PARENTERAL ADMINISTRATION OF IVERMECTIN IN A PATIENT WITH DISSEMINATED STRONGYLOIDIASIS

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Abstract. We report the case of a 23-year-old Caribbean man with disseminated strongyloidiasis (co-infected with human T cell lymphotrophic virus I/II)), severe hypoalbuminemia, and a paralytic ileus. Subcutaneous ivermectin (200 μg/kg) was administered daily for 14 days because of the inability to effectively administer oral albendazole and oral ivermectin. Three hours after the third daily dose of oral ivermectin, the serum ivermectin concentration was only 0.8 ng/mL, but it increased several fold to 5.8 ng/mL 16 hours after the first dose of subcutaneous ivermectin. During the course of subcutaneous treatment, ivermectin clearance was higher than expected (46.0 L/hour, normal = 31.8 L/hour). This is likely the result of severe hypoalbuminemia since ivermectin is highly protein bound. The ability to achieve adequate levels of ivermectin after oral administration in patients with disseminated strongyloidiasis may be impaired, highlighting the need for alternative routes of administration of ivermectin in these patients.

INTRODUCTION

Strongyloides stercoralis infects at least 30 million people worldwide.1 Most individuals infected with intestinal strongyloides are asymptomatic or have minor gastrointestinal symptoms. However, immunosuppressed individuals, particularly those co-infected with human T cell lymphotrophic virus I/II with hematologic malignancies or those receiving corticosteroids, are at high risk for developing disseminated disease with a mortality rate up to 70%. In disseminated disease, there is extensive larval infiltration of the small bowel and migration to many other organs.2 Impaired oral absorption of anthelmintic agents in those with a paralytic ileus and disseminated strongyloidiasis may compromise effective delivery of treatment of this life-threatening condition.3,4 Unfortunately, there are no parenteral formulations of these drugs approved for use in humans and the appropriate dose, pharmacokinetics, and potential toxicity are unknown. There are only two previous case reports of ivermectin administered by other than the oral route (one subcutaneous5 and one rectal5), but neither reported pharmacokinetic data.

We describe the clinical course of a patient with disseminated strongyloidiasis who was treated for two weeks with oral albendazole and a veterinary formulation of subcutaneous ivermectin. To assess the pharmacokinetics and potential for toxicity, ivermectin levels in the serum and cerebrospinal fluid (CSF) were determined.

CASE REPORT

A 23-year-old man from St. Vincent came to our hospital with a two-week history of epigastric pain, weight loss of 15 pounds, nausea, vomiting, and not having passed stools for three days prior to admission. On admission, he was hypotensive, afibrile, and dehydrated, and had severe, generalized abdominal tenderness with guarding. Initial blood tests showed significant leukocytosis (but a normal eosinophil count of 0.2 × 10^9/L [reference range < 0.5 × 10^9/L]), pre-renal azotemia, mildly abnormal liver enzyme levels, and significant hypoalbuminemia (albumin = 7 g/L, reference range = 35–51 g/L). Intravenous fluids and ticarcillin-clavulanate were administered and the patient underwent an emergency laparotomy for a suspected bowel perforation. During surgical exploration, diffuse, severe distension and thickening of the small bowel, enlarged mesenteric lymph nodes, and ascites were found, but there was no evidence of mechanical obstruction or bowel perforation. A lymph node biopsy was performed for diagnostic purposes.

Four days after admission, the lymph node biopsy showed S. stercoralis larvae. Treatment with albendazole (400 mg twice a day) and ivermectin (15 mg [200 μg/kg] once a day) was initiated and administered via a nasogastric tube. Abundant, motile larvae were subsequently observed in nasogastric aspirate fluid and sputa. On the sixth day after admission, 48 hours after starting anthelmintic therapy, the patient became drowsy, hypoxic, hypotensive, and febrile, which necessitated intubation, mechanical ventilation, and vasopressor support. During the next 24 hours, the gastric output was extremely high (the nasogastric tube could not be clamped even for 15 minutes) and the effectiveness of administering albendazole and ivermectin by nasogastric tube was questioned. A veterinary formulation of subcutaneous ivermectin (Ivomec, Merial Canada Inc., Victoriaville, Quebec, Canada) was therefore obtained and administered on the seventh day after admission (Table 1). Albendazole was administered for 13 days though only two previous case reports of ivermectin administered by other than the oral route (one subcutaneous5 and one rectal5), but neither reported pharmacokinetic data.

