Treatment of Human Disseminated Strongyloidiasis with a Parenteral Veterinary Formulation of Ivermectin

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There are no parenteral antihelminthic drugs licensed for use in humans. We report the successful treatment of disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin in a patient presenting with severe malabsorption and paralytic ileus. To our knowledge, ivermectin levels are reported for the first time in this situation.

**Strongyloides stercoralis** infection affects 50–100 million people worldwide [1]. Initially acquired by percutaneous penetration of filariform larvae present in infested soil, this nematode perpetuates itself through autoinfection cycles [2]. It usually causes no or minor gastrointestinal and respiratory symptoms in travelers to and residents of areas where it is endemic [3], but on occasion it is associated with multimorgan dissemination and a high mortality in patients infected with human T cell lymphotropic virus type 1 (HTLV1) and in patients who receive corticosteroids, chemotherapy, or transplants [2, 4–6].

Oral administration of ivermectin is the preferred treatment for strongyloidiasis in immunocompetent [7] and immunocompromised humans [2, 8]. However, patients with severe strongyloidiasis frequently present with paralytic ileus [2, 5, 6, 9, 10] that precludes oral administration of ivermectin when it is urgently needed. No parenteral antihelminthic drugs are licensed for use in humans, but parenteral ivermectin is commonly used in veterinary medicine. We describe a patient who had disseminated strongyloidiasis that was successfully treated with a parenteral veterinary formulation of ivermectin.

**Case report.** A 54-year-old Jamaican man presented with back pain and fatigue in February 2004. He had multiple myeloma diagnosed in 1998 and received cyclophosphamide, melphalan, prednisone, and pamidronate therapy, but he did not seek follow-up care for a year. The patient also had HTLV1-associated myelopathy. He visited Jamaica frequently. On 10 March 2004, the patient presented with new vertebral compression fractures and an IgG level of 8.6 g/dL, and he began a treatment regimen of doxorubicin, weekly dexamethasone, and zolendronic acid.

The patient was hospitalized on 27 April 2004 with persistent vomiting and occasional diarrhea. The findings of an abdominal CT were interpreted as early high-grade small-bowel obstruction. No mechanical obstruction was apparent from laparotomy. After the laparotomy, the patient continued to experience vomiting and occasional loose stools. A fat-pad biopsy specimen tested negative for amyloidosis. Examination for ova and parasites was declined because the patient had been hospitalized for >5 days when stool specimens were submitted. His condition improved with metoclopramide treatment, and he was discharged on 7 May 2004.

The patient was readmitted to the hospital on 9 June 2004 with persistent vomiting, abdominal pain, and diarrhea. On examination, he was afebrile; he had temporal wasting, oral thrush, a distended abdomen with bowel sounds present, paraparesis with no sensory level, and dependent edema. Radiological examination of the abdomen demonstrated a distended, fluid-filled stomach. Relevant laboratory findings were a sodium level of 127 mmol/L, an albumin level of <1.5 g/dL, and a leukocyte count of 7830 cells/μL, with 45% polymorphonuclears, 40% bands, and 0% eosinophils.

An upper gastrointestinal endoscopy, performed on 11 June 2004, demonstrated moderate esophagitis and a friable gastroduodenal mucosa with a thin layer of exudate, after abundant gastric contents were aspirated. Subsequent nasogastric outputs were 1000–2000 mL/day. Duodenal biopsy and stool specimens, submitted concurrently, were diagnostic of *S. stercoralis* infection (figure 1). Unconcentrated stool specimens demonstrated abundant filariform larvae and many female adults and eggs per low-power field.

The patient received ivermectin (200 μg/kg) on 14 June 2004 via nasogastric tube. This was followed by ivermectin (400 μg/kg) in 40% ethanol solution, given to the patient on 15 June and 16 June 2004, to maximize absorption of the drug [11]. The nasogastric tube was clamped for 2 h after each dose. He received cefotaxime preemptively and fluconazole for *Candida*
esophagitis, which was proven by biopsy. Dexamethasone therapy was discontinued.

