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 0.013 mcg/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