

## Case Report: Subcutaneous Ivermectin Pharmacokinetics in Disseminated *Strongyloides* Infection: Plasma and Postmortem Analysis

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**Abstract.** Parenteral ivermectin treatment of disseminated strongyloidiasis and hyperinfection is increasing, although not licensed in humans and with limited pharmacokinetic data available. Plasma and postmortem tissue analysis in an human immunodeficiency virus (HIV)/hepatitis C virus–positive man with disseminated strongyloidiasis suggests loading subcutaneous ivermectin doses are required, from which the central nervous system is protected.

### INTRODUCTION

The soil-transmitted nematode, *Strongyloides stercoralis*, is endemic in tropical and subtropical regions infecting more than 370 million people.<sup>1,2</sup> Host autoinfection with filariform larvae, unique in the *Strongyloides* life cycle, can lead to persistent long-lasting infection. With immunosuppression, notably corticosteroids, organ transplantation and human T-cell lymphotropic virus type 1 (HTLV-1) infection, a high intestinal burden can lead to hyperinfection, causing paralytic ileus and dissemination.<sup>2–4</sup> Hyperinfection and dissemination carry a 50–100% mortality rate and are an emerging threat globally as immunosuppressive therapy and organ transplantation indications expand.<sup>4,5</sup> In uncomplicated infection, ivermectin is highly active against the intestinal stages of *Strongyloides*. A single oral 200 µg/kg dose produced peak levels between 16 and 101 ng/mL in healthy volunteers and was 64–100% efficacious in clinical studies of gastrointestinal strongyloidiasis.<sup>6</sup> In *Strongyloides* hyperinfection, ivermectin is recommended at a dose of 200 µg/kg/day orally, or rectally, until stool and/or sputum are negative for larvae for 2 weeks.<sup>4,7</sup> However, impaired intestinal absorption may necessitate parenteral ivermectin, which is licensed only for veterinary use.<sup>7,8</sup> Access to parenteral ivermectin and pharmacokinetic data to guide therapy is limited.<sup>9</sup> Serial plasma and postmortem ivermectin analysis from our patient is described.

### CASE REPORT

A 27-year-old man, with 6 weeks of diarrhea and 10 kg weight loss, was diagnosed with Crohn's disease on colonoscopic biopsy but deteriorated on prednisolone 40 mg/day and azathioprine 150 mg/day and was admitted to hospital with paralytic ileus 6 weeks later. He was previously well and had visited remote indigenous communities in central Australia 1 year earlier.

Paralytic ileus was managed with intravenous fluids, nasogastric (NG) drainage, hydrocortisone, piperacillin/tazobactam, reduced azathioprine dose, and total parenteral nutrition. Laparotomy and loop ileostomy 2 weeks after

admission identified nonspecific abnormal ileal mucosa. He was transferred to our tertiary referral hospital 1 week later for mechanical ventilation, inotrope support, and antibiotic escalation for septic shock and respiratory failure. A centrally spreading abdominal purpuric macular rash was noted (Figure 1A). Further history identified a recent male sexual partner and negative human immunodeficiency virus 1 (HIV-1) serology 9 months earlier. Additional investigations identified *S. stercoralis* larvae in skin and ileal biopsy (Figure 1B) and bronchioalveolar lavage. No stool or ileal fluid was produced for larval analysis. Serology for HIV-1 Ag/Ab and hepatitis C virus (HCV) Ab was positive. HIV viral load was 115 million copies/mL, HIV-1 p24Ag 192 pg/mL, and CD4 340 mm<sup>-3</sup> (17%). Hepatitis C virus viral load was 32 million copies/mL, genotype 3. Serology for hepatitis B, syphilis, and HTLV-1 was negative. Eosinopenia persisted at 0.06 × 10<sup>9</sup>/L (0.4%).

Disseminated strongyloidiasis treatment was initiated with ivermectin (200 µg/kg) NG 12 mg/day and albendazole NG 800 mg/day. However, as the patient had a nonfunctioning ileum, family and jurisdictional consent was obtained to use the veterinary parenteral preparation of ivermectin (Ivomec™; Merial, Duluth, GA). Subcutaneous ivermectin 12 mg/day was coadministered with NG ivermectin and albendazole for 14 days (Figure 2A). Therapeutic efficacy was assessed by phase-contrast microscopy of daily endotracheal aspirates for larval motility. On days 5, 6, 10, 11, and 12 of ivermectin therapy, subcutaneous ivermectin was doubled to 24 mg/day in response to persistent larval motility (Figure 2A). During this period, the patient's course was complicated by acute kidney injury, requiring continuous venous hemodialysis; broncho-pleural fistulae; sepsis; *Clostridium difficile* colitis treated with metronidazole, vancomycin, and tigecycline; cytomegalovirus (CMV) viremia (19,500 copies/mL) treated with ganciclovir; and pancytopenia requiring blood transfusions. Daily serum samples collected for ivermectin levels were stored at –70°C and results were obtained on days 7, 14, and 21 of ivermectin therapy.

