215

Ganciclovir and Valganciclovir

Camille E. Beauduy and Mark A. Jacobson

1. DESCRIPTION

Ganciclovir (GCV) (9-[[2-hydroxy-1-(hydroxymethyl)-ethoxy]methyl] guanine) is a synthetic acyclic nucleoside analog of guanine. GCV sodium is marketed by Roche Laboratories under the trade names Cytovene and Cymevene.

Valganciclovir (VGCV), marketed under the trade name Valcyte, is a prodrug of GCV that facilitates its oral absorption. VGCV is the hydrochloride salt of the L-valyl ester of GCV, and it exists as two diastereomers; it is also available rapidly deesterified and completely converted to GCV after oral administration. Valcyte is available as a 450-mg tablet for oral administration. A flavored, 50 mg/ml oral solution for children is also available (Pescovitz *et al.*, 2007; Genentech, 2015).

GCV and VGCV are currently the drugs of choice for the management of cytomegalovirus (CMV) disease. Oral VGCV, the prodrug of GCV, has largely replaced intravenous GCV as the preferred administration route, although GCV remains available for intravenous and intravitreal injection.

The molecular formula of GCV is $C_9H_{12}N_5NaO_4$. The molecular weight of the sodium salt is 277.22. Thus 1 μg/ml is approximately equal to 3.6 μM. The molecular formula of VGCV is $C_{14}H_{22}N_6O_5$, and it has a molecular weight of 390.83. The chemical structures of GCV and VGCV are shown in Figure 215.1.

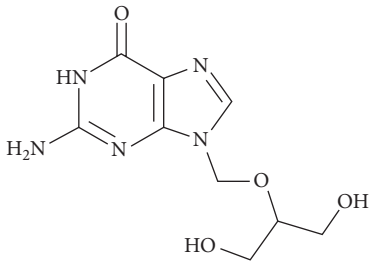

Figure 215.1. Chemical structure of ganciclovir.

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

GCV has activity against most herpesviruses and certain other DNA viruses (Martin *et al.*, 1983; see Table 215.1). In clinical studies, GCV has been shown to be active against CMV and herpes simplex virus (HSV) infections. GCV is a prodrug and requires triphosphorylation inside of infected cells to have antiviral activity. The antiviral effects of GCV last for only the duration that GCV triphosphates remain within infected cells. Thus, like all antiviral drugs, GCV inhibits replication of viruses and is therefore virustatic (Mar *et al.*, 1983).

CYTOMEGALOVIRUS

When tested *in vitro* in viral plaque reduction assays, using CMV DNA synthesis or viral yield as end points, GCV inhibited the laboratory-adapted AD169 and Towne strains of CMV as well as clinical isolates with half maximum effective concentration (EC_{50}) values of sensitive strains ranging from 0.1 to 9 μM (0.025–2.28 μg/ml) (Tocci *et al.*, 1984; Plotkin *et al.*, 1985; Rush and Mills, 1987; Prichard *et al.*, 1990; Andrei *et al.*, 1991; Boivin *et al.*, 1993; Freitas *et al.*, 1993a; Hamzeh *et al.*, 1993). The mean EC_{50} ranges from 1.7 to 5.9 μM, well within the plasma concentrations of drug that can be achieved clinically (Plotkin *et al.*, 1985; Cole and Balfour, 1987; Boivin *et al.*, 1993). The EC_{90} for GCV against the AD169 strain has been variably reported to range from 0.5 to 19 μM (Neyts *et al.*, 1990; Freitas *et al.*, 1993a) and from 0.6 to 16 μM for clinical isolates (Plotkin *et al.*, 1985). Although the concentrations of GCV that cause cellular toxicity are generally considerably higher than those required for antiviral activity, this is not true for bone marrow progenitor cells, which appear to be especially sensitive to the drug. The EC_{50} for GCV against bone marrow colony-forming cells is approximately 2.7 ± 0.5 μM (Sommadossi and Carlisle, 1987). GCV is 10- to 25-fold more active against CMV than aciclovir using plaque reduction assays (Tyms *et al.*, 1984; Cole and Balfour, 1987) but is less effective against CMV *in vitro* than cidofovir (Shigeta *et al.*, 1991; see Chapter 216, Cidofovir and brincidofovir).