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Ganciclovir and Valganciclovir Use in Children

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Ganciclovir and its prodrug valganciclovir, are used for the prevention or treatment of cytomegalovirus (CMV) disease in immunocompromised or immunosuppressed patients.[1] While valganciclovir has been only recently approved for use in children by the Food and Drug Administration (FDA), both of these drugs are a common part of treatment protocols following renal, hepatic, lung, cardiac, or bone marrow transplantation in children of all ages.[2-4] Several recent studies suggest that these agents are very effective in preventing CMV in children with transplants and are generally well tolerated. Other recent papers have described successful treatment of congenital or neonatal CMV infection with these agents. This issue of *Pediatric Pharmacotherapy* will review the basic pharmacology of ganciclovir and valganciclovir and provide an overview of recent studies of their use in pediatric patients.

Mechanism of Action

Ganciclovir is a synthetic acyclic nucleoside analogue of 2'-deoxyguanosine. Valganciclovir is the L-valyl ester of ganciclovir. After oral administration, it is rapidly cleaved by esterases in the intestine wall and liver to form active ganciclovir. Ganciclovir inhibits replication of herpes viruses, including CMV and herpes simplex virus (HSV). In CMV-infected cells, ganciclovir undergoes phosphorylation to a monophosphate form by a CMV-encoded (UL97 gene) protein kinase. Significantly greater phosphorylation occurs in CMV-infected cells than in non-infected cells. Ganciclovir monophosphate is then converted to diphosphate and triphosphate forms by cellular kinases.[1-4]

Ganciclovir triphosphate, the active moiety, persists for several days in CMV-infected cells. It inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate as a substrate for viral DNA polymerase. Ganciclovir triphosphate is also incorporated into viral DNA, resulting in termination of viral DNA elongation and inhibition of viral replication. The *in vitro* median concentration of ganciclovir that inhibits CMV replication ranges from 0.1 to 3.48 mcg/mL. Viral resistance to ganciclovir has been demonstrated *in vitro* and *in vivo*, with treatment failures reported in patients on long-term therapy for CMV retinitis. After prolonged administration, selection of mutations in UL97 or in the viral polymerase gene UL54 results in a reduced formation of ganciclovir triphosphate.[1-4]

Pharmacokinetics

Ganciclovir is poorly absorbed after oral administration, with a bioavailability of approximately 5%. Administration with food increased bioavailability slightly to 6-10%. After oral administration of standard adult doses, maximum serum ganciclovir concentrations typically are 0.5 to 1.5 mcg/mL. After IV administration, maximum serum ganciclovir concentrations of 7 to 19 mcg/mL are typically achieved. Oral bioavailability is significantly improved with valganciclovir, with an average value of 59.4$\pm$6.1% reported from premarketing clinical trials in adults. The mean maximum serum ganciclovir concentration achieved after valganciclovir administration (with food) was 5.61$\pm$1.52 mcg/mL.[2-4]

At steady-state, the volume of distribution of ganciclovir is approximately 0.74$\pm$0.15 L/kg. Ganciclovir is only minimally bound to serum proteins (1-2%). Ganciclovir is primarily eliminated through renal glomerular filtration and active tubular secretion. Over 90% of a dose is eliminated as unchanged drug. The average elimination half-life is approximately 3 to 5 hours in adults. Renal impairment significantly reduces ganciclovir clearance. In patients with severe renal impairment, elimination half life may exceed 20 to 50 hours. Hemodialysis reduces ganciclovir serum concentrations by approximately 50%.[2-4]

The pharmacokinetic profile of ganciclovir and valganciclovir in infants and children has been evaluated in several studies. In 1993, Trang and colleagues evaluated the pharmacokinetic characteristics of IV ganciclovir in 27 neonates

(2 to 49 days of age).[5] The maximum serum concentration was 5.5±1.6 mcg/mL after a dose of 4 mg/kg and 7.0±1.6 mcg/mL after 6 mg/kg. Mean volume of distribution was 669±70 mL/kg for the 4 mg/kg group and 749±59 mL/kg for the 6 mg/kg group. Volume of distribution increased with increasing weight ($r = 0.689$, $p = 0.0001$). The mean elimination half-life was 2.4 hours.

In a 2003 study by Zhang and colleagues conducted in 11 children (mean age 11.0±3.9 years), the maximum concentration after an IV dose of 5 mg/kg given every 12 hours for 15 days was 11.77±2.82 mcg/mL, with an AUC of 42.29±17.57 mcg·hr/mL.[6] Administration of an oral dose of 50 mg/kg every 12 hours for 3 months produced a maximum concentration of 2.70±1.07 mcg/mL and an AUC of 18.97±9.36 mcg·hr/mL. The authors concluded that the doses administered produced adequate serum ganciclovir concentrations for treatment.

