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Review Article

Clinical Pharmacology of Ganciclovir and Valganciclovir in Infants and Children

Gian Maria Pacifici*

Associate Professorof Pharmacology, Italy

***Corresponding author**
Gian Maria Pacifici, Associate Professorof Pharmacology, via Sant'Andrea 32, 56126 Pisa, Italy, Email: pacifici44@tiscali.it

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Abstract

Ganciclovir is an acyclic guanine nucleotide analogue and valganciclovir is the L-valyl ester prodrug of ganciclovir. Ganciclovir inhibits all herpes viruses and is especially active against cytomegalovirus. Ganciclovir inhibits viral DNA. Ganciclovir diphosphate and ganciclovir triphosphate are formed by host enzymes. The oral bioavailability of ganciclovir is < 10% whereas that of valganciclovir is about 60% and food further increases its bioavailability. Ganciclovir is effective in the treatment of cytomegalovirus retinitis. The intravenous dose of ganciclovir is 6 mg/kg twice-daily in infants and in children it is 5 mg/kg twice-daily. Ganciclovir has been found efficacy and safe in infants and children but it may induce adverse-effects. The mean elimination half-life of ganciclovir is 2.4 hours and the mean distribution volume is about 700 ml/kg in infants. Ganciclovir is converted into ganciclovir triphosphate in human cytomegalovirus infected cells and the elimination of ganciclovir triphosphate is about 48 hours in these cells. Ganciclovir interacts with drugs and the treatment and prophylaxis with ganciclovir have been extensively studied in infants and children. Ganciclovir penetrates into the cerebrospinal fluid of infants and children in significant amounts and treated the meningitis caused by human herpesvirus 6 and by cytomegalovirus. Ganciclovir is poorly transferred across the human placenta. The aim of this study is to review the published data on ganciclovir dosing, efficacy and safety, effects, adverse-effects, pharmacokinetics, metabolism, drug interactions, therapeutic use, treatment, prophylaxis, penetration into the cerebrospinal fluid, and treatment of meningitis in infants and children, and the transfer across the human placenta.

INTRODUCTION

Ganciclovir is an acyclic guanine nucleotide analogue that is similar in structure to aciclovir. Valganciclovir is the L-valyl ester prodrug of ganciclovir. Ganciclovir has inhibitory activity against all herpesviruses and is especially active against cytomegalovirus [1].

MECHANISM OF ACTION OF GANCICLOVIR

Ganciclovir inhibits viral DNA. It is monophosphorylated intracellularly by viral thymidine kinase during herpes simplex virus infection and by a viral phosphotransferase encoded by the UL97 gene during cytomegalovirus infection. Ganciclovir diphosphate and ganciclovir triphosphate are formed by host enzymes. At least 10-fold higher concentrations of ganciclovir triphosphate are present in cytomegalovirus-infected than in uninfected cells. The triphosphate is a comparative inhibitor of dGTP incorporation into DNA polymerase. Incorporation into viral DNA causes eventual cessation of DNA chain elongation [1].

Absorption distribution metabolism and elimination of ganciclovir

The oral bioavailability of ganciclovir is low, only 6 to 9% following ingestion with food. On the other hand, oral doses of the prodrug valganciclovir are well absorbed and hydroxylated rapidly to ganciclovir; thus valganciclovir provides greater bioavailability of the vanciclovir moiety, about 60%. Food further increases the bioavailability of valganciclovir by about 25%. Following intravenous administration of ganciclovir, vitreous fluid levels are similar to or higher than those in plasma and decline with a half-life of 23 to 26 hours, intraocular sustained-release ganciclovir implants provide vitreous levels of about 4.1 µg/ml. The plasma elimination half-life is about 2 to 4 hours in adults. Intracellular ganciclovir triphosphate concentrations are 10-fold higher than those of aciclovir triphosphate and decline much more slowly, with an intracellular elimination half-life longer than 24 hours. These differences may account in part for ganciclovir's greater anti- cytomegalovirus activity and provide the rationale for single daily doses in suppressing human cytomegalovirus infections. Over 90% of ganciclovir is eliminated unchanged by renal excretion. Plasma elimination half-life increases in patients with severe renal insufficiency [1].

