Case Report: Failure of Subcutaneous Ivermectin in Treating Strongyloides Hyperinfection

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Abstract. A man with Escherichia coli meningitis and bacteremia, while on dexamethasone, developed Strongyloides hyperinfection syndrome and died despite salvage therapy with subcutaneous ivermectin. We report the first documented total and free levels of subcutaneous ivermectin used for therapy.

INTRODUCTION

Strongyloides stercoralis is an intestinal nematode, endemic to sub-tropical and tropical areas that can complete its life cycle within a human host.1 Immigrants to Canada from Southeast Asia have high seroprevalence for strongyloidiasis.2 Although usually benign, in immunocompromised hosts an accelerated cycle of autoinfection (hyperinfection) produces increased larval burden and migration through tissues, which can cause gram negative septic shock and multiorgan failure.3 Current treatment options are limited. Regimens are extrapolated from data obtained from treatment of chronic strongyloidiasis; however, many patients with disseminated disease have complications that preclude using oral drugs. There have been six published cases describing use of the parenteral form of ivermectin for treating hyperinfection.4–9

We describe the clinical course of a hypoalbuminemic patient with Strongyloides hyperinfection who was treated with oral followed by subcutaneous ivermectin. This is the first report of total and free ivermectin levels in a patient. This case provides insight into the binding and pharmacokinetics of ivermectin, and underscores the difficulty in treating this serious infection.

CASE REPORT

A 67-year-old Laotian immigrant with recurrent craniopharyngioma was treated with stereotactic radiation 6 months before consultation. This was complicated by compressive optic neuropathy requiring treatment with dexamethasone 4 mg q8h. Six weeks after starting corticosteroids he presented to the hospital with headache, nausea, and fever. Physical examination revealed meningeal signs. Complete blood count showed normal white blood cell (WBC) count and normal eosinophils. Cerebrospinal fluid (CSF) analysis revealed 760 × 106/L WBC (81% neutrophil), 1757 mg/L protein, and 0.3 mmol/L glucose. The CSF and blood cultures were positive for Escherichia coli. He was treated initially with ceftriaxone 2 grams IV q6h and ampicillin 2 grams IV q4h. Nine days later, his treatment was changed to oral ciprofloxacin 750 mg q12h for 6 weeks, and he was discharged after 12 days in the hospital.

Within a week of discharge, the patient returned to the hospital complaining of nausea, vomiting, abdominal bloating, and constipation. A computed tomography (CT) scan of the abdomen and pelvis showed diffuse hyperemia, dilation, and vascular engorgement within the proximal and mid-small bowel. An esophagogastroduodenoscopy the next day showed edematous and friable mucosa in the third part of the duodenum. A repeat CT abdomen and pelvis 3 days later showed a small bowel obstruction. Abdominal ultrasound and endoscopic retrograde cholangiopancreatography showed a moderately distended gallbladder with sludge and dilatation of the common bile duct. A completion cholangiogram showed no filling defects. The following day, the patient developed septic shock, which precipitated an exploratory laparotomy. Intraoperatively, an isolated band adhesion was found, however the bowel perforated during attempts to milk the small bowel contents so a small bowel resection with primary anastomosis was performed. Postoperatively, the patient was transferred to the intensive care unit and treated intravenously with hydrocortisone 100 mg q8h, fluconazole 400-mg daily, and imipenem/cilastin 500 mg q6h. Blood cultures and a central venous catheter tip from the same day eventually grew Candida utilis. Total parenteral nutrition was started, and he was rapidly tapered from inotropic and vasopressor support. Albumin concentration during hospitalization never exceeded 15 g/L.

He was extubated 3 days later. Pathology from the bowel resection showed a heavy burden of helminthic larvae in the resected bowel and lymphatics. Nasogastric and tracheal aspirates showed the presence of S. stercoralis larvae. Special access for ivermectin was obtained from Health Canada and ivermectin 12 mg (Stromectol, Merck Frost, Haarlem, The Netherlands) was administered via the nasogastric tube for 2 days. The patient had high gastric residuals so a parenteral veterinary form of ivermectin (Ivomec, Merial Ltd., Duluth, GA) was obtained from a local veterinary hospital. Informed consent was obtained from the patient and Health Canada was also contacted. The patient was given 200 μg/kg of subcutaneous ivermectin daily in the arms. Plasma samples were obtained and stored at −80°C until processing. Ivermectin concentration was analyzed by high-performance liquid chromatography.10 The plasma protein binding of ivermectin was determined by equilibrium dialysis.11 The drug
regimen, plasma total, and free ivermectin levels are summarized in Figure 1.

