

Failure of Ivermectin per Rectum to Achieve Clinically Meaningful Serum Levels in Two Cases of *Strongyloides* Hyperinfection

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Abstract. Two cases of *Strongyloides* hyperinfection are presented. Ivermectin was initially administered orally and per rectum pending the availability of subcutaneous (SC) preparations. In neither case did rectal suppositories of ivermectin achieve clinically meaningful serum values. Clinicians should use SC preparations of ivermectin as early as possible in *Strongyloides* hyperinfection and dissemination.

CASE 1

A 38-year-old Nigerian-born female with no prior medical history presented with worsening nausea and vomiting over a 6-week period. One year prior admission she had traveled to Nigeria for 1 month. Two months before admission she was referred to a gastroenterologist for dyspepsia and underwent upper endoscopy with a small bowel biopsy. At the time of her presentation to hospital, endoscopic biopsy results showed filariform larvae of *Strongyloides stercoralis*. On admission she was ill appearing, afebrile, with a blood pressure of 90/50 mmHg, heart rate of 115 beats/min, and normal oxygen saturations. Her examination was unremarkable apart from a tender epigastrium and diminished bowel sounds.

Blood examination revealed a normal complete blood count, creatinine, and liver function tests. Computed tomography (CT) of her abdomen with contrast demonstrated a thickened proximal small bowel wall and evidence of ileus. *Strongyloides* hyperinfection syndrome was suspected, and she was empirically treated with crystalloid resuscitation and albendazole (400 mg PO BID) while an urgent request for ivermectin was made to Health Canada (ivermectin is a special access drug in Canada available only with the authorization of the Health Protection Branch). In addition, intravenous ceftriaxone and metronidazole were administered for presumed gram-negative sepsis. The patient was unable to tolerate oral albendazole because of intractable nausea and vomiting, so albendazole was administered via nasogastric (NG) tube although there was concern regarding poor absorption given her ileus and persistent vomiting. Pending the availability of subcutaneous (SC) ivermectin, we had a compounding pharmacy prepare oral ivermectin into rectal suppositories; we administered these in the evening on her first and second hospital day (200 µg/kg, totaling 15 mg per rectum (PR)). Her persistent ileus prompted the General Surgery service to perform an urgent laparotomy on her second hospital day. She was found to have a dilated proximal small bowel, what appeared to be a fecal bezoar as a result of the ileus that was milked distally. She required nor-epinephrine for blood pressure control during the operation

and for 6 hours immediately after. She was extubated shortly after her laparotomy and was able to tolerate oral medications the following day at which point she was given oral ivermectin. Table 1 shows her medication schedule and microbiology results during and after her hospital stay. Serum ivermectin levels were measured on hospital day 2, 3, and 8 as per the protocol described previously in a study.¹ PR ivermectin did not achieve clinically meaningful serum levels. Her symptoms of nausea, vomiting, and abdominal pain gradually improved after surgery and the initiation of oral ivermectin, and she was discharged after 16 days of hospital stay. She received a total of 3 weeks of oral ivermectin (15 mg daily). The patient was found to be human immunodeficiency virus (HIV) negative, and human T-cell leukemia virus type 1 (HTLV-1) positive, a risk factor for disseminated *Strongyloides* infection.² She was well during clinic appointments at 1, 2, and 3 months after discharge. Her family members were counseled and screened for HTLV-1 infection.

CASE 2

A 58-year-old Haitian-born male presented to hospital with a 2-week history of bilateral leg weakness, leg pain, urinary retention, constipation, and abnormal gait. His past medical history was significant for a marginal zone pulmonary lymphoma treated 2 years previously with rituximab, cyclophosphamide, vincristine, and prednisone. On admission he was on maintenance rituximab. His most recent visit to Haiti was over 20 years ago.

Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) cytology during his admission were concerning for central nervous system (CNS) lymphoma; for this reason, he was given intravenous dexamethasone before initiating intrathecal chemotherapy on the third day in hospital. His HIV serology was negative but HTLV-1 serology was positive. He continued on tapering doses of dexamethasone with gradual neurologic improvement until hospital day 41 when he had a rapid hemodynamic deterioration and was admitted and intubated in the ICU with presumed septic shock. He had experienced intermittent abdominal pain and nausea for 3 days previously. In the ICU, he was started empirically on imipenem and vancomycin for presumed bacterial sepsis. On day 42, filariform and rhabditiform larvae of *S. stercoralis* were visualized in a bronchoscopic alveolar lavage (BAL) sample. Stool samples were subsequently positive for *S. stercoralis* filariform larvae. CT of

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TABLE 1
Serum ivermectin levels in two patients with *Strongyloides* hyperinfection following ivermectin administration via PO, NG, PR, and SC routes

Case 1				Case 2			
Days after hospital admission*	Anthelmintic agent administered	<i>S. stercoralis</i> filariform larvae result	Serum ivermectin levels (ng/mL)	Days after hospital admission	Anthelmintic agent administered	<i>S. stercoralis</i> filariform larvae result	Serum ivermectin levels (ng/mL)
1	PO albendazole PR ivermectin	Present on biopsy from upper GI endoscopy	–	42	NG albendazole PR ivermectin	Present in sputum	–
2	NG albendazole PR ivermectin	Present in vomitus and stool	< 0.19*	43	NG albendazole NG ivermectin	Test not performed	< 0.19
3	PO ivermectin	Test not performed	0.56†	44	NG albendazole NG ivermectin SC ivermectin	Test not performed	< 0.19
4	PO ivermectin	Present in stool	–	45	NG albendazole SC ivermectin	Test not performed	14.1
5	PO ivermectin	Present in stool	–	46	NG albendazole SC ivermectin	Test not performed	13.2
6	PO ivermectin	Present in stool	–	47	SC ivermectin	Present in sputum and stool	23.8
7	PO ivermectin	Present in stool	–	48	SC ivermectin	Present in sputum and stool	42.3
8	PO ivermectin	Test not performed	25.3	49	SC ivermectin	Test not performed	54.9
9	PO ivermectin	Present in stool	–	50	SC ivermectin	Test not performed	–
10	PO ivermectin	Test not performed	–	51	SC ivermectin	Test not performed	–
11	PO ivermectin	Absent from stool	–	–	–	–	–
15	PO ivermectin	Absent from stool	–	–	–	–	–
16	PO ivermectin	Absent from stool	–	–	–	–	–
17	PO ivermectin	Absent from stool	–	–	–	–	–
51	Nil	Absent from stool	–	–	–	–	–

NG = nasogastric; PO = oral; PR = rectal; SC = subcutaneous.

*Quantifiable limit = 0.19 ng/mL.

†Sample drawn prior to administration of oral ivermectin.

the abdomen on day 42 showed small bowel dilatation with ileus and multifocal small and large bowel thickening, and there was no evidence of peripheral eosinophilia. He was started that same day on a rectal preparation of ivermectin (200 µg/kg, totaling 12 mg) PR, prepared by a local compounding pharmacy, while waiting for SC ivermectin and albendazole (400 mg PO BID) pending special access approval from Health Canada, which was obtained the following day.

SC ivermectin was obtained from a veterinary supplier and was given with hospital approval and the patient's family's consent. SC ivermectin (200 µg/kg, totally 12 mg daily, administered as 6 mg at two different body sites) was continued daily given the patient's ongoing ileus and concern that therapeutic levels were not being achieved via PO and PR routes. Oral, rectal, and SC ivermectin were administered as per Table 1. Serum ivermectin levels were drawn daily between hospital days 43 and 49, inclusive, and processed as per the protocol outlined previously in a study.¹ Antibiotics were continued given the concern of gram-negative sepsis.

MRI of the brain on day 48 demonstrated nonhemorrhagic infarcts along the frontoparietal cortex bilaterally and on the right cerebellum in addition to new bilateral subdural collections. The patient stabilized from a hemodynamic point of view but had not recovered neurologically. After discussions with the family he was extubated on day 58, transferred to a palliative care facility on day 61, and died on day 64. An autopsy was not performed.

