Use of Ganciclovir for Cytomegalovirus Infection

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ABSTRACT

Ganciclovir (9-(1,3-dihydroxy-2-propoxymethyl)guanine, DHPG) is an acyclovir analog with excellent antiviral activity against human cytomegalovirus (CMV). Clinically, CMV infection occurs in from 60 to 90% of all renal transplant recipients and it is responsible for significant patient morbidity and graft loss. The likelihood of infection is closely related to the CMV status of both donor and recipient, with the greatest risk arising in the combination of a seronegative patient receiving a seropositive organ. Intracellularly, DHPG is converted to DHPG-triphosphate, which competitively inhibits DNA polymerase. This conversion is accelerated up to 10-fold in virally infected cells, providing some selectivity of action. Uncontrolled studies demonstrated DHPG efficacy in CMV disease, but experience in children remains limited. Although bone marrow suppression is a major immediate toxicity, long-term concerns about carcinogenesis and infertility mandate careful patient selection. Recently at the University of Minnesota, 93 solid organ recipients (45 renal transplants) including some children have been treated for tissue-invasive CMV with DHPG. All had a characteristic clinical picture and either a positive CMV culture or a biopsy with CMV inclusions. The patients received i.v. DHPG (10 mg/kg/day) with appropriate adjustments for renal function. In renal allograft recipients, 89% recovered within 30 days, although 21% had to be retreated with DHPG. Although no patient died, allograft survival was significantly reduced (P= 0.02). An additional subgroup of patients (N = 18) who had both biopsy-proven rejection and invasive CMV disease were simultaneously treated for both processes. All of these patients recovered from their CMV infection, but two grafts were lost to rejection. Initial results with DHPG are encouraging and should prompt aggressive efforts toward the early diagnosis of CMV disease, so that appropriate therapy may begin.

Key Words: Kidney, transplantation, antiviral, pediatric

It is known that nearly two thirds of all children are rehospitalized at least once in the first 6 months after renal transplantation. Of those hospitalized, 28.5% are a result of infection and 29.4% are secondary to rejection (1). Therefore, the diagnosis of a fever arising in a recently transplanted child poses a challenge to the clinical acumen of every physician caring for that child. Although the clinical picture and timing of the fever may suggest a diagnosis, any differential diagnoses must include both rejection (2) and infection (3). Frequently, the clinical picture is more complex, and it should be remembered that infection and rejection may regularly coexist. This review will emphasize the diagnosis of cytomegalovirus (CMV) infection and its treatment with ganciclovir (DHPG), specifically in children after renal transplantation.

DIAGNOSIS

CMV is recognized as a major viral pathogen in solid organ transplant recipients (4). As increasingly potent immunosuppressive regimens are developed, there appear to be even more clinically overt cases of CMV disease. Because the group at highest risk to develop significant CMV disease is clearly patients who were originally CMV naive and who received an organ from a CMV-positive individual, all patients and donors should have preoperative CMV serology documenting their status (5). Such studies permit the prospective identification of patients at highest risk, aid in the diagnosis of postoperative fever, and allow attempts at prophylaxis to be focused on the most vulnerable patient cohort.

The actual CMV infection may be entirely subclinical, appearing only retrospectively as a change in serial antibody titers. Alternatively, a spectrum of clinically apparent CMV disease exists, ranging from mild to fatal infections. The mildest form often presents as a hectic daily fever that resolves over time. Such patients may also exhibit arthralgia, myalgia, malaise, or lethargy. Some patients will develop mild to moderate neutropenia, thrombocytopenia, or elevation of liver enzymes. Definition of these cases may
be entirely based on serologic evidence or a conventional viral culture appearing after the clinical symptoms have spontaneously resolved. These patients constitute the majority of cases in pediatric renal transplants and are rarely serious enough or recognized soon enough to warrant drug treatment.

