Zidovudine (Retrovir®, AZT)

Class:
Zidovudine is a thymidine analog in the nucleoside reverse transcriptase inhibitor class.

Antiviral Activity:
Zidovudine is more active against acutely infected cells as compared to chronically infected cells.

Mechanism of Action:
Zidovudine is phosphorylated to zidovudine-triphosphate, which competes with endogenous nucleotides for incorporation into the viral DNA and once incorporated causes chain termination due to the lack of a 3' OH group.

Mechanism of Resistance:
Resistance to NRTIs occurs through two mechanisms; decreased incorporation of NRTIs into the viral DNA and increased excision of NRTIs from the viral DNA.

Pharmacodynamics:
In vitro IC_{50} (50% inhibitory concentration) was 0.003 to 0.013mcg/mL and the IC_{90} (90% inhibitory concentration) was 0.03 to 0.3 mcg/mL.

Pharmacokinetics:
Zidovudine is well absorbed and undergoes first-pass hepatic glucuronidation to zidovudine glucuronide. Peak plasma concentrations occur at 0.5-1.0 hour after dosing in the fasted state. Both zidovudine glucuronide and zidovudine are eliminated through renal excretion with tubular secretion contributing to the elimination.

Adverse Effects:
Anemia, neutropenia, headache, fatigue, nausea, and myalgia are the most common toxicities.

Dosage:
100mg capsule (100 capsule bottle)
300mg tablet (60 tablet bottle)
Syrup 50mg/5ml (240mg bottle)

Adult: 300mg twice daily
600mg once a day has been studied. This dose has been shown to have antiviral activity. However, it is less marked and more slowly achieved than 300mg twice a day.

Pediatric:
Preterm Infants (<30 weeks gestational age)
Oral: 2 mg/kg q12h IV: 1.5 mg/kg q12h (Both increased to q8h at four weeks of age)
Preterm Infants (=30 weeks gestational age)
Oral: 2 mg/kg q12h IV: 1.5 mg/kg q12h (Both increased to q8h at two weeks of age)
Neonates (within 12 hours after birth through 6 weeks of age)
Oral: 2 mg/kg q6h IV: 1.5 mg/kg, infused over 30 minutes, q6h
Pediatrics (6 weeks to 12 years)
Oral: 160 mg/m^2 q8h IV intermittent: 120 mg/m^2 q6h IV continuous: 20 $mg/m^2/hr$

Take with or without food

Disease state based dosing:
Clcr >10 mL/min - 300 mg twice daily
Clcr <10 mL/min - 300 mg once daily
Hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) - 300 mg once daily

Hepatic failure – no significant data to make recommendations on dose adjustments Severe hepatic failure –the daily dose should be reduced 50% or the dosing interval should be doubled.

Contraindications/Warnings/Precautions:
Zidovudine should be used with caution in patients who have bone marrow compromise (i.e. granulocyte count <1,000 cells/mm ^{3} or hemoglobin <9.5 g/dL)
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of NRTIs.

Drug Interactions:
The use of zidovudine and stavudine (d4T) concomitantly is contraindicated due to antagonism that occurs between these two thymidine analogues. Zidovudine plasma concentrations are decreased 25% by concurrent nevirapine use. Ritonavir induces glucuronidation and has been found to reduce the zidovudine AUC by approximately 25%.

Ganciclovir, interferon-alpha and other cytotoxic or bone marrow suppressive agents (trimethoprim-sulfamethoxazole, dapsone, pyrimethamine, flucytosine, adriamycin, vinblastine, sulfadiazine, hydroxyurea, vincristine and amphotericin B) may increase the risk of hematologic toxicity associated with zidovudine. Both doxorubicin and ribavirin have demonstrated *in vitro* inhibition of zidovudine phosphorylation and antagonize its antiviral activity. Probenecid increases the AUC of zidovudine by 106%.

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

Zidovudine has proven effective in preventing mother to child transmission of HIV infection.
Recommended dosing regimen:
Women >14 weeks pregnant (continued until onset of labor):
100 mg orally 5 times per day OR
200 mg orally three times daily OR
300 mg orally twice daily
During labor and delivery:
2 mg/kg (using mother's total body weight) IV over 1 hour then 1 mg/kg/hour (using mother's total body weight) continuous IV infusion until clamping of the umbilical cord
Infant (start within 8 to 12 hours):
2mg/kg orally every 6 hours for the first six weeks of life

Monitoring Requirements:
Frequent blood counts in patients with advanced HIV disease, periodic blood counts in patients with asymptomatic or early HIV disease.

Brand names/Manufacturer:
Retrovir®
GlaxoSmithKline