Pharmacokinetics of antiviral agents for the treatment of cytomegalovirus infection

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Cytomegalovirus (CMV) is an important infectious pathogen that affects short- and long-term outcomes after transplantation. Various antiviral medications, including oral and intravenous (i.v.) ganciclovir, oral valganciclovir, oral valacyclovir, foscarnet, cidofovir, and CMV immune globulin, may be used prophylactically or therapeutically. These agents can be difficult to use because of their complexity and lack of familiarity with prophylactic and therapeutic regimens, in addition to the need for dosage adjustment for patients with organ dysfunction. Adverse effects can be problematic and may require a multidisciplinary approach to care. Several agents are administered by the i.v. route, which is inconvenient for long-term therapy or use in the outpatient setting. The high cost of some medications may also limit their use in some patients.

Researchers and clinicians have sought to apply their knowledge of pharmacokinetics to devise antiviral drug regimens with improved efficacy, reduced risk for toxicity and antiviral drug resistance. Several factors contribute to the emergence of antiviral drug resistance (see the article by Razonable in this supplement). No one factor is solely responsible for resistance. Prolonged periods of viral replication in the presence of low antiviral drug concentrations is one of the most important factors leading to the emergence of antiviral drug resistance in transplant patients. Pharmacokinetic research has focused on achieving and maintaining therapeutic antiviral drug concentrations to reduce the risk for resistance.

The concentration of an antiviral agent needed to achieve 50% viral inhibition (IC$_{50}$) is used to determine whether the plasma concentration of the drug is sufficiently high to inhibit growth. The precise definition of IC$_{50}$ for antiviral agents depends on the phenotypic or genotypic assay used to determine CMV susceptibility. Caution must be used in comparing results obtained from different sources because the assay and units of measure can vary.

Ganciclovir

Ganciclovir has been a focus of pharmacokinetic research because of its proven efficacy in preventing CMV disease in solid organ transplant recipients. Ganciclovir is a nucleoside guanosine analog with potent antiviral activity against CMV. When the drug enters a cell, it is
phosphorylated by a viral protein kinase encoded by the UL97 gene to form ganciclovir monophosphate. Phosphorylation by cellular enzymes converts ganciclovir monophosphate to ganciclovir diphosphate and then to ganciclovir triphosphate, which is the active moiety. Ganciclovir triphosphate inhibits viral DNA polymerase, which is encoded by the UL54 gene, thereby interfering with viral DNA synthesis and replication. Resistance to ganciclovir may be the result of mutations in the UL97 or UL45 gene.

The oral bioavailability of ganciclovir is low (5% in fasting conditions and 6–9% after food). The drug exhibits linear pharmacokinetics and 6–9% after food). The oral bioavailability of ganciclovir is low (5% in fasting conditions and 6–9% after food). The UL45 gene. Resistance to ganciclovir may be the result of mutations in the UL97 or UL45 gene.

Valganciclovir

Valganciclovir, the L-valyl ester of ganciclovir, is a prodrug. It undergoes hydrolysis by hepatic and intestinal esterases, which cleave the amino acid valine from valganciclovir to yield ganciclovir.

The pharmacokinetics of valganciclovir were studied in an open-label, randomized, four-way, crossover, dose-selection study of 39 CMV-seropositive patients with human immunodeficiency virus infection, but no prior history of CMV infection or disease, good renal function (creatinine clearance > 70 mL/min), and normal hematologic indices. The patients were divided into two groups based on whether valganciclovir was taken with or without food (i.e., in the fed or fasted state), and patients in each group received valganciclovir 450 mg, 875 mg, 1750 mg, and 2625 mg orally once daily for three days in random order. These doses were selected based on models projecting a ganciclovir AUC comparable to that achieved by administering oral and i.v. ganciclovir.

In the 32 patients who completed the study, valganciclovir was rapidly absorbed and converted to ganciclovir. Systemic exposure to unchanged valganciclovir was low in all groups. The 24-hour ganciclovir AUC increased proportionally with valganciclovir dose and was significantly higher in the fed patients than in the patients who fasted. The peak plasma concentrations and time to peak plasma concentrations were slightly higher in the fed state compared with the fasted state, but the differences were not significant. Linear regression analysis and modeling of 24-hour AUC values in the fed group revealed that a single daily 900 mg oral valganciclovir dose would provide a similar systemic ganciclovir exposure as the standard i.v. ganciclovir dosage of 5 mg/kg/day.

