Table 225.6. Potential drug interactions with zidovudine.

Type of drug that may interact with zidovudine	Known examples with possible clinical significance	Effect
Drugs associated with bone marrow suppression	Ganciclovir Cotrimoxazole Interferon-alpha Cytotoxic chemotherapy	Severe hematologic toxicity that may necessitate dose reduction or a change in therapy
Drugs that inhibit the glucuronidation of zidovudine	Probenecid Atovaquone Methadone	Increased zidovudine levels (not necessarily associated with toxicity)
Drugs with glucuronidation inhibited by zidovudine	Acetaminophen (paracetamol)	Possible increased risk of hepatotoxicity (well tolerated in most reports)
Drugs that inhibit zidovudine phosphorylation substantially	Ribavirin[a] Doxorubicin[a]	Clinical significance unknown
Drugs with phosphorylation inhibited by zidovudine	Stavudine[a]	Theoretical antagonism. Co-administration not recommended
Other	Ibuprofen	Prolonged bleeding time and increased frequency of spontaneous hemorrhage in HIV-infected men with hemophilia

[a]Based on *in vitro* data.

The combination of zidovudine (in doses of 600–1200 mg/day) with ganciclovir (5–10 mg/kg/day) is rarely tolerated, with severe anemia and/or neutropenia in the majority of patients with AIDS undergoing treatment for CMV infection (Hochster *et al.*, 1990; Causey, 1991). Similarly, use of co-trimoxazole (in prophylactic doses) with zidovudine has been associated with neutropenia grades 3–4 at a rate of 56.3 cases/100 patient-years in patients commencing combination antiretroviral therapy in Abidian; despite most of the 80% of patients using co-trimoxazole at baseline having a normal count before the addition of zidovudine (Moh *et al.*, 2005). Clinicians commonly use these drugs together, but with clinical caution and hematologic monitoring. The majority of data suggest that zidovudine use with recombinant interferon-alpha is also associated with high rates of hematologic (particularly neutropenia) and nonhematologic (malaise, anorexia, fatigue) toxicity, which may be dose limiting (Kovacs *et al.*, 1989; Krown *et al.*, 1990; Krown *et al.*, 1992) and are not prevented by the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) (Davey *et al.*, 1991). Zidovudine use in combination with cytotoxic chemotherapy is associated with high rates of myelotoxicity (Gill *et al.*, 1997).

DRUGS METABOLIZED BY GLUCURONIDATION

The co-administration of zidovudine with other drugs metabolized by glucuronidation may theoretically increase the activity or toxicity of either agent. Drugs that may theoretically prolong the half-life of zidovudine by this mechanism include probenecid, nonsteroidal anti-inflammatory agents, narcotic analgesics, and sulfonamide antibiotics (Yarchoan *et al.*, 1989). Atovaquone inhibits zidovudine glucuronidation, resulting in a significant increase in the zidovudine AUC (Lee *et al.*, 1996). *In vitro* data suggest that probenecid substantially impairs zidovudine glucuronidation (Sim *et al.*, 1991). Further, probenecid increases the amount of unchanged zidovudine excreted in patients' urine (Kornhauser *et al.*, 1989), increases the peak serum concentration and half-life, and reduces the time to t_{max}. In patients with HIV infection taking 100 mg zidovudine with 500 mg probenecid, the resulting concentration-time curves for zidovudine were similar to those after 200 mg of zidovudine alone (McDermott *et al.*, 1992). Several other agents inhibit zidovudine glucuronidation *in vitro*, including chloramphenicol, indomethacin, naproxen, ethinylestradiol, testosterone, codeine, morphine, amphotericin B, ketoconazole, miconazole, fluconazole, cyclophosphamide, methotrexate, etoposide, and vinblastine (Sim *et al.*, 1991; Rajaonarison *et al.*, 1992; Rajaonarison *et al.*, 1993; Sampol *et al.*, 1995), but clinical data to support significant interactions are generally lacking. In a study of nine patients, the average AUC of zidovudine was marginally (1.4-fold) higher in methadone recipients than in controls (Schwartz *et al.*, 1992).

Zidovudine may also inhibit the glucuronidation of other drugs, and has been shown in a rat model to completely inhibit acetaminophen (paracetamol) glucuronidation (Ameer *et al.*, 1992). Both *in vitro* and the majority of *in vivo* data support the safety of standard doses of acetaminophen in patients receiving treatment with zidovudine (Steffe *et al.*, 1990; Sattler *et al.*, 1991; Sim *et al.*, 1991; Burger *et al.*, 1994b). However, a case of severe hepatotoxicity has been reported in a patient undergoing zidovudine therapy who received 3.3 g of acetaminophen over a 24-hour period (Shriner and Goetz, 1992).

INTERACTIONS RELATED TO PHOSPHORYLATION OF ZIDOVUDINE TO THE ACTIVE FORM

Zidovudine competitively inhibits the intracellular phosphorylation of stavudine in human lymphocytes (Ho and Hitchcock, 1989; Havlir *et al.*, 2000). Patients treated with zidovudine and