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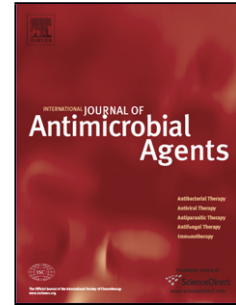
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## Ganciclovir treatment in children: evidence of subtherapeutic levels

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## ABSTRACT

Ganciclovir (GCV) is used to treat babies and older children with cytomegalovirus-related disease. Treatment courses are generally derived from adult studies and there are few data relating to the pharmacokinetics of GCV in children. In adults, low trough GCV levels have been associated with treatment failure and virological resistance. Data regarding suitable drug levels for use in therapeutic drug monitoring (TDM) in the paediatric age group do not currently exist. In this study, anonymised data for all GCV levels sent to the UK Antibiotic Reference Laboratory from 1 November 1999 to 31 March 2007 were reviewed and analysed by age group. In total, 339 specimens were received from 129 patients; 192 specimens were from patients aged <18 years. There were significantly more trough GCV levels <0.5 mg/L in those aged <6 months and 6–12 months compared with adults (64.8% and 53.9%, respectively, vs. 15.9%;  $P < 0.001$ ). Those aged 5–18 years also had significantly more trough samples with levels <0.5 mg/L (80.0% vs. 15.9%;  $P < 0.001$ ). There was a significant difference between median peak GCV levels in those aged <6 months and adults (4.8 mg/L vs. 5.7 mg/L, respectively;  $P = 0.047$ ). In conclusion, GCV levels associated with treatment failure and considered subtherapeutic in adult patients were observed more often in specimens from paediatric patients. These lower levels may have implications for dosing in the paediatric age group, particularly during periods of rapid change in renal function such as the neonatal period. Clinicians should be aware of the relatively low drug exposure noted in this study and consider TDM and increasing drug dose where virological response is poor.

## 1. Introduction

The antiviral agent ganciclovir (GCV) may be used to treat infants with congenitally or postnatally acquired human cytomegalovirus (hCMV) infection as well as older children who have primary or secondary immunosuppression and CMV-related disease.

Currently, the dose of GCV recommended for intravenous (i.v.) administration in the British National Formulary for Children (BNF-C) is the same as for adults, i.e. 5 mg/kg twice daily (<http://www.bnfc.org>); a higher dose of 6 mg/kg twice daily is recommended for use in neonates. These doses are based on the results of pharmacokinetic trials involving small cohorts of infected children ( $N = 14$ ) [1,2] and neonates ( $N = 27$ ) [3,4].

The role of therapeutic drug monitoring (TDM) during treatment with GCV is unclear. Serum peak and trough levels of GCV are generally measured, whereas the active compound is intracellular GCV in its triphosphorylated form. Although there is some evidence that serum levels are a reasonable surrogate for the intracellular form, precisely how these relate to toxicity and treatment efficacy is less certain [5].

In vitro values of the 50% inhibitory concentration ( $IC_{50}$ ) and minimum inhibitory concentration (MIC) for GCV have been estimated at 0.02–3.48 mg/L and 0.31–1.63 mg/L, respectively, depending on the strain of hCMV being used [6]. However, these levels have generally been derived from hCMV grown on human foreskin fibroblasts, and virus cultured in this way is known to differ significantly from wild-type virus. Values obtained from such assays may therefore be unsuitable for TDM purposes.

The therapeutic ranges often quoted in clinical studies were first derived from a study in five bone marrow transplant patients and one acquired immune deficiency virus (AIDS) patient with documented CMV retinitis or pneumonitis [7]. In that study, peak plasma concentrations ranged from 4.75 mg/L to 6.2 mg/L and trough concentrations from 0.25 mg/L to 0.63 mg/L. Although the area under the drug concentration–time curve (AUC) is often used when describing drug exposure in clinical studies, obtaining sufficient samples for such measurements is not always practical in the clinical setting, particularly in the paediatric age group. However, owing to the first-order kinetics exhibited by GCV, AUC has been shown to correlate with both peak drug concentration ( $C_{max}$ ) and trough levels, which are taken for TDM, suggesting that these parameters may be useful indicators of AUC [8]. Lower trough levels (<0.6 mg/L) have been associated with a higher incidence of disease progression in a study of CMV retinitis in adult human immunodeficiency virus (HIV) patients, although other authors have not been able to correlate drug levels with clinical or virological efficacy [5,6,9]. Other factors may also potentially affect treatment efficacy, including virus genotype, host immune responses and levels of GCV-triphosphate actually achieved in target body tissues; some of these parameters may be anticipated to vary significantly with age.