Therapeutic use of ganciclovir

In cytomegalovirus retinitis, initial induction treatment (5 mg/kg intravenous twice-daily for 10 to 21 days) is associated with improvement or stabilization in about 85% of patients.

Reduced viral excretion is usually evident by one week, and funduscopic improvement is seen by 2 weeks. Because of the high risk of relapse, patients with AIDS with retinitis require suppressive therapy with high doses of ganciclovir (5 mg/kg daily). Oral ganciclovir (1,000 mg thrice-daily) is effective for suppression of retinitis after initial intravenous treatment but has been replaced in practice by oral valganciclovir. Oral valganciclovir (900 mg daily for 21 days of initial treatment) is comparable with intravenous dosing for initial control and sustained suppression (900 mg daily) of cytomegalovirus retinitis. Intravitreal ganciclovir injections have been used in some patients and intraocular sustained-release ganciclovir implants is more effective than systemic dosing in suppressing retinitis progression. Ganciclovir therapy (5 mg/kg twice-daily for 14 to 21 days) may benefit other cytomegalovirus syndromes in patients with AIDS or recipients of solid-organ transplants. Ganciclovir has been used for both prophylaxis and preventive therapy of cytomegalovirus infections in transplant recipients. A ganciclovir ophthalmic gel formulation (Zigran) is effective in treating herpes simplex virus keratitis. Oral ganciclovir also reduces hepatitis simplex virus DNA levels and aminotransferase levels in chronic hepatitis B virus infection but the drug is not approved for this indication [1]. (Figure 1)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "ganciclovir dosing infants, children", ganciclovir efficacy, safety infants, children", "ganciclovir effects infants, children", "ganciclovir adverse-effects infants, children", "ganciclovir pharmacokinetics infants, children", "ganciclovir metabolism", "ganciclovir drug interactions", "ganciclovir therapeutic use infants, children", "ganciclovir treatment infants, children", "ganciclovir prophylaxis infants, children", "ganciclovir penetration into the cerebrospinal fluid", "ganciclovir treatment of meningitis infants, children", and "ganciclovir placental transfer". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] were consulted.

RESULTS

Administration schedules of ganciclovir in infants and children

Administration to infants [2]

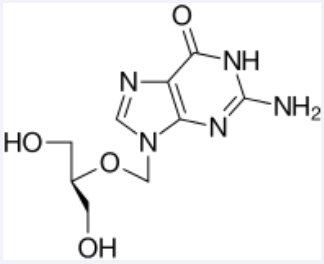

Figure 1 Molecular structure of ganciclovir (molecular weight = 255.23).

Infants. Give: 6 mg/kg of ganciclovir intravenously twice-daily.

Infants. Give: 16 mg/kg orally of valganciclovir twice-daily.

The clinical toxicity of ganciclovir includes granulocytopenia, anaemia, and thrombocytopenia. Significant neutropenia will occur in the majority of treated infants. Discontinue the treatment if the neutropenia does not resolve after reducing the dosage. Ganciclovir is incompatible with fat emulsion, aztreonam, cefepime, and piperacillin-tazobactam [3].

Administration to children [4].

Intravenous prevention of cytomegalovirus disease (pre-emptive therapy in children with drug-induced immunosuppression)

Children aged 12 to 17 years. Give: initially 5 mg/kg twice-daily for 7 to 14 days, then give a maintenance dose of 5 mg/kg once-daily.

Intravenous prevention of cytomegalovirus disease (universal prophylaxis in children with drug-induced immunosuppression)

Children aged 1 month to 17 years. Give: 6 mg/kg once-daily, on 5 days of the week, alternatively 5 mg/kg once-daily.

Intravenous treatment of cytomegalovirus disease (in immunocompromised children)

Children. Give: initially 5 mg/kg twice-daily for 14 to 21 days, then give a maintenance dose of 5 mg/kg once-daily. On 5 days of the week, alternatively give a maintenance dose of 5 mg/kg, the maintenance dose for children at risk of relapse; if disease progress initial induction of the treatment may be repeated.

Intravenous congenital cytomegalovirus infection of the central nervous system [4]

Infants. Give: 5 mg/kg twice-daily for 6 weeks.