We describe the clinical course of a patient with disseminated strongyloidiasis who was treated for two weeks with oral albendazole and a veterinary formulation of subcutaneous ivermectin. To assess the pharmacokinetics and potential for toxicity, ivermectin levels in the serum and cerebrospinal fluid (CSF) were determined.

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Ivermectin is metabolized in the liver and the very low concentration of ivermectin (in animals ranges from 1.2 to 4 days). The half-life of ivermectin range for intestinal strongyloides is not known, but at pharmacokinetic data on subcutaneous ivermectin in humans is well known. Fifty to sixty percent of ivermectin administered as a tablet or capsule is absorbed. Ivermectin is detectable in plasma within one hour and reaches peak levels ranging from 20 to 54.4 ng/mL 4–5 hours after a single dose of 200 μg/kg. Ivermectin is metabolized in the liver and its metabolites are excreted primarily in the bile. In some patients, an enterohepatic cycle produces a secondary plasma peak between 6 and 12 hours after dosing. The half-life of the parent drug is 12–56 hours and the half-life of its metabolites is up to three days. The therapeutic plasma ivermectin range for intestinal strongyloides is not known, but at a dose of 200 μg/kg/day for 1–2 days, parasitologic cure rates range from 83% to 97%. Unfortunately, parenterally administered antihelminthics have not been approved for use in humans, and the experience with alternatives to oral administration is limited to one report of rectal thiabendazole, one report of rectal ivermectin, and one report of subcutaneous ivermectin. There are no pharmacokinetic data on subcutaneous ivermectin in humans but the kinetics have been studied extensively in large animals. The time to maximum concentration (Cmax) in large animals ranges from 1.2 to 4 days. Assuming an absorption half-life in humans of approximately one day (extrapolated from animal data) and a relatively short elimination half-life of 12–56 hours, steady state should be reached within

**DISCUSSION**

Disseminated strongyloidiasis is frequently fatal. This may be partly explained by impaired absorption of orally administered antihelmintics. The very low concentration of ivermectin (0.8 ng/mL) achieved in our patient after administration of ivermectin through a nasogastric tube confirms that oral bioavailability is inadequate in patients with an ileus. Conversely, subcutaneous administration produced significantly higher ivermectin levels (11.4–17.2 ng/mL) than oral administration.

The pharmacokinetics of orally administered ivermectin in humans is well known. Fifty to sixty percent of ivermectin administered as a tablet or capsule is absorbed. Ivermectin is detectable in plasma within one hour and reaches peak levels ranging from 20 to 54.4 ng/mL 4–5 hours after a single dose of 200 μg/kg. Ivermectin is metabolized in the liver and its metabolites are excreted primarily in the bile. In some patients, an enterohepatic cycle produces a secondary plasma peak between 6 and 12 hours after dosing. The half-life of the parent drug is 12–56 hours and the half-life of its metabolites is up to three days. The therapeutic plasma ivermectin range for intestinal strongyloides is not known, but at a dose of 200 μg/kg/day for 1–2 days, parasitologic cure rates range from 83% to 97%. Unfortunately, parenterally administered antihelminthics have not been approved for use in humans, and the experience with alternatives to oral administration is limited to one report of rectal thiabendazole, one report of rectal ivermectin, and one report of subcutaneous ivermectin. There are no pharmacokinetic data on subcutaneous ivermectin in humans but the kinetics have been studied extensively in large animals. The time to maximum concentration (Cmax) in large animals ranges from 1.2 to 4 days. Assuming an absorption half-life in humans of approximately one day (extrapolated from animal data) and a relatively short elimination half-life of 12–56 hours, steady state should be reached within

