Case Report: Ivermectin and Albendazole Plasma Concentrations in a Patient with Disseminated Strongyloidiasis on Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy

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Abstract. Disseminated strongyloidiasis is often fatal, despite treatment with oral albendazole and parenteral ivermectin (IVM). Here, we report elevated plasma IVM and albendazole sulfoxide concentrations in the context of extracorporeal membrane oxygenation and continuous renal replacement therapy in a patient with disseminated strongyloidiasis treated with subcutaneous IVM and nasogastric albendazole. Despite elevated drug plasma concentrations, live filariform larvae were detected in endotracheal aspirates after 2 weeks of treatment.

INTRODUCTION

It is estimated that between 30 and 100 million people are infected with *Strongyloides*. People with *Strongyloides* infection are increasingly exposed to immunosuppressive therapy, which is often administered without consideration of the risks for dissemination of the infection. The prognosis of disseminated strongyloidiasis is poor; even with recommended therapy, mortality rates are approximately 60%. No randomized controlled trials describe the optimal treatment regimen for disseminated strongyloidiasis. Ivermectin (IVM) and albendazole (ABZ) are recommended treatment, but it is not clear what dose or duration of therapy is optimal. Previous publications report tissue and plasma concentrations of IVM; however, none describe plasma ABZ concentrations in patients with disseminated strongyloidiasis or either drug in the context of advanced life support, specifically continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO). Patients with disseminated *Strongyloides* are often admitted to critical care with multiple organ failure, requiring multiple therapies that may affect treatment success. By describing IVM and ABZ plasma concentrations in the context of CRRT and venovenous ECMO, we hope to contribute to the understanding of the pharmacokinetics of medications used in the treatment of this often lethal yet preventable disease.

CASE PRESENTATION

A 62-year-old male with a recent diagnosis of granulomatous interstitial nephritis presented to the hospital with abdominal distension. Ten weeks before hospital admission, the patient had been started on 75 mg of prednisone daily followed by a slow taper. At the time of presentation, he was taking 35 mg of prednisone daily and was admitted for conservative treatment of gastric ileus. Three weeks earlier, the patient had been admitted for *Klebsiella pneumoniae* bacteremia and was discharged with ongoing abdominal pain. Past medical history was significant for poorly controlled type 2

diabetes, hypertension, and dyslipidemia. The patient was born and raised in Fiji and immigrated to Canada 41 years earlier. He had returned to Fiji on multiple occasions. His last visit was 20 years before presentation. In his youth, he occasionally walked around barefoot in rural Fiji. His travel history also included a visit to Saudi Arabia 3 years before presentation, and Malaysia and Singapore 10 months before presentation, where he walked barefoot on the beach.

Eight days after admission, the patient developed septic shock, *Enterococcus faecium* bacteremia, hypoxemic respiratory failure, and acute kidney injury. He was intubated and started on meropenem and vancomycin with norepinephrine, vasopressin, and CRRT support (continuous venovenous hemodiafiltration and ST150 filter). On day 9, *Strongyloides stercoralis* filariform larvae were seen on a Gram stain of an endotracheal tube aspirate. Anthelmintic therapy, including nasogastric IVM (15 mg daily), veterinary formulation of intramuscular IVM (30 mg daily, 353 µg/kg), and ABZ (400 mg via nasogastric tube daily) was initiated. Parenteral IVM was obtained through a veterinary clinic and oral IVM was obtained through Health Canada's Special Access Program. The first doses of parenteral IVM were delivered intramuscularly rather than subcutaneously, as there was concern that peripheral edema would reduce the bioavailability of subcutaneous IVM. The patient had not taken oral IVM before receiving prednisone.

On day 11, the patient was transferred to a tertiary care hospital and was started on venovenous ECMO. Initial investigations on transfer demonstrated hemoglobin of 72 g/L, platelets of $100 \times 10^9/L$, and leukocytes of $9.1 \times 10^9/L$, with a differential demonstrating normal eosinophils ($0.26 \times 10^9/L$). The patient's albumin was 35 g/L. Serology tests for human T-lymphotrophic virus-1 and human immunodeficiency virus were negative. Computed tomography of the abdomen showed gastric, duodenal, and jejunal distension. The route of IVM administration was changed to subcutaneous 17 mg daily (200 mcg/kg), and nasogastric IVM was discontinued. On day 13, the nasogastric tube was advanced to a post-pyloric location to increase the delivery of ABZ to the small intestine. Throughout the admission, the patient received stress-dose hydrocortisone (50 mg IV q6h). On day 15, he received pulse steroids (methylprednisone 1 g IV daily $\times$ 3 days) because of radiographic findings suspicious for organizing pneumonia after brief radiographic improvement.

