Subcutaneous ivermectin use in the treatment of severe Strongyloides stercoralis infection: two case reports and a discussion of the literature

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Background: Strongyloides stercoralis infection presents with varying degrees of severity, but it often primarily involves the small bowel. In severe infection and cases of hyperinfection, ileus and small-bowel obstruction may prevent enteral absorption of anthelmintics such as ivermectin. At present there are no parenteral anthelmintics licensed for use in humans.

Methods: Here, we describe two cases of severe S. stercoralis infection treated with an unlicensed veterinary preparation of subcutaneous ivermectin, and we discuss the published reports of the use of this treatment elsewhere.

Results: Both patients were successfully treated with subcutaneous ivermectin, and both recovered completely.

Conclusions: Despite the limited published experience of parenteral ivermectin use, there is evidence that it may be a safe and effective treatment for severe strongyloidiasis. However, more data are needed to guide dosing schedules and monitoring for toxicity.

Introduction

Between 30 and 100 million people are affected by Strongyloides stercoralis infection yearly, with the majority of cases occurring in endemic areas such as South America and South-East Asia.¹ Some cases are seen outside these areas, however, and diagnosis in such cases may be significantly delayed. Tropical infections are understandably lower on the list of differential diagnoses unless a clear history of recent travel is given. As S. stercoralis can complete its life cycle within a single human host, in a process called ‘auto-infection’, infection can persist for many years after the original exposure, and its cause may not be recognized after a superficial travel review.

Infection may re-emerge in the form of severe or hyperinfection following immune suppression, an increasingly frequent occurrence in an ageing and medically complex population. Steroid use, human T lymphocyte virus 1 (HTLV-1) infection and organ transplantation are risk factors for hyperinfection—a rapid increase in the reproduction and migration of the Strongyloides larvae, which can lead to life-threatening illness. Delay in diagnosis reduces the efficacy of conventional therapy, and it can lead to treatment failure.

The most effective anthelmintic used to treat Strongyloides infection is ivermectin, which paralyses nematodes by increasing membrane permeability to chloride ions. Currently, the only administration route licensed for use in humans is oral; however, in severe Strongyloides infection, there is often extensive small-bowel involvement, so enteral administration is poorly tolerated or not possible. With treatment, the mortality rate of hyperinfection is close to 60%;² without effective treatment, it is likely to be around 100%. Rectal administration has been tried, but it appears to have limited efficacy. One case study describes the intravenous use of ivermectin; however, the patient died.³

There are limited data on the unlicensed subcutaneous use of ivermectin in such patients. Here, we describe our experience of the successful use of subcutaneous ivermectin in two patients with severe and complicated Strongyloides infection where enteral treatment was not possible, and we summarize the published cases to date.

Case 1

A 52-year-old woman presented to her general practitioner with a 2 month history of abdominal bloating, postprandial vomiting and weight loss. Blood tests done by the general practitioner showed iron-deficiency anaemia (haemoglobin concentration 91 g/L, mean corpuscular volume 74 fL, ferritin concentration 14 μg/L), leucocytosis with neutrophilia (neutrophils 10.4 × 10⁹/L, lymphocytes 1.5 × 10⁹/L, eosinophils 0.3 × 10⁹/L), hypoalbuminaemia (29 g/L) and hyponatraemia (serum sodium concentration 125 mmol/L).

Although the patient was born in Ecuador, she had not travelled outside Western Europe in 8 years. Other than having...
received successful treatment for pulmonary tuberculosis and cervical cancer, she was fit and well.

The results from a gastroscopy were macroscopically normal and negative for Helicobacter pylori, but a duodenal biopsy showed acute-on-chronic duodenitis and numerous worms with morphology consistent with Strongyloides stercoralis. The patient was referred to the Infectious Diseases team to start oral ivermectin, but her condition deteriorated over the next 4 days, so she was admitted to hospital.

On admission, the patient was confused, dehydrated and severely cachectic with generalized abdominal distension and tenderness but no peritonitis. She had worsening hyponatraemia (121 mmol/L), leucocytosis with neutrophilia and lymphopenia (neutrophils 14.4×10^9/L, lymphocytes 0.5×10^9/L, eosinophils 0.3×10^9/L), and her hypoalbuminaemia had worsened (22 g/L). She was HIV-negative, but she tested positive for HTLV-1.

