Clinical and laboratory observations

Azithromycin for treatment of severe Cryptosporidium diarrhea in two children with cancer

Sergio L. Vargas, MD, Jerry L. Shenep, MD, Patricia M. Flynn, MD, Ching-Hon Pui, MD, Victor M. Santana, MD, and Walter T. Hughes, MD

From the Departments of Infectious Diseases and Hematology-Oncology, St. Jude Children’s Research Hospital, and the Department of Pediatrics, University of Tennessee, Memphis

Two children with cancer received azithromycin for Cryptosporidium-associated diarrhea that was unresponsive to supportive care. One child had cholera-form diarrhea requiring daily fluid replacement of up to 65% of his total body weight; the other had protracted diarrhea and wasting. In both cases, administration of azithromycin was followed by prompt clinical improvement. (J Pediatr 1993;123:154-6)

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Reprint requests: Sergio L. Vargas, MD, Department of Infectious Diseases, St. Jude Children’s Research Hospital, 332 North Lauderdale St., Memphis, TN 38105-2794.

Best known as a pathogen in patients with the acquired immunodeficiency syndrome, Cryptosporidium species can also cause life-threatening illness in other immunocompromised hosts, including patients with cancer who are receiving chemotherapy. Serious Cryptosporidium infection is usually manifested as chronic debilitating diarrhea. Although several therapeutic approaches have been investigated, none has proved effective.

Drugs investigated as possible therapies for Cryptosporidium infection include diloxanide furoate, furazol-
done, quinine plus clindamycin, interleukin-2, amprolium, various macrolide antibiotics, and intravenous preparations of immune globulin administered orally.²,⁴ Perhaps the most promising of these agents are the macrolide antibiotics. Of the five macrolides tested to date at St. Jude's Children's Research Hospital—clarithromycin, spiramycin, erythromycin, oleandomycin, and azithromycin—Rehg²,⁶ found azithromycin to be the most effective in decreasing the parasitic load in the ileum of immunosuppressed experimental animals infected with Cryptosporidium.

We recently treated two young children with cancer who had severe Cryptosporidium-associated diarrhea that was unresponsive to aggressive supportive care. We selected oral azithromycin for use in this empiric trial because of its safety, availability, and promising results in experimental animals.

CASE REPORTS

Patient 1. A 14-month-old boy with newly diagnosed epithelioid sarcoma of the mediastinum had diarrhea 1 day after completing initial chemotherapy (a 4-day course of ifosfamide, carboplatin, and etoposide) and 8 days after initiation of antibiotic treatment for a Staphylococcus aureus infection at the incision site for biopsy of his mediastinal tumor. Cryptosporidium oocysts were identified by modified acid-fast stain of stool specimens; no other enteric pathogens were found in bacterial or fungal cultures and results of tests for rotavirus and Clostridium difficile toxin were negative. The patient's diarrhea progressively worsened during the ensuing 7 days; fluid requirements increased to a daily volume of 650 ml/kg, necessitating transfer to the intensive care unit. Azithromycin (Zithromax capsules), was administered at a dose of 500 mg (40 mg/kg) orally once daily. A Foley catheter was used to facilitate monitoring of urine output and stool loss. The volume of fluid lost in the feces decreased steadily, and diarrhea resolved during the first 10 days of azithromycin treatment (Figure). The patient was discharged from the hospital and continued treatment with azithromycin as an outpatient. Stool examinations revealed Cryptosporidium organisms on several occasions during the next 2 weeks, although there was no diarrhea. Four days after completing a 3-week course of azithromycin, severe diarrhea and dehydration again developed. Stool examinations revealed Cryptosporidium as the sole pathogen. Diarrhea resolved promptly again after resumption of azithromycin therapy. Four consecutive stool examinations done after an additional 2 weeks of azithromycin treatment found no Cryptosporidium organisms. Azithromycin (250 mg twice daily) was continued until the patient completed the same phase of his chemotherapy regimen. No further episodes of diarrhea occurred, and no adverse effects were associated with azithromycin therapy.

Patient 2. A 3-year-old boy with disseminated neuroblastoma was admitted to the hospital with a 1-week history of diarrhea that had begun 33 days after an autologous bone marrow transplant with a preparative regimen consisting of etoposide and carboplatin. The patient had not recently been treated with antibiotics, and his bone marrow function had fully recovered. Both C. difficile toxin and Cryptosporidium organisms were detected in his stool. The C. difficile toxin cleared from the stool after a 7-day oral course of vancomycin, but diarrhea progressively worsened, resulting in a loss of almost 15% of his body weight. He did not respond to intravenous fluid therapy and became listless. Because of Cryptosporidium organisms in the stool and the patient's progressive wasting, oral azithromycin therapy was initiated empirically at a daily dose of 500 mg (40 mg/kg). Listlessness and diarrhea improved within 4 days, and the illness resolved during a 10-day period. The dosage of azithromycin was then reduced to 250 mg until a 21-day course was completed. Stool samples were not reexamined.

DISCUSSION

The degree to which treatment with azithromycin hastened the recovery of these two patients is not certain. Anecdotal reports can be misleading; spiramycin was once thought to be effective for cryptosporidiosis on the basis of anecdotal reports, but this impression was not confirmed in a controlled clinical trial.² Nevertheless, the course of infection in these two patients does suggest a beneficial effect of azithromycin, especially in the first patient, who apparently responded to azithromycin, became worse when it was withdrawn, and again improved when the therapy was resumed.
The optimal dosage of azithromycin in children is unknown. The dose that we selected was empiric and may have been unnecessarily high, but there are few data to guide treatment in young children. In addition, the azithromycin preparation that we used contains lactose, which could exacerbate diarrhea in patients with primary or acquired lactose intolerance. Although treatment caused no overt adverse effects in these two patients, use of a preparation that does not contain lactose would be advisable.

The apparent clinical responses to azithromycin observed in these two patients, characterized by rapid normalization of stool output and weight recovery, are concordant with the results of animal experiments and indicate that azithromycin may have a role in the treatment of human Cryptosporidium-associated diarrhea. Further assessment of the therapeutic effect of azithromycin in cryptosporidiosis must await the results of a randomized, controlled clinical trial. If the drug should be proved effective, our experience indicates that young children with Cryptosporidium-associated diarrhea will tolerate azithromycin well.

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REFERENCES