Another group of solid organ recipients will present with more impressive symptoms of overt disease. They most frequently have respiratory disease characterized by fever, cough, and dyspnea. Other patients will have primary gastrointestinal symptoms, with nausea, vomiting, and diarrhea (6). These latter patients may experience gastrointestinal bleeding from ulcers. A smaller number of patients will develop exudative retinitis, which is initially silent and detected early only by clinical examination of the retina. The most severe CMV infections are extensions of these clinically moderate syndromes with progressive respiratory failure, massive gastrointestinal hemorrhage or perforation, hepatitis, pancreatitis, secondary infections and sepsis, and finally, marked hypotension and death.

Although the history and clinical findings may suggest the diagnosis of CMV, they are usually not sufficient to provide a firm diagnosis or to permit the empirical initiation of specific drug therapy. Serology with an increasing titer of antibody to CMV does permit the diagnosis, but usually these changes become significant only after the clinical symptoms have resolved. Positive conventional viral cultures clearly define CMV infection, but the time actually required to detect a cytopathologic effect may be several weeks. Newer, more sensitive diagnostic techniques now permit the recognition of CMV antigen (7,8) or DNA (4,9) in a timely manner, and these techniques will likely become standard in many diagnostic microbiology laboratories in the near future.

**TREATMENT**

Although acyclovir has antiviral activity against some species of herpesvirus and may have a role in CMV prophylaxis (10), it is of no proven benefit in treating established CMV disease. However, a new guanosine analog, DHPG, has shown clinical effectiveness in the treatment of CMV syndromes in a variety of immunocompromised patients (11). DHPG becomes biologically active after phosphorylation to a triphosphate derivative that competitively inhibits DNA synthesis and terminates DNA elongation (11-13). The selective antiviral effect of the drug seems to arise primarily from its preferential binding to viral DNA polymerase (4) and from a 10-fold increase in DHPG phosphorylation, which occurs in virally infected cells (12).

Because the pH of the DHPG solution is 11, therapy must be given i.v. and slowly (over 1 h). For this reason, it should not be given by s.c. or i.m. injection. The reported experience with DHPG in children is still somewhat limited (14-16), and the optimal dosage is unclear. A DHPG dose of 2.5 mg/kg every 8 h is known to result in average peak levels of 5 μg/mL and trough levels of about 0.5 μg/mL in adults (17), whereas CMV replication has been shown to be 50% inhibited at concentrations ranging from 0.1 to 2.75 μg/mL (18). We usually begin all patients on a dose of 5 mg/kg every 12 h. Studies have found that >90% of ganciclovir is excreted into the urine; therefore, we adjusted the dose by serum creatinine, generally following the adult guidelines shown in Table 1. For smaller children, the dosage reduction was more carefully specified according to the estimated creatinine clearance.

**COMPLICATIONS**

The antimetabolic toxicity of DHPG in mammalian cells is most immediately seen as bone marrow suppression, primarily neutropenia (absolute neutrophil count, <1,000) occurring in as many as 40% of patients. Thrombocytopenia is also seen in about 20%. Elevations of liver enzymes or serum creatinine have been recognized but are difficult to interpret in the presence of an active viral infection, which can affect both liver and kidneys. Acyclovir is already documented as causing renal toxicity (19), apparently as the result of tubular secretion and precipitation of microcrystals in the tubules. Because DHPG also undergoes significant tubular secretion (17), similar problems may arise in patients receiving DHPG. Finally, the long-term carcinogenic potential of DHPG and risks to future fertility present serious concerns and require a careful risk-benefit analysis before its use in each child.

**OUTCOME**

Our clinical approach is to evaluate all children presenting with fever and elevated creatinine levels after renal transplant by cultures, chest X-ray, renal ultrasound, and as indicated, percutaneous renal biopsy. However, our experience with DHPG in children is still somewhat limited (14-16), and the optimal dosage is unclear. A DHPG dose of 2.5 mg/kg every 8 h is known to result in average peak levels of 5 μg/mL and trough levels of about 0.5 μg/mL in adults (17), whereas CMV replication has been shown to be 50% inhibited at concentrations ranging from 0.1 to 2.75 μg/mL (18). We usually begin all patients on a dose of 5 mg/kg every 12 h. Studies have found that >90% of ganciclovir is excreted into the urine; therefore, we adjusted the dose by serum creatinine, generally following the adult guidelines shown in Table 1. For smaller children, the dosage reduction was more carefully specified according to the estimated creatinine clearance.