A plain abdominal film showed distended small-bowel loops. A diagnosis of paralytic ileus secondary to Strongyloides hyperinfection was made. The patient was given supportive treatment with intravenous fluids, anti-emetics and intravenous thiamine. Despite the regular administration of anti-emetics, she was unable to tolerate oral ivermectin, so she commenced subcutaneous ivermectin treatment (200 μg/kg), receiving 12 mg once daily in divided doses (6 mg) into each upper arm.

Over the next few days, the patient’s serum sodium concentration continued to drop, reaching a nadir of 115 mmol/L on day 4 of treatment. She had fluctuating confusion and hallucinations attributed to the hyponatraemia. Serum and urine osmolalities were consistent with syndrome of inappropriate antidiuretic hormone (SIADH). Fluid restriction to less than 1.5 L daily was initiated. No other cause for SIADH was found, despite extensive investigation.

The patient tolerated the subcutaneous formulation, and after 6 days of treatment she was opening her bowels, her vomiting hadsettled and she was able to tolerate oral medications. She wasswitched to oral ivermectin (9 mg) once daily for 7 days, then once weekly for a further 4 weeks and monthly for 3 months. Despite the patient’s intermittent compliance with fluid restriction, her serum sodium concentration slowly increased (121 mmol/L on day 7, 126 mmol/L on day 14 and 132 mmol/L on day 21), and her confusion settled. With regular dietician input, she began to gain weight. She was discharged on day 26 and followed up monthly, with stool remaining negative for Strongyloides, and she was referred to a specialist centre for management of her HTLV-1.

Case 2

A 56-year-old man had been under investigation for more than a year for symptoms of upper abdominal pain, nausea and weight loss. A gastroscopy showed mild gastritis and an incompetent pylorus with bile reflux. The results of a Campylobacter-like organism test (CLO test) for Helicobacter pylori were negative. He was treated symptomatically; however, his condition continued to worsen, and 6 months after the gastroscopy he was admitted to hospital.

The 6 weeks preceding admission had seen a marked increase in the patient’s abdominal pain, which was now ameliorated only by avoiding eating. He described early satiety after two or three spoons of food. He had lost 10 kg in the past 6 weeks, and he was unable to tolerate any oral intake. When examined, he was dehydrated and cachectic, with diffuse upper abdominal tenderness and scanty bowel sounds.

Other than his gastrointestinal symptoms, the patient had a background of hypertension and prostate cancer, which had been treated with brachytherapy in 2005. On admission, his medications were omeprazole, ranitidine, tadalafil, calcium and vitamin D supplements. He had been born in Sierra Leone but had lived in the UK for more than 20 years, with occasional travel back to Sierra Leone.

The patient was admitted to receive intravenous fluids, and a nasogastric tube was inserted. Initial blood tests showed mild neutrophilia (neutrophils 8.4×10^9/L, lymphocytes 1.0×10^9/L), moderately raised C-reactive protein concentration (102 mg/L), hypoalbuminaemia (albumin 31 g/L) and hyponatraemia (serum sodium concentration 129 mmol/L). After several days in hospital, it became apparent that his oral intake was insufficient for his nutritional requirements, so total parenteral nutrition was started. A CT scan showed pancreatic duct dilatation and diluted small-bowel loops. Because of the presence of large quantities of thick biliary material, the ampulla was not visualized by endoscopic ultrasonography, so a push enteroscopy was performed. Duodenal biopsies showed large numbers of adult female worms, larvae and eggs, with lymphocytic infiltrates.

The patient was started on oral ivermectin; however, his ongoing intolerance of any oral intake prevented enteral absorption. He commenced subcutaneous ivermectin treatment (200 μg/kg), receiving 12 mg per day in divided doses (6 mg) into each upper arm. Other than causing aching at the injection sites and some mild arthralgia, the medication was well tolerated and rapidly improved the patient’s symptoms. After 3 days his symptoms improved sufficiently to allow a soft diet to be started. A repeat endoscopy 1 month after the initial investigation showed normal macroscopic appearances, and biopsies showed no evidence of ongoing parasite infection.

Having received eight doses of subcutaneous ivermectin therapy, the patient was started on oral ivermectin therapy. Four weekly doses of 200 μg/kg were followed by three monthly doses, with monthly examination of stool for evidence of ongoing infection. HTLV-1 serology was positive, and the patient was referred for further infection management at a specialist centre. When he was reviewed in clinic 3 months after therapy was started, the patient had gained 20 kg and, in his words, felt ‘extremely better’.