Pescovitz et al. conducted an open-label, four-way, randomized, crossover study in 28 liver transplant recipients to identify the dosage of oral valganciclovir that would provide a ganciclovir systemic exposure that is lower than that provided by i.v. ganciclovir but higher than that provided by oral ganciclovir. Patients were randomized to receive oral ganciclovir 1 g three times at 6-hour intervals on 1 day, oral valganciclovir 450 mg as a single dose, oral valganciclovir 900 mg as a single dose, and i.v. ganciclovir as a single 5-mg/kg infusion over 1 hour, with a 3–7 day washout period between treatments.

Valganciclovir was rapidly absorbed and converted to ganciclovir after oral administration. Less than 2% of the dose appeared as ganciclovir in the plasma within 3–4 hours after administration. Valganciclovir plasma concentrations were undetectable within 3–4 hours after administration.

Valganciclovir 450 mg provided a ganciclovir systemic exposure (24-hour AUC) comparable to that produced by oral ganciclovir (Table 1). The ganciclovir peak plasma concentration was higher and the time to peak plasma concentration was shorter with valganciclovir 450 mg than with oral ganciclovir.

The systemic exposure was comparable with valganciclovir 900 mg and i.v. ganciclovir, although the ganciclovir peak plasma concentration was higher and the time to peak plasma concentration was shorter with i.v. ganciclovir than with valganciclovir 900 mg. The absolute bioavailability of both valganciclovir doses was nearly ten times higher than that of oral ganciclovir. The results demonstrated that doses of 450 or 900 mg of valganciclovir provide exposures similar to those achieved with oral and i.v. ganciclovir, respectively.

Bioavailability advantage. Intestinal peptide transporters located in the brush border of the intestines play an important role in the gastrointestinal (GI) absorption of certain nutrients and drugs. Proteins are large molecules that are poorly ab-
sorbed unless they are broken down into small peptides and amino acids by gastric and pancreatic proteases and peptidases. Intestinal peptide transporters carry these peptides and amino acids from the GI lumen into the bloodstream. The process is an energy-dependent one that also involves the transport of hydrogen ions.

Prodrugs of drugs with poor oral bioavailability (e.g., angiotensin converting-enzyme inhibitors, beta-lactam antibiotics) have been developed to target intestinal peptide transporters. The use of prodrugs with a high affinity for these transporters has resulted in improved oral bioavailability.

The interactions of ganciclovir and valganciclovir with the intestinal peptide transporter PEPT1 were compared in an experimental setting. Valganciclovir (but not ganciclovir) was found to interact with the transporter. These findings demonstrate that the greater oral bioavailability of valganciclovir may be the result of its recognition as a substrate by PEPT1. The intestinal peptide transporter PEPT1 has a high affinity for valganciclovir. Recognition of the L-valyl ester on valganciclovir by PEPT1 explains the high bioavailability of the prodrug. The presence of a peptide bond is not required for recognition of ganciclovir as a substrate.

Dosage adjustment. Because the kidneys are the primary route of elimination for ganciclovir, valganciclovir dosage adjustment is required for patients with impaired renal function (Table 2). Profound neutropenia and thrombocytopenia may develop if ganciclovir accumulates in patients with renal dysfunction.

Challenges and benefits

The use of valganciclovir presents clinicians with both challenges and benefits. The challenges include the need for dosage adjustment in patients with renal impairment, the lack of clinical experience in pediatric patients, the financial challenges in unfunded patients, and the risk of adverse effects. Proper dosing can minimize adverse effects. Valganciclovir is available as film-coated tablets that cannot be crushed for patients who are unable to swallow solid oral dosage forms (e.g., patients with nasogastric tubes). Extemporaneous compounding of liquid formulations may be an alternative. Stability data for two valganciclovir suspensions have been published.

The benefits of using valganciclovir include its greater oral bioavailability compared with ganciclovir, which may translate into a lower risk of emergence of antiviral drug resistance if sufficiently high plasma drug concentrations are maintained. The convenience and patient adherence associated with the oral route of administration also are advantages of the use of valganciclovir over i.v. therapies. The daily patient pill burden is lower with valganciclovir (two 450-mg tablets) than ganciclovir (six 500-mg tablets).