**TABLE 1. Adjustment of DHPG dosage by renal function**

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/dL)</th>
<th>Ccr (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.4</td>
<td>≥80</td>
<td>5.0 mg/kg/12 h</td>
</tr>
<tr>
<td>1.5-2.5</td>
<td>50-79</td>
<td>2.5 mg/kg/12 h</td>
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<tr>
<td>2.6-4.5</td>
<td>25-49</td>
<td>2.5 mg/kg/24 h</td>
</tr>
<tr>
<td>&gt;4.5</td>
<td>&lt;25</td>
<td>1.25 mg/kg/24 h</td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td>1.25 mg/kg/48 h</td>
</tr>
</tbody>
</table>

* Ccr, creatinine clearance.
transplant biopsy. Neutropenia is initially managed by the reduction or withholding of the dose of azathioprine. First episodes of significant acute transplant rejection are regularly treated by increased oral prednisone dosage and, as indicated, humoral [anti-lymphoblast globulin or OKT3] therapy. In symptomatic patients, when the diagnosis is confirmed by the detection of CMV antigen in blood, in bronchoalveolar lavage fluid, or by histology, we begin treatment with DHPG.

It should be emphasized again that the majority of children with CMV after renal transplantation have that diagnosis made retrospectively, often by serology. These children usually do well without any specific therapy. In sicker pediatric transplant recipients, our initial results of DHPG treatment for CMV have been reported (14). In that report, there were six children with solid organ transplants; all survived, five of the six improved with DHPG therapy, and one patient required further treatment. Our more recent experience continues to mirror these earlier results, and to date, no pediatric fatalities have occurred. Several children have relapsed after DHPG treatment was discontinued and required subsequent treatment. Although described elsewhere (20), DHPG-resistant CMV has not yet emerged as a major problem in our patient population. Our broader experience in 93 solid organ transplant patients with tissue-invasive CMV disease who received DHPG has also been very encouraging, with 89% improving clinically and 21% requiring further treatment (21).

As noted earlier, some patients will experience concomitant rejection and CMV infection. Eighteen adult patients have been recognized as having tissue-invasive CMV infection simultaneously with acute rejection (22). These patients were begun on concurrent i.v. DHPG and increased steroids. Subsequently, humoral therapy was added in 13 patients. At 1 month, all CMV infections were adequately treated but two grafts were lost due to unrelenting rejection; additionally, there were two late infectious deaths.

CONCLUSIONS

DHPG is an antiviral agent that can be used effectively to treat CMV in pediatric transplant recipients. Dosages and side effects in children seem to be similar to those of adults. The integration of DHPG with other pharmacologic agents [e.g., foscarinet [11,13]] and humoral agents (23,24) or its possible use as a prophylactic agent (25) remain to be clearly defined.

A pediatric transplant recipient suspected of having symptomatic CMV infection should initially have an aggressive diagnostic evaluation including serology, cultures, X-ray studies, and a careful retinal examination. Transplant biopsy, bronchoscopy, and endoscopy should be performed promptly as clinically indicated.

On the basis of our experience, if tissue-invasive CMV infection is recognized, we would recommend: (1) prompt initiation of i.v. DHPG treatment for at least 14 days (or longer as indicated), adjusted for renal function, followed by 12 wk of oral acyclovir; (2) modulation of azathioprine and DHPG dosage to minimize bone marrow toxicity; (3) careful observation with multiple cultures to identify secondary infections; (4) transplant kidney biopsy for unexplained increases in serum creatinine; (5) cautious treatment of allograft rejection as long as CMV infection is improving.

The availability of DHPG is a promising beginning to the effective treatment of serious CMV infection. The appropriate use of DHPG should significantly improve patient and allograft survival after solid organ transplantation in children.

REFERENCES