Published experience of subcutaneous ivermectin use

There are 17 published reports of subcutaneous ivermectin use in 20 patients with Strongyloides infections, summarized in Table 1.3–19 In all cases, patients had severe strongyloidiasis or hyperinfection, and many had failed to improve with oral albendazole or ivermectin. The subcutaneous doses used varied from 75 μg/kg/day4 to 285 μg/kg/day; however, the majority of studies used 200 μg/kg/day on alternate days. Treatment course length was generally dictated by clinical response and varied from 3 doses6 to 11 doses.3

Of the 20 patients described in these case reports, nine survived treatment and were considered to have been cured.3,6,11–16 Seven patients achieved microbiological ‘cure’ but died of complications or other comorbidities after treatment.3,6,10,15,17,18 Four patients died during treatment3,5,9,19
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<tr>
<td>Gupta et al,3 2006</td>
<td>52-year-old Puerto Rican man, haematopoietic stem cell transplant</td>
<td>alveolar haemorrhage, respiratory failure</td>
<td>15 mg daily</td>
<td></td>
<td>symptoms improved initially, but patient died of septic shock and respiratory failure</td>
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<tr>
<td>Donadello et al,4 2013</td>
<td>56-year-old man from the Democratic Republic of the Congo, post renal transplant</td>
<td>disseminated Strongyloides with severe gastroparesis</td>
<td>5 days of 75 μg/kg/day = 6 mg then 200 μg/kg/day = 16 mg for 9 days</td>
<td>trough serum levels during treatment (days 5, 6 and 7) = 5.6 - 19.7 ng/mL; post-treatment (day 13) &gt;40 ng/mL</td>
<td>cured, but death from Pseudomonas aeruginosa infection 1 month later; encephalopathy, with ataxia then coma, resolved with cessation of ivermectin</td>
</tr>
<tr>
<td>Moura et al,5 2012</td>
<td>56-year-old Brazilian man, agranulocytosis, 80 mg of prednisolone daily</td>
<td>disseminated Strongyloides, shock, respiratory failure</td>
<td>15 mg per day for 4 days (214 μg/kg/day), stopped then further 7 days of 20 mg per day (285 μg/kg/day)</td>
<td></td>
<td>cured; survived to discharge; confusion and coma; concurrent herpes simplex virus encephalitis—therefore, it is unclear whether ivermectin toxicity was present</td>
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<tr>
<td>Lichtenberger et al,6 2009</td>
<td>59-year-old American woman, liver transplant rejection, alemtuzumab and methylprednisolone</td>
<td>nausea, abdominal pain, malabsorption</td>
<td>200 μg/kg at 0, 12 and 60 h</td>
<td></td>
<td>cured; survived to discharge; probable neurotoxicity—generalized tonic-clonic seizure</td>
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<tr>
<td>Hamilton et al,7 2011</td>
<td>39-year-old woman, renal transplant, tacrolimus, mycophenolate mofetil and prednisolone</td>
<td>abdominal pain, rash</td>
<td>200 μg/kg, alternate days, 11 doses</td>
<td></td>
<td>cured; survived</td>
</tr>
<tr>
<td>Fusco et al,8 2010</td>
<td>61-year-old South Korean woman, renal transplant rejection, pulsed methylprednisolone</td>
<td>disseminated strongyloidiasis, pulmonary involvement</td>
<td>200 μg/kg, alternate days, 3 doses</td>
<td></td>
<td>cured</td>
</tr>
<tr>
<td></td>
<td>76-year-old Jamaican woman, 8 mg of dexamethasone daily</td>
<td>pulmonary infiltrates, colitis</td>
<td>200 μg/kg, every 72 h, 3 doses</td>
<td></td>
<td>cured, but died of multiorgan failure</td>
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<tr>
<td></td>
<td>59-year-old Puerto Rican man, 60 mg of prednisolone daily for thymoma</td>
<td>ileus, fever, respiratory failure</td>
<td>200 μg/kg, 10 doses over 12 days</td>
<td>during treatment: 7.9 - 35.4 ng/mL; peak 99.8 ng/mL day 6 post-treatment</td>
<td>not cured; died; elevated ALT</td>
</tr>
<tr>
<td>Leung et al,9 2008</td>
<td>67-year-old Laotian man, craniopharyngioma, 12 mg of dexamethasone daily</td>
<td>Escherichia coli bacteraemia and meningitis, vomiting</td>
<td>200 μg/kg/day for 8 days</td>
<td>after five doses: 28.3 ng/mL</td>
<td>not cured; died with active parasites on nasogastric aspirate</td>
</tr>
<tr>
<td>Turner et al,10 2005</td>
<td>23-year-old man from St Vincent, HTLV-1-positive</td>
<td>disseminated Strongyloides, hypoalbuminaemia, ileus</td>
<td>15 mg (200 μg/kg/day) for 14 days</td>
<td>12 h post-first dose: 5.8 ng/mL; during treatment: 11.4 - 17.2 ng/mL; 48 h after last dose: 14.8 ng/mL</td>
<td>cured, but died: neurotoxicity—coma and hypersalivation</td>
</tr>
<tr>
<td>Marty et al,11 2005</td>
<td>54-year-old Jamaican man, multiple myeloma, prednisolone, HTLV-1 myelopathy</td>
<td>severe malabsorption, ileus</td>
<td>200 μg/kg/day, alternate days, 3 doses</td>
<td>during treatment: 2 - 7.9 ng/mL; 20.3 ng/mL at end of therapy</td>
<td>cured; survived to discharge</td>
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Continued
Five case reports include serum ivermectin concentrations, although there is a lack of consistency in the timing of measurement of levels. Serum ivermectin concentrations measured during treatment vary from 2.7 ng/mL after three doses of 200 μg/kg \(^1\) to 35.4 ng/mL after seven doses of 200 μg/kg.\(^2\) Serum concentrations were noted to rise further following cessation of treatment.\(^4,8\)