The pharmacokinetics of valganciclovir in children were first described in a case report of a 6 year old girl with CMV.[7] A single 4.4 mg/kg IV ganciclovir dose was compared to 13.2 mg/kg and 26.3 mg/kg oral valganciclovir doses. The two doses of valganciclovir provided area under the serum concentration-time curve (AUC) values of 14.3 and 28.7 mcg·hr/mL, respectively. Earlier this year, Zhao and colleagues utilized nonlinear mixed-effects modeling (NONMEM) techniques to evaluate valganciclovir pharmacokinetics in 22 renal transplant patients between 3 and 17 years of age.[8] The model provided an estimated systemic clearance value of 10.1 L/hr (or 0.30 L/hr/kg), with a volume of distribution of 5.2 L, similar to values reported in adults. Based on their model, the authors suggest that a valganciclovir dose of approximately 500 mg once daily would produce an AUC of 43±10.6 mcg·hr/mL, thus achieving adequate concentrations for CMV prophylaxis.

Clinical Studies in Children

The first report of ganciclovir treatment in an infant with CMV was published in 1988.[9] Since that time, a variety of case reports and clinical studies have been published describing the use of ganciclovir in infants and children. In addition, a small number of papers have documented the efficacy of valganciclovir. The efficacy of valganciclovir as prophylaxis for CMV in pediatric liver transplant patients was evaluated by Clark and colleagues in 2004. In their retrospective study, the authors evaluated 10 children (mean age 4.9±5.6 years). The majority of the patients (50%) were CMV negative and received a CMV positive organ. All of the children were receiving steroids and tacrolimus, with 30% also getting mycophenolate. Patients received a valganciclovir dose of 15 to 18 mg/kg given once daily. All patients tolerated valganciclovir, with no reports of bone marrow suppression or renal dysfunction. Asymptomatic CMV infection was detected on routine CMV antigenemia in one child at one week of treatment, but cleared with a dose increase to 15 mg/kg twice daily. After three negative tests, the dose was reduced to once daily. Based on their initial experience, the authors suggest that valganciclovir is an acceptable therapy for CMV prophylaxis in pediatric transplant patients.

Valganciclovir has also been used successfully in the treatment of infants with congenital CMV infection. In 2007, Galli and colleagues treated 8 infants with severe CMV disease with IV ganciclovir for 1 week followed by oral valganciclovir for 5 weeks. The first four infants were treated with 15 mg/kg once daily, but this resulted in a suboptimal mean maximum concentration of 0.42 mcg/mL (range 0.40-0.74 mcg/mL). Dosing for the second group of four infants was increased to 15 mg/kg twice daily, which produced a maximum concentration of 3.1 mcg/mL (range 2.5-3.9 mcg/mL). Average urine CMV viral load prior to treatment was 6.9±1.32 copies/mL. Viral load lowered during treatment to 3.72±0.71 and 2.66±0.51 copies/mL in the two groups, respectively).

The most current research with these agents has focused on optimizing drug administration. In a study published last year in *Transplantation*, Gerna and colleagues conducted a randomized, open-label study of ganciclovir prophylaxis versus preemptive therapy along for prevention of CMV in pediatric liver transplant patients. Twenty-one children were randomized to receive either ganciclovir 5 mg/kg twice daily for 30 days (prophylaxis) or preemptive therapy, where treatment was initiated only after the CMV viral load reached 100,000 DNA copies/mL and stopped when two consecutive tests were below the cut-off. At the 24 month interim analysis, similar numbers of patients in each group had developed CMV disease, 7 of the 10 children (70%) in the prophylaxis group and 9 of the 11 (81%) in the preemptive group; however, infection occurred significantly later in the prophylaxis arm (54 versus 24 days, $p = 0.05$). There was no difference in overall response to infection. As a result, the authors suggest that long-term prophylaxis may not be necessary.

Drug Interactions

Ganciclovir and valganciclovir should be used with caution in patients receiving other cytotoxic drugs, such as amphotericin, dapsone, doxorubicin, flucytosine, pentamidine, trimethoprim/sulfamethoxazole, vinblastine, and vincristine, Seizures have been reported in patients taking imipenem-cilastatin and ganciclovir. The combination of imipenem-cilastatin and either ganciclovir or valganciclovir should not be used. Nephrotoxic drugs, including cyclosporine and amphotericin, as well as probenecid should be used with caution in patients taking ganciclovir or valganciclovir, as the resulting increase in ganciclovir concentrations may produce toxicity.[1-4]

When ganciclovir is administered simultaneously with, or within 2 hours prior to, didanosine, the AUC of didanosine may be reduced by 10-40%. If the drugs are given simultaneously, the AUC of ganciclovir may be decreased by up to 20%, although studies conducted with didanosine administered 2 hours prior to a ganciclovir dose produced no significant effect. A similar result occurs with simultaneous administration of ganciclovir and zidovudine. The steady-state AUC of ganciclovir may be decreased by up to 20%, while the AUC of zidovudine may be increased by 11-74%. Use of valganciclovir with didanosine or zidovudine should be expected to produce the same interactions.[1-4]

Precautions

Ganciclovir and valganciclovir can produce significant neutropenia, anemia, and thrombocytopenia. They should be used with caution in patients with underlying blood dyscrasias and should not be administered to patients with an absolute neutrophil count less than 500 cells/mcL, a platelet count less than 25,000 cells/mcL, or a hemoglobin less than 8 g/dL. If neutropenia occurs, it typically resolves within a week of discontinuation.[1-4]