Efficacy and safety of ganciclovir in infants and children

In symptomatic congenital cytomegalovirus infection in infants, valganciclovir is as efficient as ganciclovir and the former has fewer adverse-effects [5]. Intravenous ganciclovir and oral valganciclovir are effective in the congenital infection caused by cytomegalovirus [6]. Congenital cytomegalovirus infection can cause significant neurologic morbidity and antiviral therapy with ganciclovir or valganciclovir improves hearing and neurodevelopmental outcomes [7]. Asymptomatic congenital cytomegalovirus infection is likely to be a leading cause of sensorineural hearing loss in infants and intravenous ganciclovir therapy is effective in treating hearing loss [8]. Ganciclovir therapy begun in the neonatal period in symptomatically infected infants with cytomegalovirus prevents hearing deterioration at ≥1 year [9]. Ganciclovir regimen including a higher dose and more prolonged therapy is effective in infants with symptomatic congenital cytomegalovirus infection [10]. Ganciclovir is effective in the treatment of cytomegalovirus infection in children [11]. Valganciclovir appears to be efficacious and safe as ganciclovir in children with cytomegalovirus infection undergoing solid-tissue transplantation [12].

Effects of ganciclovir in infants and children

Ganciclovir treatment is beneficial in infants with cytomegalovirus-associated intrahepatic cholestasis [13]. Intravenous ganciclovir is efficacious in the treatment of cytomegalovirus infection in infants [14]. Valganciclovir and ganciclovir administrated during pregnancy treated cytomegalovirus infections in newborn infants [15]. Ganciclovir and oral valganciclovir are effective in the prevention and treatment of paediatric cytomegalovirus infection in children [16]. Ganciclovir is efficacious in the treatment of complicated cytomegalovirus infection in children [17].

Adverse-effects of ganciclovir in infants and children

Both ganciclovir and valganciclovir identify risk factors associated to the development of long-term sequelae in infants [18]. The main adverse-effect of treatment with valganciclovir or ganciclovir was transient neutropenia in infants [19]. Valganciclovir and ganciclovir caused different adverse-effects in infants. The major adverse-effects are carcinogenesis, teratogenesis, azoospermia and deposition into bone or dentition in infants [20]. In a child with impaired renal function valganciclovir and ganciclovir induced neurotoxicity [21]. Early liver dysfunction, elevated serum creatinine, and low marrow cellularity are risk factors for ganciclovir-related neutropenia. Neutropenia in ganciclovir recipients after marrow transplantation is an independent risk factor for mortality [22]. Neutropenia occurred in 11of 31 children (35.5%) and in nine (60%) of 15 (60.0%) children undergoing bone marrow transplant recipients who were treated with ganciclovir [23].

Pharmacokinetics of ganciclovir in infants

Trang et al. [24] studied the pharmacokinetics of ganciclovir in two groups of newborn infants with cytomegalovirus infections. Infants of group A (N = 14) had a postnatal age of 18±3 days and were weighing 6,100±500 grams and infants of group B (N = 13) had a postnatal age of 15±3 days and were weighing 5,300±400 grams. Ganciclovir was administered by intravenous infusion at a dose of 4 or 6 mg/kg twice-daily for 6 weeks and the concentration of ganciclovir was assessed in plasma. (Table 1)

This table shows that the distribution volume is lower than water volume, there is a remarkable interindividual variability in the pharmacokinetic parameters and the pharmacokinetic parameters are not different in the two groups of infants.

Zhou et al. [25] investigated the pharmacokinetics of ganciclovir in 27 newborn infants with symptomatic congenital cytomegalovirus infection. These authors did not report the demographic characteristics of infants. Ganciclovir was administered by intravenous infusion at a single dose of 4 or 6 mg/kg. (Table 2)

This table shows that the ganciclovir distribution volume is larger than the water volume and there is a remarkable interindividual variability in the total body clearance and in the distribution volume.

