

Entry of zidovudine into brain interstitial fluid is thought to occur by transport of the drug from the choroid plexus into CSF, diffusion across the ependymal lining of the ventricle and subsequent diffusion into brain tissue. It is not measurably transported across the blood–brain barrier (Terasaki and Pardridge, 1988).

As the blood–testes barrier may limit the penetration of zidovudine into the testes, it is likely that seminal levels of zidovudine are derived from prostatic fluid rather than seminal fluid (Henry *et al.*, 1988; Sikka *et al.*, 1991). A study in four asymptomatic HIV-infected men found that both zidovudine and zidovudine glucuronide levels were higher in semen than in plasma at all time points other than 1 hour after dose (peak plasma level) (Anderson *et al.*, 2000). Similarly, a study of 12 HIV-infected men on triple therapy, including zidovudine, demonstrated semen zidovudine levels that approximated those of blood plasma early in the dose interval but exceeded blood plasma levels later in the dose interval (Pereira *et al.*, 2002).

Zidovudine rapidly crosses the placenta by simple diffusion (Bawdon *et al.*, 1992; Dancis *et al.*, 1993). The amount of zidovudine which is transferred to the fetal circulation is proportional to the level in the maternal blood (Liebes *et al.*, 1990). Neither zidovudine nor its glucuronide conjugate accumulates in the fetus (Bawdon *et al.*, 1992).

Zidovudine enters breast milk. In mice who receive an intraperitoneal injection of zidovudine, drug levels 30 minutes later in milk are up to 5.5 times the serum concentration (Ruprecht *et al.*, 1990). Data from a lactating rat model, however, suggest that, at steady state, zidovudine enters breast milk by simple diffusion, with a plasma/milk ratio of 1.0 ± 0.29 (Alcorn and McNamara, 2002). In a study of 20 mother–infant pairs in Botswana, the median concentration of zidovudine in breast milk from women on combination antiretroviral therapy was 3.21-fold the median concentration in maternal serum (Shapiro *et al.*, 2005).

5c. Clinically important pharmacokinetic and pharmacodynamic features

Zidovudine has a plasma half-life of about 1 hour (Balis *et al.*, 1991) and an intracellular half-life of 3–4 hours (Furman *et al.*, 1986; Stretcher *et al.*, 1992; Stretcher *et al.*, 1994b). The concentration of zidovudine triphosphate (the active metabolite) within cells is likely to correlate better with the drug's activity and toxicity than levels of zidovudine in plasma (see [section 3.](#), Mechanism of drug action). However, although methods of measuring levels of phosphorylated zidovudine derivatives in peripheral blood mononuclear cells have been developed (Stretcher *et al.*, 1991; Barry *et al.*, 1994; Robbins *et al.*, 1994), these are not widely available for use in therapeutic drug monitoring. The intracellular concentration of phosphorylated zidovudine in peripheral blood mononuclear cells has been reported to range from 0.33 to 3.54 pmol/10⁶ cells and to be unrelated to serum zidovudine levels.

Levels did not vary during a 4-hour dosing interval, although plasma levels of zidovudine declined. However, the level of phosphorylated zidovudine derivatives in peripheral blood mononuclear cells declined in the study population with increasing duration of therapy (Stretcher *et al.*, 1991; Stretcher *et al.*, 1994b). In HIV-infected patients, a positive correlation has been documented between the AUC of intracellular phosphorylated zidovudine levels and change in CD4 T-cell percentage (response to zidovudine therapy), as has a negative correlation between AUC and change in hemoglobin after initiation of therapy (confirming toxicity with higher levels) (Stretcher *et al.*, 1994a). In one report, zidovudine was phosphorylated more efficiently in HIV-infected patients than in healthy volunteers (Barry *et al.*, 1994).

5d. Excretion

The major route of zidovudine elimination is by hepatic glucuronidation to form the inactive (no antiviral activity) metabolite 3'-azido-3'-deoxy-5'-O-beta-D-glucopyranuronosylthymidine (GAZT) followed by excretion in the urine (Dudley, 1995). In addition, < 20% of zidovudine can be recovered unchanged in the urine (Cload, 1989).

Zidovudine is thought to undergo both glomerular filtration and renal tubular secretion because its renal clearance (estimated at 400 ml/min/70 kg) exceeds that of creatinine. Following i.v. administration, 18 ± 5% of the dose is excreted unchanged by the kidney and 60% is converted to GAZT. The GAZT is cleared rapidly from the plasma with a half-life of about 1 hour (Cload, 1989). There is considerable variation in the clearance of zidovudine between patients. In a useful study by Burger and colleagues (1994a), zidovudine clearance was found to be reduced in patients with a lower body weight, in women, and in patients with advanced HIV infection but did not seem to alter with age or duration of zidovudine use.

5e. Drug interactions

Despite a multitude of studies demonstrating possible alterations in the pharmacokinetics or activity of zidovudine when co-administered with other drugs (see also [section 2c](#), Synergy and antagonism), there are relatively few drug interactions with zidovudine that are known to be of clinical significance. The interaction between zidovudine and stavudine (see discussed later in this section), however, means that these two agents should not be prescribed together. Potential drug interactions with zidovudine are summarized in [Table 225.6](#).

DRUGS THAT HAVE ADDITIVE TOXICITY WITH ZIDOVUDINE

The manufacturers warn that co-administration of zidovudine with drugs that are nephrotoxic or cytotoxic or that suppress the bone marrow may increase the risk of toxicity; thus caution is required (Retrovir, product information, 2011). Some examples have been well studied.