmacokinetics of pentamidine isethionate. The antiprotozoal mechanisms of action of pentamidine isethionate have not been fully elucidated, but presumably several mechanisms are involved, with variability between the different types of protozoa. Most information on the antiprotozoal activity of aromatic diamidines such as pentamidine has been derived from studies involving trypanosomes. In vitro, pentamidine appears to be directly lethal to Pneumocystis jiroveci, although the drug only moderately inhibits glucose metabolism, protein and RNA synthesis, and intracellular amino acid transport in this organism at concentrations attainable in vivo.[7] Pentamidine may interfere with nucleotide incorporation into RNA and DNA; inhibit oxidative phosphorylation and biosynthesis of DNA, RNA, protein, and phospholipid; or interfere with folate transformation.[8]

In an early study in PCP patients, plasma pentamidine concentrations did not vary appreciably throughout the day and did not increase with successive doses of the drug. Although plasma drug concentrations generally did not increase immediately after dose administration, any increase usually occurred within 1 hour of administration. Highest plasma drug concentrations occurred in patients with varying degrees of renal impairment.[9] Following a single 4 mg/kg intramuscular (IM) or IV dose of pentamidine isethionate in patients with AIDS and PCP, peak plasma concentrations averaged 209 ng/ml approximately 40 minutes after the IM dose and 612 ng/ml after completion of the IV infusion. Following IV administration of pentamidine isethionate 3.7 to 4 mg/kg daily in HIV infected patients with PCP, mean peak plasma concentrations were 175.3, 210.9, or 256.7 ng/ml on Day 1, 4, or 7, respectively.[10] Following oral inhalation of pentamidine isethionate via nebulization, bronchoalveolar lavage fluid concentrations of the drug are substantially higher (at least 5 to 10 times) than those attained following IV administration. Pentamidine appears to undergo limited absorption from the respiratory tract into systemic circulation; Cmax appears to occur at or

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near completion of the inhalation administration. Systemic accumulation of pentamidine does not appear to occur during oral inhalation therapy.[11]

Pentamidine isethionate is rapidly distributed and bound to tissues after administration. Data from AIDS patients indicate that, after parenteral administration of pentamidine, highest concentrations of the drug are found in the liver, followed by the kidneys, adrenals, spleen, lungs, and pancreas. Further studies are needed, but these data also suggest that continued parenteral administration beyond the first week of therapy may not substantially increase accumulation of pentamidine in lung tissue. Pentamidine is not effective for the treatment of trypanosomiasis involving the central nervous system (CNS), leading researchers to believe that the drug penetration of the CNS is poor. Limited data from AIDS patients suggest that pentamidine may distribute into the CNS in some patients, but only in very low concentrations and after prolonged (a month or longer) therapy.[12] Aerosolized pentamidine produces concentrations approximately 10 to 100 times higher in lungs than would a comparable dose of IV pentamidine.[13]

Deposition of orally inhaled pentamidine shows considerable interindividual variation and appears to depend on several factors, including delivery device, particle size of aerosolized drug, dose, patient position, and nebulization efficiency. Limited data from patients with HIV infection indicate that distribution of the drug in the lungs following oral inhalation via nebulization is more uniform when the patient is in the supine, rather than sitting, position.[14]

Pentamidine isethionate is in FDA Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women, and animal reproduction studies have not been performed to date. However, studies in rabbits have shown that systemic pentamidine was associated with an increased incidence of post-implantation losses and delayed fetal ossification.[15] The drug should be used during pregnancy only when clearly needed. Spontaneous abortion has been reported during pentamidine inhalation therapy, but a causal relationship has not been established. It is not known whether pentamidine isethionate affects fertility in humans or is distributed into milk, but it apparently crosses the placenta. Because of the potential for serious adverse reactions to pentamidine isethionate in nursing infants, a decision should be made whether to discontinue taking the drug or nursing, taking into account the importance of treatment.[16]

In vitro, pentamidine is reportedly 69% bound to serum proteins. Following a single IM or IV dose of pentamidine in patients with AIDS and pneumocystis pneumonia who had normal renal function, plasma concentrations of the drug declined in a biphasic manner, with a mean elimination half-life of 54 and 18 minutes in the initial phase, respectively, and 9.4 and 6.4 hours in the terminal elimination phase, respectively. Pentamidine appears to be eliminated very slowly from tissues in which the drug principally accumulates (e.g., liver, lungs); currently available assays may be inadequate to determine a third, prolonged elimination phase. Limited data suggest that the elimination half-life is not substantially altered in patients with mild to moderated renal impairment but may be prolonged up to 2 days or longer in patients with severe renal impairment.[17]

Little is known about the elimination of pentamidine in humans.[18] Following daily IM administration of pentamidine isethionate in a study in patients with PCP who had varying degrees of renal function, 24 hour urinary drug excretion after 1-10 days of therapy was generally 15% to 20% of the daily dose; most urinary excretion occurred within the first 6 hours after administration of a dose. In several patients, decreasing amounts of pentamidine were excreted in urine for up to 6 to 8 weeks after discontinuance of the drug. Following a single 4 mg/kg IM or IV dose in patients with normal renal function, about 2.5% to 5% of the dose was excreted in urine as unchanged drug in 24 hours, mainly within the first 8 hours after administration of the drug; similar amounts were also excreted in urine as unchanged drug in 24 hours in patients with mild to moderate renal impairment. There is no information available regarding human fecal excretion of pentamidine, but in mice, the amount excreted in urine and feces is in a ratio of about 4:1.[19] Limited data suggest

