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. On day 42, filariform and rhabditiform larvae of Strongyloides stercoralis were visualized in a bronchoscopic alveolar lavage (BAL) sample. Stool samples were subsequently positive for S. stercoralis filarial larvae. CT of
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 day on a rectal preparation of ivermectin (200 \( \mu \)g/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 \( \mu \)g/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.\(^7\),\(^9\),\(^11\),\(^12\) Several studies that measured plasma concentrations of subcutaneously administered ivermectin\(^8\),\(^9\),\(^11\),\(^12\) 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 practice\(^12\) or awaiting approval for use in non-formulary, off-label settings.\(^8\),\(^12\) 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.\(^1\),\(^11\),\(^12\) 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 others\(^4\) successfully treated a case of disseminated *Strongyloides* following renal transplantation with PR ivermectin by crushing ivermectin tablets (200 \( \mu \)g/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 others\(^5\) 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

### Table 1

<table>
<thead>
<tr>
<th>Days after hospital admission*</th>
<th>Anthelmintic agent administered</th>
<th>S. stercoralis filariform larvae result</th>
<th>Serum ivermectin levels (ng/mL)</th>
<th>Days after hospital admission</th>
<th>Anthelmintic agent administered</th>
<th>S. stercoralis filariform larvae result</th>
<th>Serum ivermectin levels (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PO albendazole PR ivermectin</td>
<td>Present on biopsy from upper GI endoscopy</td>
<td>–</td>
<td>42</td>
<td>NG albendazole PR ivermectin</td>
<td>Present in sputum</td>
<td>–</td>
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<tr>
<td>2</td>
<td>NG albendazole PR ivermectin</td>
<td>Present in vomitus and stool</td>
<td>&lt; 0.19*</td>
<td>43</td>
<td>NG albendazole NG ivermectin</td>
<td>Test not performed</td>
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<td>3</td>
<td>PO ivermectin</td>
<td>Test not performed</td>
<td>0.56†</td>
<td>44</td>
<td>NG albendazole SC ivermectin</td>
<td>Test not performed</td>
<td>&lt; 0.19</td>
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<tr>
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<td>Present in stool</td>
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<td>NG albendazole SC ivermectin</td>
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<td>Present in stool</td>
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<td>47</td>
<td>SC ivermectin</td>
<td>Present in sputum and stool</td>
<td>23.8</td>
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<td>Present in sputum and stool</td>
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<td>49</td>
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<td>51</td>
<td>SC ivermectin</td>
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<tr>
<td>11</td>
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<td>Absent from stool</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NG = nasogastric; PO = oral; PR = rectal; SC = subcutaneous
* Quantifiable limit = 0.19 ng/mL
† Sample drawn prior to administration of oral ivermectin
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 others 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. 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.

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; 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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