

GANCICLOVIR (and valganciclovir)

Use

Ganciclovir is a toxic antiviral agent used in the IV treatment of neonatal cytomegalovirus (CMV) infection, otherwise known as human herpes virus 5 (HHV-5). Valganciclovir is a prodrug that can be given by mouth.

Pharmacology

Ganciclovir is a synthetic nucleoside with properties similar to aciclovir (q.v.) developed in 1980 that accumulates after phosphorylation in CMV infected cells inhibiting virus replication. It is much more toxic than aciclovir, frequently causing neutropenia and thrombocytopenia and treatment needs to be suspended if the neutrophil counts falls below 750 cells/mm^3 . Concurrent treatment with zidovudine (q.v.) increases the drug's toxicity. It is very poorly absorbed by mouth, and rapidly excreted by the kidney with an average half life of 3 hours. It crosses the placenta, and is known to be teratogenic in animals. Animal studies suggest that it is also a potential mutagen and carcinogen. Fertility can be affected, and breastfeeding is inappropriate. Checking the amount of virus in the urine may help find a dose that minimises viral replication without causing toxicity.

Cytomegalovirus infection

Fifty percent of all women of childbearing age in the UK have already had an asymptomatic infection before the start of pregnancy (often in early childhood), but primary or reactivated infection is thought to cause congenital or perinatal infection in about one in every 300 UK pregnancies. Most of these babies show few signs of overt infection, but about 5% develop disseminated cytomegalic inclusion disease with thrombocytopenic petechiae, hepatitis, chorioretinitis, intracranial calcification and/or microcephaly. Cerebral palsy can occur, and severe progressive deafness may develop even after an apparently asymptomatic infection especially when this occurred in the first trimester of pregnancy. Overt cytomegalic inclusion disease can also result from neonatal cross-infection, or exposure to CMV-infected blood or human milk; such babies often develop pneumonia as well as many of the symptoms listed above. Proof that infection was congenital requires the collection of a positive culture, or polymerase chain reaction (PCR) test, within two weeks of birth. Handwashing is important to prevent congenitally infected babies causing iatrogenic cross infection. Staff are at little increased risk of personal infection as long as proper precautions against cross infection are observed.

There is only limited evidence that any antiviral agent can alter the course of congenitally acquired infection, but ganciclovir can temporarily eradicate virus excretion, and sustained use after birth seems to reduce the risk of later progressive hearing loss. Giving the mother 8 grams of valaciclovir (a prodrug of aciclovir) daily may reduce fetal damage, but giving the mother 200 U/kg of hyperimmune globulin (with, on occasion, more of the same product into the fetal abdomen) is a strategy that has been better studied (Nigro *et al.*, 2005).

Treatment

Seek expert advice and explain that treatment is still under evaluation and seldom eliminates the virus. Watch for neutropenia, and maintain hydration. Increase the dosage interval if there is renal impairment.

IV treatment: Give symptomatic babies 6 mg/kg IV of ganciclovir (5 ml of the solution made up as described below) over one hour once every 12 hours. Switch to oral treatment before discharge home.

Oral treatment: Start by giving 15 mg/kg dose of valganciclovir twice a day. Try to optimise dosing by monitoring urinary viral shedding if facilities exist. Some clinicians aim to sustain treatment for 2–4 months.

Supply and administration

Undiluted ganciclovir is very caustic (pH ~ 11). Both products are potential teratogens and carcinogens, so gloves and goggles should be used during reconstitution. Wash at once to limit accidental contact with skin.

Ganciclovir : 500 mg vials cost £32 each. The freeze-dried powder must be reconstituted with 9.7 ml of water for injections BP to give a solution containing 50 mg/ml (water containing a bacteriostatic such as parahydroxybenzoate may cause precipitation). Shake to dissolve, and use promptly: do not use the vial if there is any particulate matter still present. To give 6 mg/kg of ganciclovir take 1.2 ml of this solution for each kilogram the baby weighs, dilute to 50 ml with 10% dextrose or dextrose saline, and infuse 5 ml over one hour.

Valganciclovir: 450 mg tablets of this pro-drug (the L-valyl ester of ganciclovir) are available cost £19 each and Roche have recently developed an oral formulation whose bioavailability is known (Kimberlin *et al.*, 2008).

References

- Kimberlin DW, Lin C-Y, Sanchez PJ, *et al.* Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003;**143**:16–25. (See also 4–6.) [RCT]
- Nigro G, Adler SP, La Torre R, *et al.* Passive immunisation during pregnancy for congenital cytomegalovirus infection. *N Engl J Med* 2005;**353**:1350–62.
- Malm G, Englan M-L. Congenital Cytomegalovirus infections. *Semin Fetal Neonat Med* 2007;**12**:154–9.
- Jacquemard F, Yamamoto N, Costa J-M, *et al.* Maternal administration of valaciclovir in symptomatic intrauterine cytomegalovirus infection. *BJOG* 2007;**114**:1113–21.
- Maruyama Y, Sameshima H, Kamitomo M, *et al.* Fetal manifestations and poor outcomes of congenital cytomegalovirus infection. *J Obstet Gynaecol Res* 2007;**33**:619–23.
- Galli L, Novelli A, Chiappini E, *et al.* Valganciclovir for congenital CMV infection: a pilot study on plasma concentrations... *Pediatr Infect Dis J* 2007;**26**:451–3.
- Müller A, Eis-Hübinger AM, Brandhorst G, *et al.* Oral valganciclovir for symptomatic congenital cytomegalovirus infection. *J Perinatol* 2008;**28**:74–6.
- Kimberlin DW, Acosta EP, Sánchez PJ, *et al.* Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis* 2008;**197**:836–45.