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CASE REPORT: RECTAL ADMINSTRATION OF IVERMECTIN TO A PATIENT WITH *STRONGYLOIDES* HYPERINFECTION SYNDROME

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Abstract. *Strongyloides* hyperinfection syndrome may be complicated by paralytic ileus that interferes with the absorption of oral anti-helminthics. We report on the administration of ivermectin as a rectal enema preparation to a renal transplant recipient with *Strongyloides* hyperinfection syndrome and progressive ileus. Attempts at treatment using nasogastric albendazole and ivermectin were unsuccessful despite clamping the nasogastric tube after drug administration. Ivermectin tablets were ground to a powder, resuspended in a commercially available suspending agent, and administered per rectum. The suspending agent was chosen for its near-physiologic osmolality to allow longer retention, in contrast to many enema preparations that have a laxative effect. The patient improved markedly within 72 hours of initiation of the therapy per rectum and recovered fully. Ivermectin administered as an enema may be beneficial in patients with severe strongyloidiasis who are unable to absorb or tolerate oral therapy.

INTRODUCTION

Strongyloides stercoralis may cause few symptoms in the healthy individual, but can produce a life-threatening illness in immunosuppressed hosts characterized by extensive dissemination of larvae to multiple organs, which is referred to as the hyperinfection syndrome.[1,2] Complications such as paralytic ileus, malabsorption, gastrointestinal hemorrhage, gram-negative bacteremia, meningitis, and severe pneumonia with adult respiratory distress syndrome can occur and mortality may be up to 77%.[1–7] Treatment options for strongyloidiasis are limited to oral formulations, with ivermectin, albendazole, and thiabendazole being the drugs most commonly used.[8,9] No parenteral formulations exist, and in patients unable to tolerate oral therapy, either due to severity of illness or the presence of gastrointestinal complications, there is little data on alternative therapies. Here we report on the successful administration of ivermectin prepared as a rectal enema that was given to a patient with *Strongyloides* hyperinfection and paralytic ileus.

CASE REPORT

A 55-year-old woman was admitted to the hospital on December 29, 2000 with a 10-day history of fever, abdominal pain and distension, nausea, vomiting, shortness of breath, and cough. On October 4, 2000 she underwent cadaveric renal transplantation for renal failure due to diabetes mellitus and hypertension. She was born and raised in rural North Carolina, and had been living in Washington, DC since the age of 18. She denied any travel. Her immunosuppressive therapy consisted of sirolimus, tacrolimus, and prednisone (20 mg a day). On physical examination, there were bilateral lung crackles, and the patient had a distended, diffusely tender abdomen with hypoactive bowel sounds. The white cell count was 15,500 cells/μL, with a normal differential count. Computed tomography (CT) of the chest and abdomen was notable for bilateral pulmonary interstitial infiltrates, diffuse small bowel wall edema, and dilated loops of duodenum and proximal jejunum. A nasogastric tube was placed for decompression. Endoscopic small bowel biopsies revealed numerous eggs and filariform larvae of *S. stercoralis* in the jejunal mucosa. Examination of nasogastric aspirate fluid, stool, and bronchoalveolar lavage (BAL) fluid also demonstrated many *Strongyloides* filariform larvae (adult females were seen in the nasogastric fluid as well), consistent with *Strongyloides* hyperinfection syndrome.

The patient was initially treated with albendazole (400 mg per day started on January 3, 2001) via the nasogastric tube. Sirolimus and tacrolimus were discontinued. Prednisone was continued throughout the illness, and high doses were temporarily administered on January 10, 2001 for presumed acute graft rejection. The serum creatinine level promptly returned to normal and a graft biopsy was not performed. Piperacillin/tazobactam was also given to treat *Klebsiella pneumoniae* that were isolated from the BAL cultures. When on January 8, 2001, after five days of albendazole therapy, the patient still had a paralytic ileus and nasogastric aspirates still showed many *Strongyloides* larvae, oral ivermectin (200 μg/kg/day, i.e., 15 mg a day for a body weight of 75 kg) was added via the nasogastric tube. However, despite clamping the nasogastric tube for several hours after administration of the drugs, the patient's condition continued to worsen, larvae were still seen in the nasogastric aspirate, and serial abdominal CTs revealed progressive, high-grade, small bowel dilatation. These findings suggested that she was not absorbing or responding to treatment. Exploratory laparotomy on January 7, 2001 showed an edematous and erythematous small bowel. A bezoar, consisting of barium and fecal matter, was removed via small bowel enterotomy. Attempts to obtain a parenteral form of either albendazole or ivermectin from the manufacturers were unsuccessful. Therefore, an ivermectin retention enema was initiated on January 11, 2001 (200 μg/kg/day, 15 mg a day) after treatment with oral albendazole and oral ivermectin for seven and three days, respectively. The enema was prepared by crushing ivermectin tablets and mixing the drug in an oral suspending agent (Ora-Plus®; Paddock Laboratories, Minneapolis, MN) The total volume of the enema was 30 mL and this was given per rectum daily for seven days. Albendazole and ivermectin via the nasogastric tube were continued concurrently.