Likewise, toxicity has not been clearly associated with drug levels in adults, although a recent study of valganciclovir (valGCV) in neonates did report a correlation both between  $C_{max}$  and AUC over a 12-h period ( $AUC_{12}$ ) with neutropenia [9]. Toxicity remains one of the main concerns with the use of GCV [10].

Therefore, at present high-quality data correlating plasma levels with clinical efficacy are lacking and are further complicated by the fact that reported levels differ depending on the patient group [11]. Data for routine TDM in the paediatric age group are currently lacking from the published literature.

Our clinical experience using a TDM service to support the dosing of GCV in infants using standard dosing regimens led us to believe that drug levels in infants may frequently be less than those quoted for adults. We therefore reviewed the current UK information base on the concentrations of GCV found in samples received from children for routine TDM purposes by the UK Antimicrobial Reference Laboratory [Bristol Centre for Antimicrobial Research and Evaluation (BCARE), Bristol, UK].

## **2. Materials and methods**

Anonymised serum GCV concentrations (reported in mg/L) from all clinical samples received by the UK Antimicrobial Reference Laboratory in Bristol from 1 November 1999 to 31 March 2007 were reviewed. Owing to the anonymised nature of the data and the limited information included on clinical requests received by the laboratory, no specific pharmacological and clinical data were available for analysis.

All samples had been assayed by a validated high-performance liquid chromatography (HPLC) assay. In brief, chromatography was performed on a Techsphere C8 HPLC column using a mobile phase of 1% phosphoric acid in a 10 g/L solution of octane sulfonic acid, with sample preparation by 1:1 dilution with perchloric acid and quantification by the external standard method. Both the intra-assay and inter-assay precision (CV) were <10% and the limit of detection ranged

from 0.5 mg/L to 0.1 mg/L depending on the instrumentation used over the period of the study.

In instances where there was no reported GCV in the sample, a value of 50% of the detection limit reported for the assay was used for analysis. Results were analysed for different paediatric age groups, and median values were compared with those from subjects aged >18 years (adults) using the Mann–Whitney *U*-test. Two × two contingency tables and Fisher’s exact test were used to compare numbers in each age group with levels above or below defined cut-off values.

### 3. Results

In total, 339 specimens were received over the stated time period from 129 patients. Only 173 (51%) of these specimens were paired pre- and post-levels. Moreover, 192 specimens (57% of all specimens) were received from 65 patients (50% of all patients) aged <18 years, 117 (61%) of which were paired pre- and post-levels. Although 95 specimens were received from children aged <6 months, only 10 samples were from four neonates (aged <28 days).

#### 3.1. Trough levels

A total of 199 trough levels were received, with 128 (64%) of these being from subjects aged <18 years. Fig. 1 and Table 1 show the distribution of trough levels for each of the age categories.



In those patients aged <6 months and 6–12 months, there was a significantly higher proportion of levels <0.5 mg/L compared with adults (64.8% and 53.9%, respectively, vs. 15.9%;  $P < 0.001$ ). Although there was only a small number of babies aged <28 days, fewer had trough levels <0.5 mg/L (50.0%) compared with the group aged <6 months as a whole. There was also a trend towards more levels <0.5 mg/L in those patients aged 1–5 years compared with adults but, possibly due to the small numbers in this group, this did not reach statistical significance (37.5% vs. 15.9%;  $P = 0.079$ ). Those aged 5–18 years had significantly more trough levels <0.5 mg/L than adults, although small numbers may again have influenced results (80% vs. 15.9%;  $P < 0.001$ ). Conversely, the paediatric age groups had fewer samples that may be considered toxic, with none of the groups having more than 7% of trough measurements >6.0 mg/L compared with 19% in adults.