Findings from chest radiographs performed on 14 June and 17 June 2004 demonstrated progressive bilateral interstitial infiltrates, which were new since the time of admission. The patient required increasing oxygen supplementation. Unconcentrated induced sputum samples obtained on 15 June, 16 June, and 17 June 2004 demonstrated many viable *S. stercoralis* filariform larvae. Urinary sediment showed moderate filariform larvae. Unconcentrated stool specimens continued to demonstrate abundant viable rhabditiform larvae, eggs, and adults.

**Methods.** Given the worsening respiratory status, clinical malabsorption, and persistent ileus despite oral administration of ivermectin treatment, we contacted the Human Research Committee at our institution and the US Food and Drug Administration for emergency administration of parenteral ivermectin (Ivomec 1% injection; Merial Limited; New Animal Drug Application [NADA] 128-409). Permission was granted under the Investigational New Drug (IND) 69,582 for the subcutaneous administration of a 200-μg/kg dose. To minimize the risk of drug-related toxicity, additional doses were permitted if administered at least 48 h apart in response to persistent viable filariform larvae in induced sputum samples and non-resolution of the ileus, independent of the findings for stool samples. The patient gave written informed consent to proceed with the treatment and to measure plasma ivermectin levels.

Daily wet mounts of stool and sputum were used initially for monitoring. When the parasite burden decreased, stool specimens were concentrated using the formalin-ethyl-acetate sedimentation technique. Sputum sample pellets were examined after digestion with dithiothreitol, which did not compromise the parasite’s viability.

Sequential plasma samples were obtained and stored at −80°C until processing. Ivermectin was analyzed by high-performance liquid chromatography by means of a modified assay [12].

**Results and clinical course.** The patient received ivermectin solution (200 μg/kg) administered subcutaneously on 17 June, 19 June, and 22 June 2004 in both upper arms because of significant dependent edema. The drug regimen, ivermectin levels, and antiparasitic effects are summarized in figure 2.

The patient experienced no local or systemic reactions. He received vancomycin therapy for catheter-related methicillin-resistant *Staphylococcus aureus* bacteremia and received acyclovir therapy for a herpes simplex virus type 2 outbreak. He experienced prolonged intermittent fevers without other identifiable etiology. Investigations included blood cultures, tests for cytomegalovirus and other viruses, CT of head and ab-

**Figure 1.** Photomicrograph of a histological section from a biopsy sample of the patient’s small bowel demonstrating adult *Strongyloides stercoralis* (black arrows) resting within intraepithelial spaces and showing several larval forms of the worm (arrowheads) in the lumen of the small bowel mucosa, with minimal acute inflammation. The plane of section demonstrates the segmented folds of the worm’s surface (white arrow) (hematoxylin and eosin stain; original magnification, ×400).
Figure 2. Ivermectin levels and *Strongyloides stercoralis* burden in relation to method of administration. The upper 2 panels are a semiquantitative representation of the parasite burden in sputum and stool samples. The relative abundance of rhabditiform and filariform larvae, adults, and eggs were taken into account for the measurement. Larvae were considered nonviable if they were completely immobile or degenerating. The ivermectin level before the initial subcutaneous administration and after cumulative doses of oral ivermectin (total dosage, 1000 μg/kg over 3 days) was only 1.1 ng/mL. The ivermectin levels after the first subcutaneous dose were between 2.0 and 4.2 ng/mL. The level at 1 week after the third subcutaneous dose was 7.9 ng/mL, with evidence of additional metabolite accumulation. Individual doses are represented by arrows; additional subcutaneous doses were administered in response to the presence of viable filariform larvae in sputum samples, independent of findings for stool samples.

domen, and gallium scan. A pulmonary embolism protocol CT revealed deep venous thrombosis involving the right femoral veins, for which the patient received enoxaparin therapy.

The albumin level remained at <1.5 g/dL, despite the resolution of diarrhea and the patient’s increased appetite. The patient developed thrombocytopenia prior to receiving ivermectin therapy, with a platelet count nadir of 47,000 platelets/μL on 21 June 2004. The cortisol level was 32 μg/dL on 15 June 2004. His highest absolute eosinophil count was 210 cells/μL (eosinophil percentage, 5.7%) on 30 June 2004. The findings of an *S. stercoralis* EIA were positive [13].