DISCUSSION

Administration of SC ivermectin is the preferred treatment for disseminated strongyloidiasis where traditional oral preparations are not tolerated mainly because of paralytic ileus.³ SC administration is the most frequent non-oral route of ivermectin

delivery and has been reported in several case reports and case series.⁴⁻¹² Although there are many cases of patient recovery, several clinical failures are reported as well.^{9,11,12} Several studies that measured plasma concentrations of subcutaneously administered ivermectin^{5,8,9,11,12} have usually demonstrated levels within a range well tolerated by healthy volunteers.¹³ A major problem with SC ivermectin is that it is only available as a veterinary formulation that is not yet licensed in humans and is frequently associated with a significant delay in drug administration. This delay can be attributed to issues procuring the drug from a veterinary practice¹² or awaiting approval for use in non-formulary, off-label settings.^{9,12} Further delays may stem from the lag time between a patient presenting for medical attention and a clinician making the diagnosis of *Strongyloides* hyperinfection or dissemination.

In addition to SC preparations, PR ivermectin has been reported in six cases of disseminated strongyloidiasis (including the abovementioned cases) where PO preparations were not tolerated.^{11,12,14} This mode of drug delivery has the benefit of rapid administration to patients because PO preparations of ivermectin can be compounded into suppositories or enemas rather quickly, thereby avoiding delays in obtaining SC ivermectin from veterinary sources. Tarr and others¹⁴ successfully treated a case of disseminated *Strongyloides* following renal transplantation with PR ivermectin by crushing ivermectin tablets (200 µg/kg/day) and creating a 230 mOsm/kg suspension as a retention enema. This patient concurrently received NG ivermectin and albendazole therapy. Serum ivermectin levels were not measured; therefore, it is unclear if there was any clinical contribution of the rectally administered ivermectin. Fusco and others¹² described two cases of PR ivermectin use, the first being in a Ghanaian woman with disseminated infection complicated by paralytic ileus. She recovered after 37 days of PO ivermectin and 7 days of PR therapy, with serum

levels unmeasured. The second patient was given SC and PR ivermectin concurrently for nine doses, followed by PO albendazole. Serum ivermectin levels were measured and achieved a steady state (30–35 ng/mL) 4 days after the first dose of PR ivermectin and 2 days after initiating SC ivermectin; however, the patient succumbed to multisystem organ failure. Given the overlap of rectal and SC drug delivery routes, the clinical benefit from PR ivermectin remains unclear. Finally, Grein and others¹¹ described a patient with disseminated strongyloidiasis following corticosteroid use for AIDS-related immune reconstitution inflammatory syndrome. PR ivermectin was administered for 17 days but serum drug levels were measured below 1 ng/mL. A 3-fold increase occurred after SC ivermectin was initiated along with a transient clinical improvement.

Therapeutic ivermectin serum levels for *S. stercoralis* are unknown; however, in vitro studies suggest levels > 2.4 ng/mL are required to paralyze 50% of *S. ratti* and *S. venezuelensis* infections.¹⁵ Older agents such as thiabendazole have efficacy against *Strongyloides* and have been administered PR in cases of disseminated disease with ileus. Successful treatment of disseminated strongyloidiasis demonstrated both detectable and sustained serum levels of thiabendazole 4 hours after administration.¹⁶

The patients described here received PR ivermectin but had undetectable or clinically insignificant serum levels 12 hours after each dose (Table 1). We used a suppository preparation of ivermectin for rapidity of drug delivery rather than the retention enema described by Tarr and others,¹⁴ however, our approach did not lead to clinical improvement or therapeutic serum levels. Serum levels rose dramatically after the initiation of SC ivermectin, or resolution of ileus and ability to tolerate PO preparations.

Oral and rectal suppository preparations of ivermectin are not effective in patients with *Strongyloides* hyperinfection accompanied by paralytic ileus. Prompt treatment with SC preparations of ivermectin is required to achieve clinically meaningful serum levels and have the best probability for a favorable clinical outcome. We recommend that hospitals enact policies to expeditiously acquire and administer SC ivermectin to patients with *Strongyloides* hyperinfection.

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