### 3.2. Peak levels

In total, 198 post-dose levels were received. Median levels in all age groups ranged from 3.7 mg/L to 5.7 mg/L (Table 1). Approximately one-third of patients aged <18 years had peak levels <3.0 mg/L (the upper limit of the  $IC_{50}$  often quoted from in vitro studies), and in infants aged 6–12 months the modal peak level was 2.0–3.0 mg/L, with nearly 35% of peak levels being <3.0 mg/L. Although a trend towards lower peak levels can be seen in the younger age groups, a significant difference was only found when comparing the median peak levels in those aged >18 years with those aged <6 months (5.7 mg/L vs. 4.8 mg/L, respectively;  $P = 0.047$ ). However, the lowest median peak levels were actually found in those aged 5–18 years (3.7 mg/L; interquartile range 2.4–5.6 mg/L), with 35.7% of levels being <3.0 mg/L.

#### 4. Discussion

In this study, we reviewed concentrations of GCV in patients for whom TDM was performed. In just over 7 years, 339 samples were received from a total of 129 patients and, although the reasons for TDM were not available, this represents one of the largest cohorts reported to date for TDM of GCV. In earlier studies, patient numbers have generally been low (<20) and the patients have either been of tightly defined disease states or the studies have been conducted under clinical trial conditions. The data presented here may give a clearer picture of the concentrations found in patients under more typical clinical conditions.

Levels from children accounted for more than one-half of samples sent to this national reference laboratory, despite the lack of any validated reference values for this population. There were significantly more trough levels <0.5 mg/L reported in young children compared with adults.

Peak GCV levels of >7.0 mg/L (the reference value often quoted for TDM) were rarely achieved in any of the age groups studied. Although a significant difference was only seen between median peak levels in those aged <6 months old compared with adults, the lowest median levels were actually noted in the 5–18 year age group.

Low trough levels have been previously reported in a small study of paediatric transplant patients, with levels <0.5 mg/L being significantly more common in younger patients [12]. The observation that fewer babies <28 days had trough levels <0.5 mg/L compared with the overall age group <6 months would be in keeping with the almost exclusive renal excretion of GCV and the known immature renal function

in newborns, giving a corresponding decrease in GCV excretion compared with older infants.

Peak levels were also in keeping with those reported in other clinical studies and were well above the MIC and IC<sub>50</sub> observed in vitro [6,7]. The relatively high frequency of peak levels <3.0 mg/L in younger age groups would, however, give rise to concerns regarding treatment failure, particularly if the disease-causing virus had an IC<sub>50</sub> at the upper range of those reported in vitro (3.48 mg/L).

We cannot offer a full explanation for the lower peak levels and the higher proportion of trough levels <0.5 mg/L seen in 5–18 year olds from these anonymised data, which lack detailed clinical and pharmacological information. However, although the patient numbers were small, this does suggest that underdosing may also affect this older age group.

One of the weaknesses of this study is the lack of clinical information, making the underlying indication for TDM sampling a potential bias. The relatively high proportion of paediatric samples may reflect the fact that recent publications have challenged the utility of TDM in adult patients, other than in specific subgroups with known risk factors such as renal impairment [11]. Therefore, a possible confounding factor is that, particularly in adults, levels may have only been sent from patients in whom there were concerns about treatment failure, toxicity or dosing of medication.

Interpretation is further limited by the absence of information on the dose and mode of administration and the reliability of reported timing of samples. Given that the oral solution of valGCV has only recently become available in the UK and that oral GCV

has not been available for some time, it can reasonably be assumed that in the younger age groups i.v. GCV was being administered in the majority of cases. In the older age groups this assumption cannot be made.