Pharmacokinetics of ganciclovir in children

Frenkel et al. [26] described the pharmacokinetics of ganciclovir in 36 immunocompromised children infected by HIV-1 and cytomegalovirus and were aged 7.4 years (range, 0.5 to 16.9). Initially, all children received ganciclovir by intravenous infusion at a dose of 5 mg/kg. After 2 days, the children received an oral dose of 10, 20, 30, 40 or 50 mg/kg of ganciclovir, and the ganciclovir concentration was measured in the serum. (Table 3)

This table shows that the peak concentration and AUC obtained following intravenous infusion are greater than those obtained after all oral doses. The apparent total body clearance obtained following intravenous infusion is lower than those obtained after the oral doses. The peak concentration and AUC obtained after infusion are greater than those obtained following all oral doses. The apparent oral total body clearance expressed as the L/h/kg is not related to the oral dose whereas the apparent

Table 1: Pharmacokinetic parameters of ganciclovir are measured in the plasma of two groups of newborn infants. Ganciclovir was administered by intravenous infusion at a dose of 4 mg/kg twice- daily (infants of group A) and at a dose of 6 mg/kg twice-daily (infants of group B). Figures are the minimum, maximum, and mean±SD, by Trang et al. [24].

	Peak conc. (µg/ml)	AUC (µg/ml*h)	K (h^{-1})	§Half-life (h)	DV (ml/kg)	TBC (ml/h/kg)	MRT (h)	DVss (ml/kg)	AUC/dose (µg/ml*h)/(mg/kg)
Infants of group A (N = 14)									
Minimum	2.5	8.4	0.1338	1.6	445	63	2.7	347	2.1
Maximum	8.0	40.9	0.4426	5.2	1,341	303	11.1	1,197	15.9
Mean	5.5	26.7	0.2852	2.4	669	189	4.8	630	6.7
±SD	0.4	3.6	0.0254	---	70	28	0.6	64	0.9
Infants of group B (N = 13)									
Minimum	4.3	17.2	0.1939	1.6	540	114	2.8	385	2.9
Maximum	10.1	36.0	0.4046	6.4	1,280	350	9.8	1,173	9.3
Mean	7.0	32.3	0.2944	2.4	749	213	4.6	686	5.4
±SD	0.5	3.8	0.0278	---	59	21	0.5	59	0.6
*P-value	0.243	0.290	0.808	---	0.389	0.485	0.806	0.528	0.268

K = elimination rate constant. §Harmonic elimination half-life (0.693/K). VD = distribution volume. TBC = total body clearance. MRT = mean residence time. DVss = distribution volume at steady-state. AUC/dose = AUC normalized for the dose administered. *Umpired student t test.

Table 2: Basic model estimates of ganciclovir population pharmacokinetic parameters for 27 newborn infants. Figures are the median, by Zhou et al. [25].

Parameter	Parameter estimate	%Coefficient of variation
ΩTBC (L/h)	0.422	8.9
ΩDV (L)	1.64	7.6
ω^2 TBC	0.183	20.6
ω^2 DV	0.154	32.3

ΩTBC = structural parameter representing the total body clearance. ΩDV = structural parameter representing the distribution volume. ω^2 = variance-covariance of random interindividual variability of the parameters.

Table 3: Pharmacokinetic parameters of ganciclovir obtained following intravenous or oral suspension in 36 children. Figures are the median and (95% CI), by Frenkel et al. [26].

Dose	N	Age (years)	Peak conc. (µg/ml)	$AUC_{0-\infty}$ (µg*h/ml)	TBC/F (L/h/kg)	TBC/F ($L/h/m^2$)
Intravenous 5 mg/kg	36	---	6.6 (5.8 – 7.3)	17.1 (14.8-19.2)	0.3 (0.27-0.32)	7.57 (6.89-8.24)
Oral administration						
10 mg/kg	5	9.3	0.3 (0.1 – 0.8)	1.8 (0.2 – 3.4)	4.8 (2.0 – 11.7)	116 (50-270)
20 mg/kg	5	4.2	0.4 (0.0 – 0.9)	2.9 (1.7 – 4.1)	5.5 (3.8 – 7.9)	138 (87 – 220)
30 mg/kg	8	6.9	0.6 (0.4 – 0.8)	3.7 (3.1 – 4.2)	6.2 (4.8 – 7.9)	139 (82 – 235)
40 mg/kg	8	10.4	1.0 (0.8 – 1.2)	4.9 (3.7 – 6.0)	7.0 (5.4 – 9.1)	186 (147 – 245)
50 mg/kg	10	7.7	1.4 (0.6 – 2.1)	6.2 (3.0 – 9.4)	6.8 (4.1 – 11.1)	153 (96 – 245)

CI = confidence interval. TBC/F = apparent oral total body clearance. F = bioavailability.

oral total body clearance expressed as $L/h/m^2$ increases with the oral dose.