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The ivermectin enemas were well tolerated, diarrhea was not induced, and the patient improved markedly within approximately 72 hours. Her nausea, abdominal pain, and shortness of breath resolved, and oxygen requirements as well as the amounts of larvae in nasogastric aspirate samples decreased. On January 19, 2001, the nasogastric tube was removed, no larvae were seen on examination of stool specimens, and treatment with sirolimus and tacrolimus was reinitiated. Total anti-helminthic treatment consisted of 14 days of oral albendazole, 14 days of oral ivermectin, and seven days of the ivermectin retention enema. An additional five-day course of oral ivermectin therapy was administered two weeks after discharge from the hospital. The patient had an uneventful subsequent course. Stool studies, done periodically and in the absence of symptoms, have been negative for *S. stercoralis*. At the most recent follow-up visit 19 months later (July 2002), the patient had no gastrointestinal symptoms, and was receiving tacrolimus (4 mg twice a day), mycophenolate mofetil (1 gram twice a day), and prednisone (5 mg a day).

Further investigations showed negative serologic test results for human immunodeficiency virus and human T cell lymphotropic virus-1. No eosinophilia or clinical syndrome compatible with strongyloidiasis was documented prior to renal transplantation, which is consistent with published experience.[4,10] The patient had not traveled to an area highly endemic for *S. stercoralis*, suggesting the acquisition of *S. stercoralis* in either North Carolina during childhood or in the District of Columbia.[11] An alternative possibility is the transmission of *S. stercoralis* via the transplanted kidney graft.[12,13] This is unlikely in this patient since the recipient of the other kidney from the same donor, who received his transplant and follow-up care until today at our institution, remains well. His immunosuppressive regimen includes tacrolimus, mycophenolate mofetil, and prednisone. He has not been treated with cyclosporine A, which, in contrast to tacrolimus,[14] may have anti-*Strongyloides* activity.[13,15]

DISCUSSION

In this study, we report the feasibility of administering ivermectin as a rectal retention enema in a patient with *Strongyloides* hyperinfection syndrome who failed to respond to conventional oral therapies due to the presence of paralytic ileus. Ivermectin was chosen because of its potentially increased efficacy compared with other anti-helminthics. The suspending agent was chosen because of its osmolality of approximately 230 mosm/kg and immediate availability. We reasoned that such a near-physiologic osmolarity would allow the enema to be retained longer and the ivermectin to be better absorbed. Many traditional enema preparations have higher osmolarities and are designed to have a laxative effect. To the best of our knowledge, our case is the first to describe the administration of both ivermectin and this oral suspending agent by enema.

Current therapeutic options for *Strongyloides* hyperinfection consist of oral agents only,[8,9,16] but in severe cases with ileus oral drugs may not be absorbed. Hexylresorcinol and thiabendazole enemas have been historically used for colonic trichuriasis,[17,18] and there are three case reports on the rectal administration of thiabendazole in patients with *Strongyloides* hyperinfection syndrome.[19–21] The first patient[19] was successfully treated with thiabendazole rectally for 13 days, supplemented with nasogastric thiabendazole. *Strongyloides* larvae and eggs were seen in the sputum during the first six days of treatment. The second patient[20] received rectal thiabendazole for 14 days. Larvae were no longer seen in the ileostomy drainage within a week, and he recovered. The third patient[21] was treated with a combination of rectal thiabendazole and two doses of oral ivermectin. The parasite burden in the sputum decreased significantly by day 15, but he died of progressive respiratory failure.

In recent years, oral ivermectin has been increasingly used for *Strongyloides* infection,[3,8,9] but it is clear that its efficacy is lower in patients with higher infectious burdens.[22] With regard to non-oral administration, a letter describes the subcutaneous administration of an unspecified preparation of ivermectin to 10 patients with severe spastic paraparesis who did not have any known parasitic infection, but no further reports on this neurologic use of ivermectin have emerged since the letter was published in 1994.[23] Another letter describes the successful subcutaneous administration of multiple doses of a veterinary preparation of ivermectin to a patient with *Strongyloides* hyperinfection syndrome.[24] The infection was reportedly controlled, but the patient died of his underlying lymphoma. The authors also reported a second patient who was treated with two subcutaneous doses of ivermectin, but the clinical outcome was not described.[23] It should be noted that the veterinary formulation of ivermectin has not been approved for human use and, in our experience, can be difficult to acquire for this purpose.

Improvement of our patient's gastrointestinal and respiratory status, and clearance of *Strongyloides* larvae from nasogastric aspirate specimens followed the initiation of the ivermectin enemas by approximately three days. However, definitive conclusions about the efficacy of rectal treatment of patients with *Strongyloides* hyperinfection cannot be drawn from our case or from the reports in the literature. Clinical improvement can be slow in transplant recipients with *Strongyloides* hyperinfection treated with oral antihelminthics, despite the tapering of immunosuppression.[4,10] In addition, oral ivermectin and albendazole were given to our patient concurrently with the enemas, in view of the potential for at least partial benefit from oral treatment. Measurement of serum ivermectin levels are not available in the United States either through commercial laboratories or through the manufacturer.

Nonetheless, each of these case reports highlights the desirability of effective non-oral treatments for patients with *Strongyloides* hyperinfection syndrome. There is a need for studies to evaluate the pharmacokinetics and the efficacy of rectal ivermectin and when suspended in different pharmaceutical vehicles. Our method of giving ivermectin by enema is easy to formulate and administer, was well tolerated by the patient, and may generate interest in the systematic evaluation of rectal treatments for patients with severe strongyloidiasis who are unable to absorb or tolerate oral therapy because of gastrointestinal complications.

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