The lower levels reported here and elsewhere would raise concerns that paediatric age groups are receiving inadequate doses of GCV and/or valGCV. Prophylactic oral dosing of GCV has been associated with GCV resistance and possible treatment failure, suspected to be due to the low serum drug levels achieved, and trough levels  $>0.6$  mg/L have therefore been proposed by some authors as being optimal [5,13,14]. There is a risk that the low concentrations seen in the paediatric population may likewise select for resistance and lead to treatment failure.

A number of studies have reported enhanced viral suppression and clinical outcome with higher drug exposure [10,15]. Other authors have not been able to correlate drug levels with clinical or virological efficacy [6,9].

As with many other drugs, a specific threshold above which GCV levels may be considered undesirable has not been described. Despite toxicity being relatively common, previous reports have failed to establish a correlation between GCV levels and clinical toxicity in adults (summarised in [11]). Although the lower levels seen in the paediatric population may imply that toxicity is correspondingly less likely, toxicity tends to have a high degree of interpatient susceptibility and studies in neonates have shown similar levels of severe neutropenia to those in adults [16].

Although the clinical relevance of the lower levels presented here is therefore uncertain, the significantly decreased exposure to GCV during standard treatment courses compared with adults is notable. Recent reports have suggested dosing algorithms for valGCV based both on weight and creatinine clearance for oral valGCV [17]. Given that such algorithms do not currently exist for i.v. GCV, and the wide interpatient and inpatient variability reported in younger children when weight alone is used for dosing, TDM may be of particular benefit to guide GCV dosing in the paediatric age group [12]. We propose that TDM should be considered in younger children, particularly if longer treatment courses are being considered where selection for viral GCV resistance is more likely, during periods of anticipated changes in renal function and if virological response appears inadequate. Based on existing data and concerns regarding undertreatment, a trough of 0.5–1.0 mg/L would seem optimal. Although not necessarily translatable to younger children, the peak reference level used for adults of 7–9 mg/L for GCV (5–7 mg/L for valGCV) are suggested as a goal. In the presence of adequate trough levels and good virological response, adjusting dose based purely on a mildly suboptimal peak, however, does not seem justifiable based on current evidence.

The need for dosing algorithms for i.v. GCV, such as those derived for valGCV, are apparent. Moreover, detailed pharmacokinetic/pharmacodynamic studies in different paediatric age groups (and at early gestations) would also seem desirable. In all age groups, the use of surrogate markers (for example virological or immunological) when designing such trials may help to define the optimal dose at different age ranges to maximise clinical efficacy while minimising toxicity. Until such studies are

conducted, the true utility of TDM with regard to clinical outcomes will remain somewhat uncertain.

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### **Competing interests**

None declared.

### **Ethical approval**

Not required.

## References

- [1] Jacqz-Aigrain E, Macher MA, Sauvageon-Marthe H, Brun P, Loirat C. Pharmacokinetics of ganciclovir in renal transplant children. *Pediatr Nephrol* 1992;6:194–6.
- [2] Zhang D, Lapeyraque AL, Popon M, Loirat C, Jacqz-Aigrain E. Pharmacokinetics of ganciclovir in pediatric renal transplant recipients. *Pediatr Nephrol* 2003;18:943–8.
- [3] Trang JM, Kidd L, Gruber W, Storch G, Demmler G, Jacobs R, et al. Linear single-dose pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infections. NIAID Collaborative Antiviral Study Group. *Clin Pharmacol Ther* 1993;53:15–21.
- [4] Zhou XJ, Gruber W, Demmler G, Jacobs R, Reuman P, Adler S, et al. Population pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infections. NIAID Collaborative Antiviral Study Group. *Antimicrob Agents Chemother* 1996;40:2202–5.
- [5] Piketty C, Bardin C, Gilquin J, Gairard A, Kazatchkine MD, Chast F. Monitoring plasma levels of ganciclovir in AIDS patients receiving oral ganciclovir as maintenance therapy for CMV retinitis. *Clin Microbiol Infect* 2000;6:117–20.
- [6] Fishman JA, Doran MT, Volpicelli SA, Cosimi AB, Flood JG, Rubin RH. Dosing of intravenous ganciclovir for the prophylaxis and treatment of cytomegalovirus infection in solid organ transplant recipients. *Transplantation* 2000;69:389–94.
- [7] Fletcher C, Sawchuk R, Chinnock B, de Miranda P, Balfour HH Jr. Human pharmacokinetics of the antiviral drug DHPG. *Clin Pharmacol Ther* 1986;40:281–6.