Metabolism of ganciclovir

In literature there is only one study on the metabolism of ganciclovir and it has been reported by Gentry and Drach [27]. The metabolism of ganciclovir was investigated in the human cytomegalovirus infected cells. Ganciclovir is converted into ganciclovir triphosphate and the peak concentration, the elimination half-life and the AUC of ganciclovir triphosphate is 43.7±0.4 pmol/10^6 cells, 48.2±5.7 hours, and 4,520±420 pmol*h/10^6 cells, respectively.

Interactions of ganciclovir with drugs

Drug interactions associated with the use of ganciclovir and foscarnet sodium are numerous and potentially dangerous [28]. The trough plasma concentrations of ganciclovir increases significantly when aciclovir is co-administered [29]. The co-administration of ganciclovir with tenofovir induces tenofovir

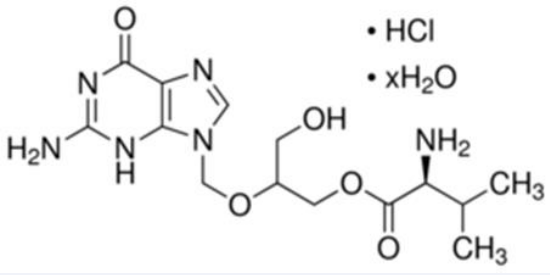

Figure 2 Valganciclovir hydrochloride hydrate molecular structure (molecular weight = 390.82 grams/mole).

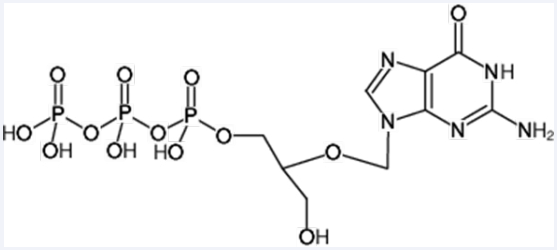

Figure 3 Molecular structure of ganciclovir triphosphate (molecular weight = 495.17).

nephrotoxicity [30]. The co-administration of ganciclovir and zidovudine induces severe toxicity in human cell lines in-vitro [31]. The combination of zidovudine and ganciclovir is poorly tolerated in children with AIDS and serious-cytomegalovirus disease and 82% of children develop life-threatening hematologic toxicity [32]. The combination of ganciclovir with zidovudine reduces the antiviral effect of these two drugs [33]. The combination of ganciclovir with relatively low doses of ribonucleotide reductase inhibitors significantly potentiates the anti-human cytomegalovirus activity of ganciclovir in-vivo and improves the clinical response to therapy [34]. Trifluorothymidine and ganciclovir are synergistic against acyclovir-susceptible HSV-1 [35]. Ganciclovir enhances the therapeutic efficacy of 5-fluorouracil, cis-platinum and taxol in Epstein-Barr virus-positive gastric cancer cells in-vitro [36]. Ganciclovir enhances the therapeutic efficacy of 5-fluorouracil, cis-platinum and taxol in Epstein-Barr virus-positive gastric cancer cells in-vitro [37]. A synergistic inhibition of cytomegalovirus replication occurs in-vitro following the co-administration of ganciclovir and foscarnet [38].

Therapeutic use of ganciclovir in infants and children

Ganciclovir may lead to clinical improvement of cytomegalovirus infection in infants [39]. Based on safety, efficacy, and tolerability, ganciclovir 0.15% gel should now be considered a front-line topical drug in the treatment of dendritic herpes simplex epithelial keratitis in children [40]. An immucompetent child was affected by cytomegalovirus and ganciclovir cured the infection [41]. Ganciclovir is effective in 80% of paediatric patients affected by cytomegalovirus infection as determined by negative antigenemia at the end of therapy [42].