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On day 19, the patient was decannulated from ECMO. On day 20, motile filariform larvae were again seen on wet mount of a tracheal aspirate. The detection of live larvae after 11 days of treatment prompted measurement of IVM and ABZ concentrations because of concerns that ECMO might alter the pharmacokinetics of the medications.

Stored plasma samples obtained from peripheral venipuncture from days 12 and 24 were sent for determination of IVM, ABZ, and ABZ metabolite concentrations (see Table 1). The day 12 sample was taken 5.5 and 17.5 hours after the last ABZ and IVM doses, respectively. The day 24 sample was taken 7.3 and 8.3 hours after the last ABZ and IVM doses, respectively. On day 12, the patient was on ECMO and CRRT and the nasogastric tube delivered ABZ to the stomach. On day 24, the patient had been decannulated from ECMO and the nasogastric tube delivered ABZ to the duodenum. Ivermectin concentrations were determined using a validated high-performance liquid chromatography (HPLC) method with fluorescent detection.¹ Ivermectin concentrations from day 12 to day 24 were 68.5 ng/mL and 109.6 ng/mL, respectively. Albendazole, albendazole sulfoxide (ABZ-OX), and albendazole sulfone (ABZ-ON) were measured using a validated LC/MS/MS method.² Albendazole is quickly oxidized to its active metabolite, ABZ-OX, in the liver, leaving low concentrations of the parent compound.^{3,4} On day 12, plasma ABZ and ABZ-OX measured 12.6 and 277.9 ng/mL, respectively. On day 24, ABZ and ABZ-OX measured 63.2 and 487.1 ng/mL, respectively.

On day 26, as the patient remained hypotensive despite vasopressors, the patient's family decided to transition therapy to comfort care measures only. The patient died soon after.

DISCUSSION

Clinical outcomes of disseminated strongyloidiasis remain poor with mortality rates around 60%.⁵⁻⁷ No randomized controlled trials exist to determine the optimal regimen for treating disseminated strongyloidiasis. The existing standard of care includes the combination of IVM with ABZ, as treatment failure has been described with IVM alone.^{5,8} Case reports clearly demonstrate that in patients with hyperinfection and ileus, subcutaneous IVM achieves higher serum concentrations than nasogastric or rectal administration.⁹⁻¹² However, appropriate target concentrations for IVM and ABZ have not been established. A wide variation of serum IVM concentrations have been described.^{5,10,13-15} Most successful treatments occur between plasma concentrations of 15 and 100 ng/mL; however, different studies describe concentrations drawn at different times after IVM administration.^{6,12-16} Peak IVM concentration after oral administration (0.2 mg/kg) ranges from 20 to 54.4 ng/mL and occurs between 3.4 and 10.3 hours after administration.¹⁷ Time to peak concentration has not yet been demonstrated for subcutaneous IVM administration.

No case reports describe ABZ concentrations in the treatment of disseminated strongyloidiasis. Albendazole concentrations have instead been described in the treatment of neurocysticercosis, hydatid disease, and lymphatic filariasis.¹⁸⁻²⁰ In neurocysticercosis, the concentrations of ABZ's active metabolite, ABZ-OX, vary considerably.^{21,22} *Taenia solium* activity was inhibited at an ABZ-OX concentration of 50 ng/mL.¹⁸

TABLE 1
Concentration for IVM, ABZ, and ABZ metabolites in serum

Sample no.	Identification	IVM (ng/mL)	ABZ (ng/mL)	ABZ sulfoxide (ng/mL)	ABZ sulfone (ng/mL)
1	Day 12 sample (13:30)	68.5	12.6	277.9	16.4
2	Day 24 sample (04:20)	109.6	63.2	487.1	5.5

ABZ = albendazole; IVM = ivermectin.
IVERMECTIN Concentrations.