- [8] Snell GI, Kotsimbos TC, Levvey BJ, Skiba M, Rutherford DM, Kong DC, et al. Pharmacokinetic assessment of oral ganciclovir in lung transplant recipients with cystic fibrosis. *J Antimicrob Chemother* 2000;45:511–6.
- [9] Kimberlin DW, Acosta EP, Sánchez PJ, Sood S, Agrawal V, Homans J, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis* 2008;197:836–45.
- [10] Wiltshire H, Paya CV, Pescovitz MD, Humar A, Dominguez E, Washburn K, et al.; Valganciclovir Solid Organ Transplant Study Group. Pharmacodynamics of oral ganciclovir and valganciclovir in solid organ transplant recipients. *Transplantation* 2005;79:1477–83.
- [11] Scott JC, Partovi N, Ensom MH. Ganciclovir in solid organ transplant recipients: is there a role for clinical pharmacokinetic monitoring? *Ther Drug Monit* 2004;26:68–77.
- [12] Vethamuthu J, Feber J, Chretien A, Lampe D, Filler G. Unexpectedly high inter- and inpatient variability of ganciclovir levels in children. *Pediatr Transplant* 2007;11:301–5.
- [13] Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. *Proc Natl Acad Sci U S A* 2000;97:8039–44.
- [14] Limaye AP, Corey L, Koelle DM, Davis CL, Boeckh M. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000;356:645–9.



- [15] Whitley RJ, Cloud G, Gruber W, Storch GA, Demmler GJ, Jacobs RF, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis* 1997;175:1080–6.
- [16] Kimberlin DW, Lin CY, Sánchez PJ, Demmler GJ, Dankner W, Shelton M, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. 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.
- [17] Vaudry W, Ettenger R, Jara P, Varela-Fascinetto G, Bouw MR, Ives J, et al.; Valcyte WV16726 Study Group. Valganciclovir dosing according to body surface area and renal function in pediatric solid organ transplant recipients. *Am J Transplant* 2009;9:636–43.

**Fig. 1.** Trough levels of ganciclovir (mg/L) in different age groups.

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**Table 1**

Peak and trough ganciclovir levels by age group

Age	Trough levels (mg/L)				Peak levels (mg/L)				
	No. of samples	Mode	Median (IQR)	<0.5 mg/L (%)	No. of samples	Mode	Median (IQR)	<3.0 mg/L (%)	>7.0 mg/L (%)
<28 days	8	<0.5	1.3 (0.3–1.9)	50.0	8	– <sup>a</sup>	4.7 (3.4–5.8)	25.0	12.5
<6 months <sup>b</sup>	71	<0.5	0.4 (0.1–1.0)	64.8	67	3–4	4.8 (3.5–6.3)	20.9	17.9
6–12 months	26	<0.5	0.5 (0.1–1.0)	53.9	29	2–3	5.2 (2.7–8.0)	34.5	34.5
1–5 years	16	<0.5	1.3 (0.2–2.3)	37.5	17	4–5	4.7 (2.4–7.9)	29.4	29.4
5–18 years	15	<0.5	0.3 (0.2–0.5)	80.0	14	3–4; 5–6 <sup>c</sup>	3.7 (2.4–5.6)	35.7	14.3
>18 years	69	1–2	2.1 (1.0–4.2)	15.9	70	4–5	5.7 (3.7–8.2)	20.0	35.7

IQR, interquartile range.

<sup>a</sup> Insufficient numbers to determine the mode.

<sup>b</sup> Includes those babies <28 days of age.

<sup>c</sup> Three children in each group.

No date of birth was given for two subjects with a pre-dose level and one subject with a post-dose level.

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Edited Figure 1