**Discussion**

Both patients described here had features of severe Strongyloides infection, with absence of eosinophilia, HTLV-1 co-infection and advanced gastrointestinal symptoms. Despite this, both responded rapidly and completely to subcutaneous ivermectin therapy, and neither suffered any adverse effects during treatment. Whereas our patients had good outcomes from treatment with doses of 200 μg/kg/day, it can be seen from the summary given earlier that overall there is a lack of data to guide clinicians when using subcutaneous ivermectin, and there is a lack of consistency on dose size and interval.

Therapeutic options for severe strongyloidiasis are limited, and there are no licensed human parenteral preparations. In some countries where human preparations of oral ivermectin are not licensed, oral veterinary preparations have been used safely,\(^20\) and parenteral veterinary preparations are available. Despite the paucity of published experiences, the efficacy of subcutaneous ivermectin is apparent from the cited case reports. Although the patients in these reports represent the most severely affected, the 40% survival rate found in these studies is comparable with the expected mortality of Strongyloides hyperinfection quoted elsewhere.\(^2\)

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**Table 1. Continued**

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<td>Chiodini et al,(^{12}) 2000</td>
<td>39-year-old man from Grenada, HTLV-1-associated T cell lymphoma</td>
<td>ileus, gastrointestinal bleeding</td>
<td>12 mg daily, multiple doses</td>
<td>Microbiological cure; died of lymphoma; some pain at injection site</td>
<td></td>
</tr>
<tr>
<td>Huston et al,(^{13}) 2009</td>
<td>61-year-old woman, renal transplant rejection, pulsed methylprednisolone</td>
<td>hyperinfection syndrome ARDS, Klebsiella pneumoniae superinfection</td>
<td>6 mg daily for 2 days</td>
<td>Cured; no complications</td>
<td></td>
</tr>
<tr>
<td>Miller et al,(^{14}) 2008</td>
<td>19-year-old Mexican man, new diagnosis of HIV</td>
<td>intussusception, fever, SIADH</td>
<td>6 mg daily for 12 days</td>
<td>Cured; survived to discharge</td>
<td></td>
</tr>
<tr>
<td>Pacanowski et al,(^{15}) 2005</td>
<td>28-year-old man from Côte d'Ivoire, HTLV-1-associated T cell leukaemia, methylprednisolone</td>
<td>hyperinfection syndrome, E. coli meningitis</td>
<td>6 mg twice daily for 12 days</td>
<td>Microbiological cure, but the patient died of lymphoma 5 weeks later; pain at injection site</td>
<td></td>
</tr>
<tr>
<td>Salluh et al,(^{16}) 2005(^a)</td>
<td>56-year-old man, 16 mg of dexamethasone daily</td>
<td>bowel perforation, shock, ARDS</td>
<td>6 mg (200 μg/kg), twice a week for 3 doses</td>
<td>Cured; survived to discharge</td>
<td></td>
</tr>
<tr>
<td>Hauber et al,(^{17}) 2005</td>
<td>77-year-old man from Paraguay, 60 mg of prednisolone daily</td>
<td>hyperinfection syndrome</td>
<td>170 μg/kg/day for 7 days</td>
<td>Microbiological cure, but the patient died of ARDS; elevated GGT, mild transaminitis</td>
<td></td>
</tr>
<tr>
<td>Takashima et al,(^{18}) 2008(^a)</td>
<td>49-year-old man, HTLV-1 and T cell leukaemia, methylprednisolone</td>
<td>fever, headache, ileus</td>
<td>9 mg (200 μg/kg), alternate days, 5 doses</td>
<td>Cure confirmed at autopsy, but the patient died of meningitis and obstructive hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Grein et al,(^{19}) 2010(^a)</td>
<td>31-year-old woman, advanced HIV, 60 mg of prednisolone daily</td>
<td>hyperinfection, pulmonary symptoms, ileus</td>