His respiratory function improved gradually. The ileus was resolved by 24 June 2004, and the diarrhea was resolved by 26 June 2004. No parasites were detected in concentrated samples of stool, urine, or sputum after 29 June 2004. He received an additional 200 μg/kg of oral ivermectin on 29 June 2004. A dose of doxorubicin, but no dexamethasone, was administered prior to discharge from the hospital on 16 July 2004.

The patient returned on 23 July 2004 with headache, fever (body temperature, 38.1°C), and lethargy. No lumbar puncture was performed at arrival because of anticoagulation therapy. The patient received multiple antibiotics empirically. A fluoroscopy-guided CSF sample obtained on 24 July 2004 demonstrated 2250 erythrocytes/μL; 675 leukocytes/μL, with a differential of 85% neutrophils and 1% eosinophils; a glucose level of 31 mg/dL; and a protein level of 321 mg/dL. No pathogens or larvae were detected. The patient improved during the days that followed. He completed 21 days of ceftriaxone therapy. An additional 2-week course of daily oral ivermectin was administered without adverse effects. The patient transferred to a rehabilitation facility on 30 July 2004 and returned home a month later. On the last day of administration of oral treatment, the ivermectin level was 20.3 ng/mL and the albumin level was 2.4 g/dL.

The results of monthly stool samples have remained negative. The patient has received 2-day courses of oral ivermectin during each cycle of chemotherapy [2].

**Discussion.** For patients with disseminated strongyloidiasis who are unable to ingest or absorb oral medication, there is no parenteral antihelminthic therapy licensed for human use. Tarr et al. [14] described a patient with ileus whose condition was successfully treated with simultaneous oral and rectal administration of ivermectin and oral administration of albendazole. Rectal drug administration was unlikely to be effective in our patient, given the concurrent diarrhea and abundant *S. stercoralis* adults and eggs seen in stool specimens, which suggested significant colonic involvement [2, 5]. Chiodini et al. [15] used subcutaneously administered ivermectin for 2 pa-
tients; the infection was controlled in 1 patient, and strongyloidiasis was not confirmed in the other patient, but no details were provided.

The administration of parenteral ivermectin licensed for veterinary use—and available in the United States and other countries—was safe and effective in treating disseminated strongyloidiasis in our patient. For the first time in this situation, ivermectin—was safe and effective in treating disseminated strongyloidiasis in humans [16], but 2.4 ng/mL of ivermectin was required to paralyze 50% of *Strongyloides ratti* and *Strongyloides venezuelensis* filariform larvae in vitro [18]. Persistent fevers after treatment may have been in part a consequence of the host response to dying disseminated larvae after discontinuation of corticosteroid therapy. We did not prove relapse or CNS dissemination at readmission, but additional ivermectin was prescribed, given the patient’s multiple risk factors for relapse [2].

The best strategy for preventing *S. stercoralis* hyperinfection and related death is to identify and treat chronically infected patients prior to initiation of immunosuppressive therapy [1, 2]. Specific antibody detection [3, 13] and serial stool sampling with special methods [2] are currently the best diagnostic strategies. The importance of preventive measures, including wearing appropriate footwear, should be communicated to patients living in or traveling to areas where *S. stercoralis* is endemic. Our patient likely acquired the infection recently, because he had previously tolerated steroid-containing chemotherapy despite having chronic HTLV1 infection. A search for this parasite is warranted for immunocompromised patients who present with diarrhea, respiratory syndromes, unexplained bacteremia or meningitis with gastrointestinal flora, malabsorption, or ileus [2, 3, 5].

In this case, the use of subcutaneous ivermectin and the preemptive use of antimicrobials [19] prevented further complications associated with disseminated strongyloidiasis and were lifesaving. Studies with parenteral ivermectin for licensing of use in humans are warranted. Meanwhile, clinicians faced with a patient who has severe strongyloidiasis and concurrent ileus or significant malabsorption should consider early treatment with subcutaneous ivermectin.

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**References**