Treatment with ganciclovir in infants and children

Anti-cytomegalovirus treatment may be beneficial for some premature infants with severe cytomegalovirus-associated gastrointestinal diseases [43]. Two immunocompetent infants with severe acquired cytomegalovirus infection respond dramatically to ganciclovir with no observed side-effects [44]. Ganciclovir is indicated for the treatment of cytomegalovirus infection in infants [45]. Ganciclovir is effective for the treatment of cytomegalovirus diseases in immunocompetent infants [46]. Non-immunocompetent infants with retinitis were treated with intravenous ganciclovir at a dose of 5 mg/kg daily and the treatment resolves haemorrhages and exudation [47]. Infants with congenital and symptomatic cytomegalovirus infections were treated with ganciclovir at a dose of 8 or 12 mg/kg daily. The infection was cured, but following the end of treatment the infection the virus reappeared in the urine, but the hearing loos was improved or stabilized [48]. Cytomegalovirus infection induces hearing loss and ganciclovir is an effective treatment and prevented the hearing loos in infants and children [49]. Ganciclovir treatment is of value in limiting the neurodevelopmental injury particularly sensorineural hearing loss caused by congenital cytomegalovirus infection [50]. Ganciclovir treatment begun in the neonatal period in symptomatically infected infants with cytomegalovirus involving the central nervous system prevents hearing deterioration at 6 months [51].

Prophylaxis with ganciclovir in children

The prophylaxis with ganciclovir prevents the herpes simplex keratitis in children [52]. Topical ganciclovir ophthalmic gel is a useful prophylaxis for herpetic keratitis in children [53]. Prophylaxis with ganciclovir is efficacy in preventing cytomegalovirus infection in children undergoing solid-tissue transplantation [54]. Prophylaxis with ganciclovir prevents cytomegalovirus infection in children undergoing solid-organ transplantation [55]. Prophylaxis with ganciclovir prevents cytomegalovirus infection in a child undergoing stem cell transplantation [56]. Ganciclovir prophylaxis performed at a dose of 15 to 25 mg/kg weekly is not adequate to prevent cytomegalovirus reactivation in children receiving marrow transplants [57]. Prophylaxis with ganciclovir prevents cytomegalovirus-associated pneumonia in children undergoing allogenic bone marrow transplantation [58]. In children with advanced AIDS, prophylactic oral ganciclovir significantly reduces the risk of cytomegalovirus infection [59]. Ganciclovir prophylaxis results efficacy in children with human immunodeficiency virus [60].

Penetration of ganciclovir into the cerebrospinal fluid of infants and children

Ganciclovir, administered as valganciclovir, penetrates the infant's cerebrospinal fluid when used at the currently recommended dose for congenital cytomegalovirus infection [61]. The mean concentration of ganciclovir 1 hour after an infusion of 5 mg/kg is 4.1 μg/ml in plasma and 0.7 μg/ml in the cerebrospinal fluid of children [62]. Ganciclovir penetrates into the cerebrospinal fluid of children with AIDS in significant amounts [63].

Treatment of meningitis with ganciclovir in infants and children

Ganciclovir or valganciclovir may be effective for the treatment of encephalitis caused by human herpesvirus 6 in an infant [64]. Treatment with ganciclovir should be considered in a child with human herpesvirus 6 infection of the central nervous system [65]. Ganciclovir successfully treats the meningoencephalitis caused by human herpesvirus 6 in a chid [66]. In AIDS children, standard ganciclovir treatment is effective in reducing but not suppressing viral replication in severe cases of cytomegalovirus infection of the central nervous system [67].

Transfer of ganciclovir across the human placenta

A pregnant woman with AIDS developed cytomegalovirus retinitis and pneumonitis, requiring intravenous ganciclovir. At 34 weeks gestation the woman delivered a girl weighing 1.4 kg. Examination of the placenta revealed transplacental passage of cytomegalovirus. Low concentrations of ganciclovir were detected in the neonate's plasma [68]. The antiviral agent ganciclovir crosses the placenta by simple diffusion, at least at therapeutic levels, and this transfer is not affected by the nucleoside transport inhibitor dinitrobenzylthioinosine [69].