High concentrations of ganciclovir have produced carcinogenic effects in animal models. As a result, ganciclovir is considered a potential carcinogen in humans. The drug should be handled with appropriate personal protective equipment, according to institutional policies. Families preparing valganciclovir suspension should understand the potential risk of direct contact with the drug and should be aware of steps to minimize exposure. After direct contact with the suspension, broken or crushed tablets, patients or caregivers should wash thoroughly with soap and water. Ganciclovir should also be considered as potentially teratogenic and may adversely affect sperm production. All patients should be informed of these risks and the importance of contraceptive use.[1-4]

Rapid administration of IV doses may result in elevated plasma concentrations and a greater likelihood for toxicity. Because of the alkaline nature of the drug (pH 11), dilution to concentrations less than 10 mg/mL is necessary to minimize the risk for pain and phlebitis. Ganciclovir should never be administered intramuscularly or subcutaneously.[1-4]

Adverse Effects

Among the most commonly reported adverse effects with ganciclovir and valganciclovir are lab test abnormalities, including neutropenia (in 3-41% of patients in adult trials), thrombocytopenia (1-65%), and an increase in serum creatinine (4-69%). Other adverse effects include fever (30-48%), nausea and diarrhea (41-48%), tremor (28%), headache (22%), anorexia (14-19%), hypertension (18%), insomnia (16%), vomiting (11-21%), diaphoresis (11-14%), pruritus (5-10%), and infections (4-15%). Retinal detachment has been reported in patients with CMV retinitis, but a relationship to treatment has not been established. Rare, but severe adverse reactions include hypersensitivity and paresthesias.[1-4]

Adverse effects reported in pediatric clinical trials have been similar to those reported in adults. In a study of 120 immunocompromised children with CMV infection, the most common adverse effects were granulocytopenia (17%) and thrombocytopenia (10%). In another study of 16 children, the adverse effects included hypokalemia (25%), decreased renal function, sepsis, or thrombocytopenia (19%), leukopenia, coagulation disorders, hypertension, pneumonia, or immune system disorders (13%).[1-4]

Dosing Recommendations

Ganciclovir prophylaxis is typically initiated at a dose of 5 mg/kg IV over 1 hr every 12 hours for 7 to 14 days post-transplant, followed by 5 mg/kg given once daily. Maintenance prophylaxis with oral ganciclovir in adults and children 13 years and older is 1,000 mg given three times daily with food. The dose of valganciclovir for CMV prophylaxis in adults is 900 mg (two 450 mg tablets) given once daily with food; pediatric patients should receive a dose of 15 to 18 mg/kg once daily. Duration varies among transplantation protocols. Children with CMV infection, including infants with

congenital CMV, should be treated with IV ganciclovir 5-6 mg/kg given every 12 to 24 hours or valganciclovir 15 to 18 mg/kg given orally twice daily. [1-12] The manufacturer recommends that doses be calculated based on body surface area and creatinine clearance. The formula is provided in the prescribing information and on the product website at www.valcyte.com.

Patients with renal impairment require lower ganciclovir or valganciclovir doses. In patients receiving IV ganciclovir who have mild renal dysfunction, the dose should be reduced by 50% to a daily dose of 2.5 mg/kg. Patients with moderate renal dysfunction should receive 25% of the regular dose (1.25 mg/kg) daily, and patients with severe renal impairment should receive 0.625 mg/kg three times per week after hemodialysis, or on a schedule determined by their ability to eliminate the drug. For patients with mild renal dysfunction who are being treated with valganciclovir, the dosing interval should be reduced to once daily. For moderate impairment, the dose should also be reduced by 50%. For severe renal dysfunction (estimated creatinine clearance < 25 mL/min), the dose should be reduced by 50% and be administered twice weekly. Valganciclovir is not recommended in patients requiring dialysis.[1-4]

Availability and Cost

Ganciclovir (Cytovene® and generics) is available as 250 and 500 mg capsules, as well as an injection (500 mg/10 mL vial). The average wholesale price (AWP) for ganciclovir is $4.72 per capsule or $73.43 for a 10 mL vial. Valganciclovir (Valcyte®) is available as 450 mg tablets and a 50 mg/mL oral suspension (100 mL bottle). The AWP is $46.61 per tablet, AWP pricing for the suspension is not yet available.[13]

Summary

Ganciclovir and valganciclovir have become standard components in most bone marrow or solid organ transplantation protocols for the prevention of CMV disease. Several recent studies describe their utility in the pediatric transplant population as well as in congenital and neonatal CMV infection.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/25/09:

1. Two additional pancrelipase products (Viokase 8® and Creon®) were added to the Inpatient and Outpatient Formularies.
2. Basiliximab (Simulect®) was added for prophylaxis of acute organ rejection after kidney transplantation.
3. Prasugrel (Effient™) was added with restriction to Cardiology.
4. Methylnaltrexone (Relistor®) was added with restriction to Palliative Care and Oncology.

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