Successful Treatment of Enterovirus Infection with the Use of Pleconaril in 2 Infants with Severe Combined Immunodeficiency

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Two patients with severe combined immunodeficiency and enterovirus infections were successfully treated with pleconaril. There were no adverse affects.

Patients with certain primary immunodeficiency diseases are prone to severe and chronic enteroviral infections [1]. The prognosis has generally been poor; most patients die despite having received high-dose iv and intrathecal gammaglobulin therapy [2]. Even patients with severe combined immunodeficiency (SCID) who have received a bone marrow transplant (BMT) may be unable to recover from enterovirus infections [3]. We describe 2 infants with SCID in whom enteroviral infections were successfully treated by use of the new antipicornaviral agent pleconaril.

An 11-month-old female infant had SCID diagnosed on the basis of a history of failure to thrive, recurrent infections, diarrhea, erythroderma, hepatosplenomegaly, lymphopenia, eosinophilia, and profoundly decreased lymphoproliferation to mitogens. By use of PCR, enterovirus RNA was detected in stool samples 3 times within 5 weeks (figure 1A, lane 1). Results of cultures of stool samples were negative for enterovirus and other pathogens. The patient received an allogeneic BMT at the age of 12 months, and she then developed hemolytic anemia and an acute cerebral vascular event; the latter was attributed to IgM-mediated agglutination.

During a subsequent neurologic evaluation, enterovirus RNA was detected in the CSF by use of PCR (figure 1A, lane 2); the results of the culture of the CSF were negative for enterovirus and other pathogens. The patient was treated with pleconaril, 3-[4-[3-(3-methyl-5-isoxazolyl)propoxy]-3,5-xylyl]-5-trifluoromethyl]-1,2,4-oxadiazole (5mg/kg t.i.d.; ViroPharma) for 7 days without having adverse reactions. Her diarrhea alleviated significantly, with stool output decreasing from 9 to 3 stools per day. Complete blood count, serum electrolytes, liver function tests and urinalysis remained unchanged. PCR results of stool (figure 1B, lane 1) and CSF (figure 1C, lane 1) samples were negative for enterovirus, 3 and 7 days after completion of treatment with pleconaril, respectively. She had no recurrence of gastrointestinal symptoms. The patient died 3 weeks later because of severe hemolysis and hemagglutination, both of which were unrelated to pleconaril. An autopsy was not performed.

A 9-month-old female infant had Omenn syndrome diagnosed on the basis of a history of failure to thrive, recurrent infections, diarrhea, erythroderma, hepatosplenomegaly, lymphopenia, eosinophilia, and profoundly decreased lymphoproliferation to mitogens. She had normal levels of IgG, IgA, and IgM, and a moderately elevated IgE level; however she produced no antibody in response to diphtheria and tetanus immunizations, and she had no detectable B cells. She continued to have an increased susceptibility to infection, including recurrent respiratory syncytial virus pneumonia and an episode of Pneumocystis carinii pneumonia. Enterovirus RNA was detected twice in stool samples by use of PCR (figure 1D, lane 2); the results of cultures of stool samples were negative for enterovirus and other pathogens. She was treated with pleconaril for 7 days without having adverse reactions. The PCR results for stool samples obtained 3 and 21 days after completion of pleconaril treatment were negative for enterovirus (figure 1E, lane 1). She then received a haploidentical BMT from her father. PCR tests on her stool samples were negative for enterovirus 2 months and 8 months after pleconaril treatment. She has had slow immunologic reconstitution after BMT, but has gained weight and has had no recurrence of diarrhea.

Neutralizing antibody appears to play a significant role in the host’s defense against enterovirus. Patients with severe antibody deficiency, such as X-linked agammaglobulinemia, SCID, and common variable immunodeficiency, have an unusual propensity to develop severe and chronic enteroviral infections of the CNS and gastrointestinal tract. Despite receiving treatment with high-dose iv immunoglobulin, most immu-
nodeficient patients with chronic systemic enteroviral infection die [1, 2]. Even some patients who survive have persistent virus, as evidenced by use of PCR, despite receiving ongoing antibody replacement therapy [1, 2, 4].

We describe 2 patients with SCID in whom enterovirus was eradicated by use of pleconaril. The diagnosis of enterovirus infection was based on clinical symptoms of diarrhea and detection of enteroviral RNA in stool and CSF by use of PCR.

Although isolation of enteroviruses in tissue cultures remains the “gold standard” for diagnosis, its usefulness in clinical practice is limited because this technique is labor intensive and time consuming, and because it requires a high level of expertise [1]. In addition, as many as 25%–35% of enterovirus serotypes (especially Coxsackie virus group A) do not grow in tissue culture. Although this yield may be improved by suckling mouse inoculation, this technique is not widely available. PCR testing for enterovirus has been found to be consistently more sensitive than culture and is almost 100% specific [5].

Pleconaril is an orally active, antipicornaviral agent with excellent penetration into the CNS, liver, and nasal epithelium [6]. It selectively inhibits picornavirus replication, and it prevents attachment and uncoating [7]. It has been shown to be beneficial in the treatment of enteroviral meningitis in immunocompetent children [8] and adults [9], and in the treatment of picornavirus respiratory infection.

We report the successful use of pleconaril to treat enterovirus infection in infants with SCID. This experience indicates that pleconaril may be a life-saving antiviral agent for immunodeficient hosts.

References