DISCUSSION

Ganciclovir is an acyclic guanine nucleotide analogue and valganciclovir is the L-valyl ester prodrug of ganciclovir. Ganciclovir is converted into ganciclovir triphosphate which is a comparative inhibitor of dGTP incorporation into DNA polymerase. Incorporation into viral DNA causes eventual cessation of DNA chain elongation. Ganciclovir has inhibitory activity against all herpes viruses, is especially active against cytomegalovirus, and it successfully treated retinitis. In adults, the retinitis caused by cytomegalovirus is suppressed with ganciclovir administered intravenously at a dose of 5 mg/kg daily, with oral ganciclovir given at a dose of 1,000 mg trice-daily or with oral valganciclovir given at a dose of 900 mg daily for 21 days. The oral bioavailability of ganciclovir is < 10% whereas that of valganciclovir is about 60%, food further increases the vanciclovir bioavailability and valganciclovir is rapidly hydrolysed into ganciclovir [1]. In infants, the intravenous dose of ganciclovir is 6 mg/kg twice-daily and the oral dose of valganciclovir is 16 mg/kg twice-daily [2]. The intravenous dose of ganciclovir for the treatment of cytomegalovirus infection is 5 mg/kg twice-daily for 6 weeks in infants, and 5 mg/kg for 14 to 21 days in children [4]. Ganciclovir has been found efficacy safe in infants and children [5-12]. Intravenous ganciclovir and oral valganciclovir have been

found efficacy in the treatment of congenital cytomegalovirus infection in infants [5, 6]. Ganciclovir and valganciclovir improve hearing deterioration and neurodevelopment outcomes in infants with congenital cytomegalovirus infection [7-9]. In infants with congenital cytomegalovirus disease, ganciclovir should be administered at high dose and for more prolonged treatment [10]. Ganciclovir is effective in the treatment of cytomegalovirus infection in children [11] and valganciclovir appears to be efficacious and safe as ganciclovir in children with cytomegalovirus infection undergoing soli-tissue transplantation [12]. The effects of ganciclovir or valganciclovir have been reported in infants and children [13-17]. Ganciclovir is beneficial in infants with cytomegalovirus-associated cholestasis [13], and ganciclovir is effective in the treatment of cytomegalovirus infection in infants [14]. Valganciclovir and ganciclovir administered during pregnancy prevents and treats cytomegalovirus infection in newborn infants [15], ganciclovir and valganciclovir prevents and treats cytomegalovirus infection in children [16], and ganciclovir is efficacious in the treatment of complicated cytomegalovirus infection in children [17]. The adverse-effects of ganciclovir have been reported in infants and children [18-23]. Both ganciclovir and valganciclovir induce long-term sequelae in infants [18], valganciclovir and ganciclovir cause transient neutropenia in infants [19], these antivirals may cause carcinogenesis, teratogenesis, azoospermia and deposition into bone or dentition in infants [20] and induce neurotoxicity in a child [21]. Ganciclovir induces liver dysfunction, elevated serum creatinine, neutropenia, and low cellularity in children [22], and ganciclovir induces neutropenia in some children [23]. The pharmacokinetics of ganciclovir is studied by Trang et al. [24] in two groups of infants. The mean elimination half-life, the total body clearance, and the distribution volume of ganciclovir is 2.4 hours, about 200 ml/min/kg, and about 700 ml/kg, respectively. The pharmacokinetics of ganciclovir have been studied following ganciclovir administered at a dose of 5 mg/kg intravenously and following five oral doses ranging from 10 to 50 mg/kg. The peak concentration and the AUC are higher following the intravenous than all oral doses, and the total body clearance is higher following the oral doses than after the intravenous dose [26]. Ganciclovir is converted into ganciclovir triphosphate in the human cytomegalovirus infected cells and the half-life of ganciclovir triphosphate is about 48 hours in these cells [27]. Ganciclovir interacts with drugs [28-38]. The combination of ganciclovir with foscarnet induces numerous dangerous effects [28], ganciclovir trough concentration is increased when is co-administered with aciclovir [29], and the co-administration of ganciclovir with tenofovir induced nephrotoxicity [30]. The combination of ganciclovir and zidovudine induces severe toxicity in human cell lines in-vitro [31], is poorly tolerated in children with AIDS and cytomegalovirus disease [32] and this combination reduces the antiviral effects of these two drugs [33]. The combination of ganciclovir with low doses of ribonucleotide reductase inhibitors potentiates the anti-cytomegalovirus activity [34]. Trifluorothymidine and ganciclovir are synergistic against acyclovir-susceptible HSV-1 [35], ganciclovir enhances the therapeutic efficacy of 5-fluorouracil, cis-platinum and taxol in Epstein-Barr-positive gastric cancer cells in-vitro [36, 37], and the combination of ganciclovir with foscarnet exerts a synergistic inhibition of cytomegalovirus in-vitro [38]. The therapeutic use of ganciclovir has been studied in infants and children [39-42]. Ganciclovir leads to clinical improvement of cytomegalovirus infection in infants [39], topical ganciclovir gel treats dendritic herpes simplex epithelial keratitis in children [40]. Intravenous ganciclovir cures cytomegalovirus infection in an immunocompetent child [41], and ganciclovir cures cytomegalovirus infection in 80% paediatric patients [42]. The treatment with ganciclovir has been studied in infants and children [43-51]. Treatment with ganciclovir is beneficial in premature infants with cytomegalovirus-associated gastrointestinal diseases [43], two infants with severe acquired cytomegalovirus infection were cured with ganciclovir [44], and treatment with ganciclovir is effective in infants with cytomegalovirus infection [45-46]. Ganciclovir treats retinitis in non-immunocompetent infants [47]. Hearing loss, caused by cytomegalovirus infection, is cured with ganciclovir in infants [48] and in children [49]. Ganciclovir treatment limits sensorineural hearing loos in infants with congenital cytomegalovirus infection [50] and this treatment begun in the neonatal period cures the central nervous system infection and prevents hearing loos caused by cytomegalovirus in infants [51]. The prophylaxis with ganciclovir has been studied in children [52-60]. Prophylaxis with systemic or topical ganciclovir prevents keratitis in children [52, 53]. Prophylaxis with ganciclovir prevents cytomegalovirus infection in children undergoing solid-organ transplantation [54, 55], in a child undergoing stem cell transplantation [56], and in children receiving marrow transplants [57, 58]. In children with AIDS, prophylactic oral ganciclovir reduces the risk of cytomegalovirus infection [59], and ganciclovir prophylaxis is efficacy in children with immunodeficiency virus [60]. Ganciclovir penetrates into the cerebrospinal fluid of infants [61] and children [62, 63] in significant amounts. Ganciclovir is effective in the treatment of meningitis caused by human herpes virus 6 in infants [64] and in children [65, 66], and ganciclovir successfully cures the central nervous system infection caused by cytomegalovirus [67]. Ganciclovir poorly crosses the human placenta in-vivo [68] and in-vitro [69].