<td>10 mg (200 μg/kg), 7 doses over 10 days during treatment: 2.7–4.5 ng/mL</td>
<td>Serum levels improved, but the patient died; active infection at time of death (gastric samples); no adverse effects seen</td>
<td></td>
</tr>
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ARDS, acute respiratory distress syndrome.

\(^a\)No details of patient nationality are available.
Subcutaneous ivermectin would appear to be a suitable rescue treatment following failure of conventional therapy due to inability to absorb because of small-bowel disease; however, there may also be an argument for using parenteral administration early to avoid the expensive and dangerous complications of this severe illness. The primary site of pathology in strongyloidiasis of any severity is likely to be the bowel, so relying on enteral absorption in any patient approaching severe disease may be unwise.

Dosing is variable; however, the majority of experts recommend the same dose as for oral treatment of disseminated strongyloidiasis: 200 μg/kg/day, repeated until stool samples are negative for *Strongyloides*. Lower oral doses have been associated with treatment failure, especially in the presence of HTLV-1 co-infection. The spacing of subcutaneous doses again varies, and it does not appear to correspond to successful treatment or survival. The number of patients here is so small, and their disease severity and comorbidities so variable, that it would be impossible to comment on any correlation. It should be noted that some authors report switching to higher doses as clinical deterioration was observed when a low starting dose, e.g., 75 μg/kg/day, was used. The manufacturers report low rates of neurotoxicity in humans treated with doses of 170 or 200 μg/kg oral ivermectin. Following one or two doses 2.8% of healthy adults experienced dizziness, and <1% reported somnolence, vertigo and tremor. The tolerability of doses up to 120 mg, and repeated oral doses has also been demonstrated in healthy subjects. It is possibly significant that those patients experiencing neurotoxicity or elevated liver enzymes while on treatment were all dosed daily. The apparent neurotoxicity observed in three of the case reports may be complicated by the critical illness of the patients concerned; however, the very small number of reports prevents any firm conclusions being drawn here. There was no evidence of neurotoxicity in either of our patients.

Reported serum ivermectin concentrations vary widely in these reports, even where dosing was identical. This finding corresponds to wide variation in peak serum concentrations (13.9–101 ng/mL) measured following 12 mg oral doses in healthy volunteers.

There is no consensus on how subcutaneous ivermectin should be monitored, and the majority of pharmacokinetic studies are in farm animals. Ivermectin is protein-bound, so pharmacokinetics are altered by hypoalbuminaemia, a common result of severe *Strongyloides* infection. For the patients described previously, clinical parameters were used to calibrate dosing: lack of response prompted dose increases and treatment was stopped where there was evidence of toxicity.

Subcutaneous ivermectin has potential as a safe and effective treatment in patients with severe strongyloidiasis, but until there is greater experience of its use in this group, dosing and monitoring remain empirical at best.

**References**


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The study was carried out as part of our routine work.

**Transparency declarations**

None to declare.