Table 1. Ganciclovir Pharmacokinetics in Liver Transplant Patients After Administration of Oral Ganciclovir, Oral Valganciclovir, and Intravenous Ganciclovir. Adapted with permission.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral Ganciclovir (n = 28)</th>
<th>Valganciclovir (n = 28)</th>
<th>Valganciclovir (n = 28)</th>
<th>Intravenous Ganciclovir (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC₂₄ (μg · hr/mL)</td>
<td>Cmax(μg/mL)</td>
<td>Tmax (hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.7</td>
<td>21.1</td>
<td>41.7</td>
<td>48.2</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>3.0</td>
<td>6.2</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>14.3</td>
<td>5.2</td>
<td>5.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Estimated absolute bioavailability (%)</td>
<td>6.3</td>
<td>60</td>
<td>59</td>
<td>NA</td>
</tr>
</tbody>
</table>

aAUC₂₄ = 24-hour area under the plasma concentration–time curve, NA = not applicable.
bAn open-label, four-way, randomized, crossover study of 28 liver transplant patients given ganciclovir 1 g orally three times at 6-hour intervals, valganciclovir 450 mg orally once, valganciclovir 900 mg orally once, and intravenous ganciclovir 5 mg/kg over 1 hour.

Table 2. Valganciclovir Dose Modifications for Patients with Impaired Renal Function.

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Induction Dosage</th>
<th>Maintenance Dosage</th>
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<tbody>
<tr>
<td>≥60</td>
<td>900 mg twice daily</td>
<td>900 mg once daily</td>
</tr>
<tr>
<td>40–59</td>
<td>450 mg twice daily</td>
<td>450 mg once daily</td>
</tr>
<tr>
<td>25–39</td>
<td>450 mg once daily</td>
<td>450 mg every 2 days</td>
</tr>
<tr>
<td>10–24</td>
<td>450 mg every 2 days</td>
<td>450 mg twice weekly</td>
</tr>
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</table>

References

Overview of transplant mycology

YOAV GOLAN

The incidence of nosocomial mycoses (fungal infections associated with therapeutic interventions) and the death rate from invasive mycoses increased markedly in the United States between 1980 and 1997. The increase in nosocomial mycoses involves patients with a variety of conditions and characteristics, including bone marrow and solid organ transplant recipients and neonatal, surgical, and critically ill patients.

Epidemiology

A wide variety of fungi can infect patients who undergo solid organ or bone marrow transplantation. *Candida* and *Aspergillus* are the two most common fungal pathogens in these patients. However, other opportunistic fungi are on the rise. These include yeasts such as *Cryptococcus neoformans*, *Trichosporon*, and *Malassezia*; hyalohyphomycetes such as *Fusarium* species; zygomycetes; and *Malassezia.* Resistance of human cytomegalovirus to antiviral drugs. *Clin Microbiol Rev.* 1999; 12:286-97.


Purpose. The epidemiology, clinical manifestation, diagnosis, and management of invasive mycoses in transplant patients are described.

Summary. The incidence of and mortality from invasive mycoses have increased in transplant patients. *Candida* and *Aspergillus* are the two most common fungal pathogens in this patient population. The use of immunosuppressive and myeloablative therapies and other factors increases the risk of invasive mycoses. A high index of suspicion and clinical clues are needed for the diagnosis of *Candida* and *Aspergillus* infections because reliable diagnostic techniques are not available and the patient presentation is nonspecific. Targeted prophylaxis for patients at high risk for morbidity and mortality and early, aggressive treatment using broad-spectrum antifungal agents are recommended. Prophylaxis using itraconazole reduces the risk of treatment failure due to resistant pathogens compared with fluconazole. Voriconazole might prove advantageous compared with fluconazole and itraconazole for prophylaxis because of its extended spectrum and predictable blood levels. Caspofungin seems as effective as and less toxic than amphotericin B for this use. Voriconazole is more effective than amphotericin B for the treatment of aspergillosis. Caspofungin is comparable to voriconazole in efficacy as salvage treatment after failure to respond to other antifungal agents.

Conclusion. Caspofungin plus voriconazole and other combination therapies often are used for the treatment of aspergillosis yet data to support such use are yet to be produced. The investigational agents posaconazole, micafungin, and anidulafungin appear promising as salvage treatment of various invasive mycoses.

Index terms: Amphotericin B; Antifungals; Aspergillosis; Blood levels; Candidiasis; Caspofungin; Diagnosis; Epidemiology; Fluconazole; Immunosuppressive agents; Itraconazole; Mortality; Mycoses; Posaconazole; Resistance; Spectrum microbial; Transplantation; Voriconazole