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**Antihelminthic therapy, parasitology, and serum ivermectin concentration**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Day of admission</th>
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<tbody>
<tr>
<td></td>
<td>3</td>
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<tr>
<td>Albendazole (oral)</td>
<td></td>
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<tr>
<td>Ivermectin (oral)</td>
<td></td>
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<tr>
<td>Ivermectin (subcutaneous)</td>
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<tr>
<td>Serum ivermectin (ng/mL)</td>
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<tr>
<td>Larvae</td>
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<tr>
<td>Stool</td>
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<tr>
<td>Nasogastric</td>
<td>3</td>
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<tr>
<td>Sputum</td>
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</tr>
<tr>
<td>Pleural</td>
<td>2</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
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</tbody>
</table>

* 0 = none; 1 = rare; 2 = moderate; 3 = abundant. Shaded areas indicate the days when drugs were administered.
one week of multiple dosing. In this patient (Table 1), the mean steady-state serum ivermectin concentration was approximately 13.6 ng/mL with an estimated clearance of 46.0 L/hour (calculated by dividing the dose rate [15 mg/24 hours] by the steady-state concentration). The estimated ivermectin clearance is higher than expected for a healthy male subject (31.8 L/hour) (Vanapalli S and others, unpublished data) and may explain why the steady-state serum ivermectin levels were lower than those observed after oral dosing (mean Cmax = 87 ng/mL after 7 days of 30 mg given orally every 72 hours in healthy fasting volunteers).6

The elevated clearance of ivermectin in this patient may have been the result of his extremely low albumin level 7 g/L [reference range = 35–51 g/L] shortly after admission, which increased slowly to only 22 g/L over the course of the next three weeks. Hypoalbuminemia is common in disseminated strongyloidiasis and was found in 67% of patients in one series from the Dominican Republic.21 ivermectin is highly bound to human serum albumin22 and the percentage of free drug therefore increases with decreasing albumin level.23 The extent of protein binding in the plasma or tissues also affects the volume of distribution of ivermectin. Individuals with low plasma protein binding will have a greater volume of distribution and lower steady-state concentrations.

The major side effect of ivermectin is neurotoxicity that usually manifests in animals and humans as mydriasis, ataxia, tреморs, and emesis, followed by lethargy, coma, and death.6,7,24–26 Humans can tolerate relatively high doses of ivermectin. In healthy, human volunteers, single doses of up to 2,000 µg/kg, and doses up to 1,091 µg/kg administered three times at 72-hour intervals produced no evidence of toxicity.6 A child who accidentally ingested 6,600–8,600 µg/kg had emesis, mydriasis, and sedation, but eventually recovered.7

The patient in this report had possible clinical signs of ivermectin toxicity (coma and hypersalivation). However, the plasma ivermectin concentrations in this patient were almost 20-fold lower than those that were well tolerated in human safety studies.8 Furthermore, ivermectin was undetectable in the CSF after five doses of subcutaneous ivermectin when the serum level was 12.1 ng/mL. Although ivermectin is well tolerated in healthy adults, approximately 10% of ivermectin-treated (150 µg/kg) patients with onchocerciasis showed adverse reactions that required additional medical treatment.27 In addition, in onchocerciasis patients in Sierra Leone, serum ivermectin levels did not correlate with adverse reactions.17 We therefore cannot rule out the possibility that the coma was due to either ivermectin or its metabolites (whose pharmacodynamic properties are unknown). Two metabolite peaks were noted on all chromatograms analyzed from post-admission days 16–23 in serum specimens, but not in CSF specimens. They were present in significant amounts with peak ratio areas of 0.54–0.85 and 0.24–0.38 ng/mL relative to an irvinemctin of 1 area ratio.

Disseminated strongyloidiasis is a challenging disease with a high mortality rate despite available effective therapy. This case highlights the need for the availability of alternative routes of administration of ivermectin given its poor oral bioavailability in the presence of an ileus. The severe hypoalbuminemia in this patient, which occurs commonly in disseminated strongyloidiasis, also raises the concern that increased clearance of ivermectin will further decrease the ability to achieve adequate levels after oral dosing. It was not completely excluded that this patient had serious CNS toxicity due to parenteral ivermectin. It would therefore be prudent for other clinicians considering using subcutaneous ivermectin in a patient with disseminated strongyloidiasis to carefully monitor signs and symptoms consistent with ivermectin CNS toxicity and to measure ivermectin levels.

Received April 1, 2005. Accepted for publication June 14, 2005.

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REFERENCES