Sixteen days after admission, the patient was intubated for a decreased level of consciousness. A CT scan of the abdomen revealed free air and fluid in the vicinity of the anastomosis. Laparotomy revealed multiple areas of perforation. These areas were resected and the bowel was reanastomosed. Two days later a second laparotomy was performed with closure of the abdominal cavity, creation of an end loop jejunostomy, and mucous fistula. Postoperatively septic shock and progressive multiorgan failure developed. Tracheal aspirates and peritoneal wound exudates were positive for *Aspergillus fumigatus*. Although larval burden from nasogastric and tracheal aspirates had decreased from >25 organisms/slide to 4 organisms/slide, a nasogastric aspirate taken before he died showed motile larvae by Baermann technique. Comfort care was initiated and he died on the same day. The patient’s family refused a post-mortem examination.

**DISCUSSION**

This case illustrates the complications of Strongyloides hyperinfection and the need for prevention. Hyperinfection is often associated with deficits in type-2 immune response, most commonly following corticosteroid use. It is estimated that 77.5% of immigrants coming to Canada over the 10-year period between 1991 and 2001 were from *Strongyloides* endemic countries. Individuals with risk factors for acquiring *S. stercoralis* should be screened and treated with ivermectin if serology or stools is positive before starting corticosteroid therapy.

Meningitis is a complication of *S. stercoralis* hyperinfection and may occur by direct invasion of the central nervous system by migrating larvae with attached fecal flora or by bacteremia secondary to disrupted bowel integrity. Gram-negative meningitis is rare in adults without previous neurosurgery and *Strongyloides* hyperinfection should be considered in the differential diagnosis.

Management of hyperinfection is very challenging. Our patient was unable to absorb medication administered enterally because of his persistent ileus. There are six case reports using subcutaneous ivermectin as an adjunct or alternative to oral ivermectin and/or albendazole. Because of the hypoalbuminemia and edema in our patient, ivermectin absorption may have been retarded and peak ivermectin concentrations may have not been reached during the sampling period from subcutaneous dosing. Ivermectin protein binding has not been previously reported in patients with disseminated strongyloidiasis. This is of some interest because hypoalbuminemia is common in hyperinfection, and it might be reasonably expected that free drug concentration would be elevated. Ivermectin is highly bound to human serum albumin, and the percent unbound increases with decreasing albumin concentration. We found less than 1% of free ivermectin in this patient. This is a surprising result in face of the albumin status of this patient. However, ivermectin is also highly bound to alpha-1 acid glycoprotein. It is tempting to speculate that because of the systemic inflammation involved with disseminated *Strongyloides*, alpha-1 acid glycoprotein levels are elevated, contributing to the low fraction unbound for ivermectin that was observed in this patient. The high protein binding may have reduced the distribution of ivermectin to tissues and contributed to poor therapeutic outcome.

It is not known what minimally effective ivermectin concentration is required for treating strongyloidiasis in humans. In *vitro* studies using *Strongyloides ratti* and *Strongyloides venezuelensis* filarial larvae have been done to determine concentration of ivermectin required to immobilize 50% of worms. However, there is no known correlation with plasma or tissue levels. In humans with disseminated disease, the tissue levels of ivermectin may be very important to the therapeutic outcome.

Currently, special access for ivermectin is required from Health Canada and may introduce a delay in administering ivermectin. There are many issues regarding ivermectin administration that are unknown. Because free levels were low in our case, a loading dose of subcutaneous ivermectin could be considered. Furthermore, once the enteral route is available, oral dosing in addition to the subcutaneous route might increase efficacy because of enterohepatic circulation.

*Strongyloides* hyperinfection has a high mortality rate and is difficult to manage. Although more studies are needed to understand the role of parenteral ivermectin in hyperinfection, the most important issue is primary prevention of hyperinfection. A critical requirement for the diagnosis is a high
index of suspicion for infection. Because the two most consistent risk factors for hyperinfection are treatment with corticosteroids and infection with HTLV-1, any patient who has lived in an endemic area with these risk factors should be screened by serologic testing and stool examination. If the results are positive, then there is a strong argument to treat empirically with ivermectin given the dire consequences of hyperinfection. The high mortality argues for early and aggressive treatment with combined parenteral and oral ivermectin.

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