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that pentamidine is not appreciably removed by hemodialysis or peritoneal dialysis; information on the pharmacokinetics of pentamidine isethionate after oral inhalation in patients with hepatic or renal dysfunction is not available.[20]

Little information is available on natural or acquired resistance of protozoa to pentamidine. In vitro studies with Trypanosoma and Crithidia suggest that resistance to pentamidine may result from reduced uptake of the drug by these organisms. Trypanosomes resistant to pentamidine are generally cross resistant to other aromatic diamidine derivatives (e.g., stilbamidine).[21]

Adverse Events/Toxicity

The most common adverse effects associated with parenteral administration or oral inhalation of pentamidine isethionate appear to be nephrotoxicity or cough and bronchospasm, respectively. Other adverse effects seen with use of pentamidine isethionate include diabetes mellitus or hyperglycemia, elevated liver function tests, hypoglycemia, hypotension, leukopenia or neutropenia, nephrotoxicity, and thrombocytopenia. Less common adverse effects include anemia, cardiac arrhythmias, pancreatitis, Stevens-Johnson syndrome, phlebitis with IV injection, sterile abscess with IM injection, GI effects, and unpleasant metallic taste. These side effects may continue after medication is discontinued and may require medical attention.[22]

Prophylactic use of aerosolized pentamidine has a very low incidence of severe side effects. Many adverse reactions will be due to other medications, concurrent infections, or HIV disease itself, and may be difficult to differentiate. Possible side effects with the use of aerosolized pentamidine may include chest pain or congestion, coughing, dyspnea, skin rash, wheezing, and bitter or metallic taste.[23]

Drug and Food Interactions

Because nephrotoxic effects may be additive, the concurrent or sequential use of pentamidine isethionate and other drugs with similar toxic potentials, such as aminoglycosides, amphotericin B, capreomycin, colistin, cisplatin, foscarnet, methoxyflurane, polymyxin B, or vancomycin, should be closely monitored or avoided.[24] Because of pentamidine's nephrotoxic potential, the drug should be used with caution in patients with renal dysfunction and the need to reduce dosage in such patients must be based on the clinical status of the patient and the potential risks and benefits.[25]

Contraindications

Pentamidine isethionate is contraindicated in patients with a history of hypersensitivity to pentamidine isethionate.[26]

The manufacturers state that parenteral pentamidine isethionate should be used with caution in patients with hypertension, hypotension, ventricular tachycardia, pancreatitis, hyperglycemia, hypoglycemia, hypocalcemia, leukopenia, thrombocytopenia, anemia, or hepatic or renal dysfunction.[27]

Clinical Trials

For information on clinical trials that involve Pentamidine, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Pentamidine AND HIV Infections.

Dosing Information

Mode of Delivery: Oral (inhalation via nebulization), intramuscular, or intravenous infusion.[28]

Dosage Form: Pentamidine isethionate solution for inhalation containing pentamidine 300 mg.[29]

Pentamidine isethionate powder for intramuscular or IV injection containing pentamidine 300 mg.[30]

Storage: Prior to reconstitution, store pentamidine isethionate for inhalation between 15 C and 30 C (59 F to 86 F) unless otherwise specified by the manufacturer.[31]

Store pentamidine isethionate sterile powder for injection between 15 C and 30 C (59 F to 86 F) and

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Dosing Information (cont.)

protect from light. Reconstituted solutions of the drug for injection or for oral inhalation should also be protected from light. To avoid crystallization, store reconstituted pentamidine isethionate between 22 C and 30 C (72 F to 86 F).[32]

Chemistry

CAS Name: Benzamidine, 4,4'-(pentamethylenedioxy)di-, bis(beta-hydroxyethanesulfonate)[33]

CAS Number: 140-64-7[34]

Molecular formula: C23-H36-N4-O10-S2[35]

C46.61%, H6.12%, N9.45%, O27.0%, S10.82%[36]

Molecular weight: 592.69[37]

Melting point: 180 C[38]

Physical Description: White or almost white crystals or powder. The drug is hygroscopic and may be odorless or have a slight butyric odor.[39]

Stability: Following reconstitution with sterile water for injection, pentamidine isethionate solutions for parenteral use containing 60 mg/ml to 100 mg/ml are reportedly stable for 48 hours at room temperature. Manufacturers recommend that unused portions of reconstituted solutions be discarded. Reconstituted solutions of drug that have been further diluted in 5% dextrose for injection to a concentration of 1 mg/ml or 2.5 mg/ml for IV infusion are stable for up to 24 hours at room temperature. Reconstituted solutions that have been diluted to a concentration of 1 mg/ml to 2 mg/ml in 5% dextrose or 0.9% sodium chloride for injection in PVC bags are reportedly stable for 24 hours when exposed to normal fluorescent light at 22 C to 26 C.[40]

After reconstitution with sterile water for injection, solutions of pentamidine isethionate for oral inhalation are reportedly stable for 48 hours in the original vial when stored at room temperature and protected from light.[41]

Solubility: About 100 mg/ml at 25 C (77 F) in water.[42]

Soluble in glycerol, with solubility increasing upon warming; slightly soluble in alcohol; and insoluble in ether, acetone, chloroform, and liquid petroleum.[43]

Other Names

Diamidine[44]

Lomidine[45]

Pentamidine mesylate[46]

Pentamidina[47]

Pentamidine isethionate[48]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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