In conclusion, ganciclovir is an acyclic guanine nucleotide analogue and valganciclovir is the L-valyl ester prodrug of ganciclovir. Ganciclovir has inhibitory activity against all herpes simplex viruses and is especially active against cytomegalovirus, and inhibits viral DNA. The oral bioavailability of ganciclovir is < 10% and that of valganciclovir is 60% and food further increases the oral bioavailability of valganciclovir. Over 90% of ganciclovir is eliminated unchanged by renal excretion. The intravenous dose of ganciclovir is 6 mg/kg twice-daily and the oral dose of valganciclovir is 16 mg/kg twice-daily in infants. The intravenous dose of ganciclovir is 5 mg/kg twice-daily in children. Infants with congenital cytomegalovirus infection are treated with intravenous ganciclovir at a dose of 5 mg/kg twice-daily for 6 weeks. Ganciclovir has been found efficacy and safe in infants and children but my cause adverse-effects. The major adverse-effects are carcinogenesis, teratogenesis, azoospermia and deposition into bone or dentition. The mean elimination half-life is 2.4 hours in infants. Ganciclovir interacts with drugs; in particular the co-administration of ganciclovir with zidovudine induces toxicity. Ganciclovir has been found effective in the treatment of cytomegalovirus infection in infants and children

and the prophylaxis with ganciclovir prevents herpetic keratitis and cytomegalovirus infection in children. Ganciclovir penetrates into the cerebrospinal fluid of infants and children in significant amounts and treats the meningitis caused by the human herpesvirus 6 and cytomegalovirus. Ganciclovir poorly crosses the human placenta. The aim of this study is to review the clinical pharmacology of ganciclovir in infants and children.

CONFLICT OF INTERESTS

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This article is a review and drugs have not been administered to men or animals.

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