Table 214.1. Susceptibility of herpes viruses to penciclovir.

Herpesvirus	Mean IC_{50} (μg/ml)[a]	References
Herpes simplex-1	0.16–1.76 (range)	Leary *et al.* (2002)
	0.4	Boyd *et al.* (1987); Perry and Wagstaff (1995)
Herpes simplex-2	0.34–3.13 (range)	Leary *et al.* (2002)
	1.5	Boyd *et al.* (1987); Perry and Wagstaff (1995)
Varicella-zoster	3.1	Boyd *et al.* (1987); Perry and Wagstaff (1995)
	1.2	Shiraki *et al.* (1993)
Cytomegalovirus	52	Boyd *et al.* (1987); Perry and Wagstaff (1995)
	18	Bacon (1996)
Epstein-Barr virus	10	Boyd *et al.* (1987); Bacon and Boyd (1995); Bacon *et al.* (1996a); Bacon *et al.* (1996b); Boon and Griffin (1996)

[a]Mean 50% inhibitory concentration by plaque reduction assay.

extracellular penciclovir because of the long intracellular half-life of penciclovir triphosphate (Shaw *et al.*, 1996). Penciclovir is also active against human hepatitis B virus (HBV) (Shaw *et al.*, 1996). Oral famciclovir inhibited DHBV replication in infected ducklings (Tsiquaye *et al.*, 1994). Chronically DHBV-infected ducks treated with either famciclovir or penciclovir suppressed DHBV replication as measured by plasma viral DNA and DNA polymerase. After cessation of treatment, there was a delay of only 2–8 days before plasma levels of these markers of DHBV replication began to increase again (Tsiquaye *et al.*, 1996). In clinical trials of famciclovir in patients with HBV infection, the results have been decidedly mixed; the consensus is that famciclovir is effective but substantially less so than drugs such as lamivudine, adefovir, and tenofovir (Berenquer *et al.*, 2001; Manns *et al.*, 2001; Matthews *et al.*, 2001; Lai *et al.*, 2002; Wolters *et al.*, 2002). However, famciclovir may rarely have a role in patients with lamivudine-resistant virus (Tang *et al.*, 2002).

2b. Emerging resistance and cross-resistance

Resistance to penciclovir is uncommon, although the frequency of cases is increasing with the widespread use of antiviral drugs over the past two decades. Antiviral drug resistance is most commonly seen in the immunocompromised subset of patients, and it appears that the frequency of penciclovir-resistant cases is similar to the number of reported aciclovir-resistant cases (Sarisky *et al.*, 2003). Clinical recovery does not appear to be influenced when resistant viral strains are isolated from immunocompetent patients (Reusser, 1996). Strains of HSV and VZV resistant to both penciclovir and aciclovir usually have mutations in the viral thymidine kinase (TK) and much less commonly in DNA polymerase genes. Viral strains resistant to aciclovir may or may not be also penciclovir resistant (Boyd *et al.*, 1987). When clinical isolates of HSV resistant to aciclovir or foscarnet were tested for susceptibility to penciclovir *in vitro*, penciclovir remained relatively active against foscarnet-resistant strains (Boyd and Safrin, 1993; Safrin and Phan, 1993). A recent paper reported that thymidine kinase–negative (TKN) mutants were the dominate mechanism of penciclovir resistance in HSV strains (Bacon *et al.*, 2003). Similarly, aciclovir-resistant strains of VZV may show cross-resistance to penciclovir, although some aciclovir-resistant strains may remain sensitive to penciclovir (Talarico *et al.*, 1993; Hasegawa *et al.*, 1995). Cross-resistance between aciclovir and penciclovir, although not always present, is a genuine danger to consider when treating patients with aciclovir-resistant HSV or VZV strains; as a consequence, drugs not dependent on TK for intracellular monophosphorylation (e.g. cidofovir and tenofovir) or drugs not dependent on any modification that act directly on the viral DNA polymerase (e.g. foscarnet) should be used until full antiviral susceptibility data are available.

3. MECHANISM OF DRUG ACTION

Famciclovir is an oral prodrug of the antiviral agent penciclovir (diacetyl 6-deoxy analog of penciclovir). It is effectively metabolized in the liver and intestinal walls, where two acetyl groups are removed to give 6-deoxy-penciclovir, which is then oxidized at the 6-position of the purine ring to form penciclovir (Vere Hodge and Perkins, 1989; Vere Hodge *et al.*, 1989; Vere Hodge, 1993; Vere Hodge *et al.*, 1993; Vere Hodge and Cheng, 1993).

Penciclovir exerts its antiviral effects by inhibiting DNA polymerase, in a similar manner to that of aciclovir. (Balzarini *et al.*, 1994). In addition, both drugs share relative higher affinity for viral DNA polymerase than for host DNA polymerases. (Iisley and Lee, 1995) Within herpesvirus-infected cells, penciclovir is phosphorylated to form initially a monophosphate compound, a process dependent wholly on the HSV- and VZV-specific TK enzymes. Subsequently penciclovir monophosphate is converted to a diphosphate and then finally a triphosphate, transformations mediated by host cell enzymes (Vere Hodge and Perkins, 1989; Figure 214.1). Penciclovir triphosphate is structurally similar to the nucleotide deoxyguanosine triphosphate (dGTP) and therefore competitively inhibits the effects of viral DNA polymerase (Earnshaw *et al.*, 1992; Vere Hodge and Cheng, 1993; Bacon, 1996). Whereas aciclovir, which lacks hydroxyl groups in the acyclic chain required for viral extensions, generates