For IVM, plasma concentrations were determined using HPLC with fluorescence detection as previously described.¹ Albendazole, ABZ-OX, and ABZ-ON were determined using a validated liquid chromatography-mass spectrometric (LC-MS/MS) method.²

In uninfected humans, a mean peak concentration of $1,200 \pm 440$ ng/mL was achieved 4.75 hours after a single 400-mg oral dose of ABZ.³

The increased ABZ-OX concentration on day 24, despite being further from documented peak concentrations, suggests altered pharmacokinetics and accumulating concentrations.^{3,23} This is corroborated by the concomitant elevation of parent compound concentrations and ABZ-OX's residence time between 14 and 20 hours.^{3,24} It is also conceivable that the post-pyloric drug delivery in our day 24 sample increased the concentrations of both ABZ and ABZ-OX.

The IVM and ABZ-OX concentrations taken when our patient was on ECMO and CRRT exceeded concentrations expected to have activity against *Strongyloides*. This finding confirms the known hepatic metabolism of these medications and complements a veterinary study demonstrating the failure of hemodialysis to decrease IVM levels.²⁵ Despite inadequate data, supplemental dosing of ABZ and IVM is not recommended during hemodialysis.²⁶

Both IVM and ABZ-OX concentrations increased after decannulation from ECMO. This suggests that both medications may be sequestered by ECMO's membrane oxygenator. Ivermectin and ABZ's lipophilic and protein-bound properties are consistent with other medications known to be sequestered by ECMO.²⁷⁻²⁹ Although ECMO priming may decrease drug concentrations by increasing effective circulating volume, this is unlikely to be a large contributor to the difference in IVM and ABZ-OX concentrations as both drugs have large volumes of distribution.^{4,17,28} Studies are needed to understand how ECMO alters serum concentrations of anthelmintic medications.

It is unknown why larvae are able to survive prolonged exposure to presumably adequate treatment doses. Parasitologic cure rates have not yet been established for the treatment of disseminated strongyloidiasis. The time interval between initiation of IVM therapy and parasitologic clearance shows significant variability, ranging between 6 and 37 days.^{11,15,16} In one study, mean duration of larval shedding

TABLE 2
IVM and ABZ dose and administration time

	IVM dose and administration time	ABZ dose and administration time
Days 9-10	15 mg via nasogastric tube at 20h00 and 30 mg intramuscular injection at 20h00 daily	400 mg via nasogastric tube at 16h00 daily
Days 11-26	17 mg subcutaneous injection at 20h00	400 mg via nasogastric tube at 08h00 and 21h00

ABZ = albendazole; IVM = ivermectin.

from stool and sputum samples was 12.7 and 12 days, respectively.³⁰ Thus, it has been recommended that treatment be continued until parasite clearance is achieved.⁸

It is unlikely that the live filariform larvae from the sputum reflect a failure of drug delivery to the respiratory tract. Previous reports document the efficacy of subcutaneous IVM at achieving measurable pulmonary concentrations.¹⁵ In addition, venovenous ECMO maintains normal circulation through the pulmonary vasculature and should not impede drug delivery to the lungs.³¹

Factors that may have contributed to our patient's delay in parasitologic clearance include steroid administration, a high-parasitic body burden, and unknown free IVM concentrations. Corticosteroids are known to stimulate the *Strongyloides* autoinfection cycle³²; thus, their continued use may reduce treatment success. We measured total IVM concentrations—which include free IVM and IVM bound to albumin and alpha-1-acid glycoprotein.¹ It has been suggested that IVM's antiparasitic activity is generated by its free form.¹⁴ Thus, adequate total IVM concentrations may not properly reflect the IVM activity.¹⁴

CONCLUSION

Despite our patient's poor outcome, IVM and ABZ concentrations during ECMO and CRRT exceeded those expected to have activity against *Strongyloides*. An increase in drug concentrations after ECMO decannulation suggests that ECMO's membrane oxygenator may sequester IVM and ABZ. In a world of increasingly mobile populations, individuals at risk for *Strongyloides* infection are frequently being treated in nonendemic regions where knowledge of this disease is limited. Immunosuppressed patients are not always screened for infection and remain at risk of complications. Patients with *Strongyloides* dissemination often present with multiple organ failure. Improved knowledge of the interplay between advanced life support and anthelmintic pharmacokinetics is needed to reduce the mortality of this preventable disease.

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