Research letters

Transparency declarations

H. H. has received research support from Steris Corporation, Inov8 Science, Pfizer and Cepheid, and lecture and other fees from Novartis, Astellas and AstraZeneca. All other authors: none to declare.

References

3 EUCAST. *Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 3.1* (2013, date last accessed).

J Antimicrob Chemother 2014
doi:10.1093/jac/dkt472
Advance Access publication 19 November 2013

Pharmacokinetics and dosage individualization of ganciclovir and valganciclovir in an infant with nephrotic syndrome associated with cytomegalovirus infection

Bo Zhang1,2, Marc Fila3, May Fakhoury2, Véronique Baudouin3, Georges Deschênes3,4, Evelyne Jacqz-Aigrain2,4,5† and Wei Zhao2,5*†

1Emergency Department, The Third Hospital of Hebei Medical University, Shijiazhuang, China; 2Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Assistance Publique—Hôpitaux de Paris, Paris, France; 3Department of Paediatric Nephrology, Hôpital Robert Debré, Assistance Publique—Hôpitaux de Paris, Paris, France; 4University Paris Diderot, Press Sorbonne Paris Cité, Paris, France; 5Clinical Investigation Center CIC9202, INSERM, Paris, France

*Corresponding author. Department of Paediatric Pharmacology and Pharmacogenetics, Clinical Investigation Center CIC 9202 INSERM, Hôpital Robert Debré, 48 Boulevard Sérié, 75935 Paris cedex 19, France. Tel: 00-33-1-40-03-36-56; Fax: 00-33-1-40-03-57-79; E-mail: wei.zhao@rdb.aphp.fr
†Wei Zhao and Evelyne Jacqz-Aigrain contributed equally to the study.

Keywords: paediatric pharmacology, paediatric pharmacokinetics, therapeutic drug monitoring, dosage optimization

Sir,

Congenital cytomegalovirus (CMV) infection causes significant long-term disability due to deafness and mental handicap.1 Ganciclovir and valganciclovir are the drugs of choice to treat CMV disease. Target area under the concentration versus time curve (AUC0–12) of 27 mg-h/L is recommended.2 The standard dose is associated with a high variability in drug exposure, in particular in children,3–5 but data are limited in infants.6 The present case report illustrates the importance of dosage individualization of ganciclovir and valganciclovir in an infant with nephrotic syndrome and CMV infection. The renal disease ultimately influenced the pharmacokinetics, making therapeutic drug monitoring (TDM)-based dosage individualization useful to attain the target drug exposure and to increase the likelihood of treatment success.

A 6-month-old infant weighing 7 kg was admitted to hospital due to persistent watery stools. There was no family history. On arrival, clinical examination highlighted severe oedema and ascites. Biological tests showed hypoalbuminaemia (28 g/L) as associated with proteinuria (28 g/L). Urea and serum creatinine concentrations were in the normal range (35 μmol/L and 5.4 mmol/L, respectively). White blood cell count, platelet count and haemoglobin concentration were 20200/mm3 (48% lymphocytes), 409000/mm3 and 10.7 g/dL, respectively. Congenital nephrotic syndrome was suspected. Symptomatic treatment included captopril (3 mg/day) and albumin infusion (1 g/kg/day). Renal biopsy highlighted a mild endocapillary cellularity and an atypical heavy tubular lesion with interstitial oedema. The clinical course of our patient is presented in Figure 1.

A PCR for CMV, performed as part of the routine tests for congenital nephritic syndrome, was positive (123 000 copies/mL; Taqman CMV test, Roche Molecular Diagnostics, Pleasanton, CA, USA). Intravenous ganciclovir was started at the standard dose of 35 mg (5 mg/kg) twice daily. Pharmacokinetic samples (n = 6) were collected just before drug administration (T0) and at 1, 2, 4, 8 and 12 h after administration at steady-state condition and ganciclovir concentrations were measured by a previously published HPLC–UV method.5 AUC0–12 and clearance were calculated using a non-compartmental method with WinNonlin (v5.2, Pharsight, Mountain View, CA, USA). The first measurement after 3 days of treatment showed a low AUC0–12 of 10.7 mg-h/L. The ganciclovir dose was increased to 50 mg and AUC0–12 increased to 29.8 mg-h/L. After 2 weeks of treatment, intravenous ganciclovir

1150

1150
was switched to oral valganciclovir at a dose of 150 mg twice daily, and the AUC$_{0–12}$ was 24.5 mg·h/L. After 19 days of treatment, CMV PCR became negative. Oral valganciclovir was stopped after 4 weeks without adverse events. Along with the CMV PCR test becoming negative, proteinuria dramatically decreased, anaemia improved and digestive symptoms disappeared. At the 1 year follow-up, a CMV test was still negative and no relapse of nephrotic syndrome was noticed.

This case report emphasizes the importance of dosage individualization of ganciclovir and valganciclovir, taking into account pharmacokinetic changes associated with renal disease. Ganciclovir is primarily excreted renally and, in the case reported here, the standard dose of 5 mg/kg resulted in a very low AUC, because nephrotic syndrome induced a high ganciclovir clearance. In order to achieve target AUC and optimize antiviral therapy, TDM-based dosage individualization of ganciclovir and valganciclovir is indispensable for children with renal disease.

**Funding**
No research funding was received for the submitted work. The data were generated as part of our routine work.

**Transparency declarations**
None to declare.

**References**

**J Antimicrob Chemother** 2014
doi:10.1093/jac/dkt478
Advance Access publication 16 December 2013

**Public health need versus sales of antibacterial agents active against multidrug-resistant bacteria: a historical perspective**

Dominique L. Monnet* and Johan Giesecke

Office of the Chief Scientist, European Centre for Disease Prevention and Control (ECDC), Tomtebodavägen 11A, SE-171 83 Stockholm, Sweden