Subsequent clinical improvement was evidenced by withdrawal of inotropes and dialysis, a functioning ileostomy, spontaneous respiration with pressure support, and non-verbal communication, although muscle wasting was severe with flaccid atonia due to axonal degeneration identified on nerve conduction studies. Ten days after completing ivermectin treatment, cholestatic hepatitis developed with bilirubin 300 µmol/L (*N* < 25), ALP 500 U/L (*N* < 126), GGT 200 U/L (*N* < 50), normal AST, ALT, mildly prolonged INR 1.3 (*N* < 1.1),

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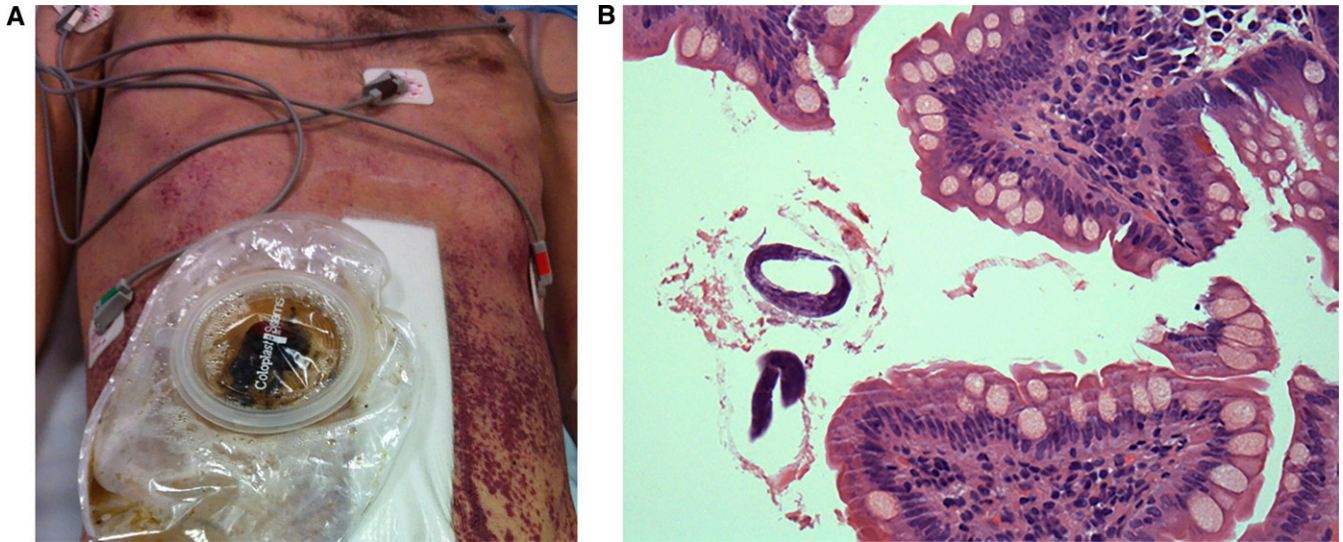


FIGURE 1. (A) Patient with ileostomy and purpuric macular abdominal rash characteristic of disseminated strongyloidiasis. (B) Ileal biopsy, magnification  $\times 400$ , haematoxylin and eosin stain (H&E) stain demonstrating rhabditiform *Strongyloides* larvae. This figure appears in color at [www.ajtmh.org](http://www.ajtmh.org).

and prothrombin time 16 seconds (*N* 12–15 seconds), and the patient succumbed to a catastrophic gastrointestinal hemorrhage. The patient’s family consented to a postmortem.

Autopsy performed 2 days after death identified marked wasting (body mass index [BMI] 13.3 kg/m<sup>2</sup>), jaundice, an abdominal ecchymotic rash, pulmonary oedema and hemorrhage, hepatosplenomegaly, and large bowel pseudomembranes. Microscopy revealed necrotic *Strongyloides* organisms with associated inflammation in the left ventricular myocardium, skin, and skeletal muscle. There was diffuse alveolar damage, a fungal pulmonary abscess, cholestatic jaundice, acute tubular necrosis with myoglobinuria, and pancreatic fibrosis. Neuropathologically, there was multifocal fungal cerebritis, non-specific microglial activation, and focal white matter necrosis. No intracerebral *Strongyloides* organisms were identified.

Serum collected during and after ivermectin treatment (Figure 2A) and 10 g of tissue from brain, kidney, muscle, skin, heart, spleen, lung, and liver, and omental fat collected at autopsy were stored at  $-70^{\circ}\text{C}$ . Plasma and tissue ivermectin concentrations were determined by reverse phase isocratic

high-performance liquid chromatography coupled with fluorescence detection (Waters Corporation, Milford, MA). Ivermectin was extracted from plasma (100  $\mu\text{L}$ ) or homogenized tissue (500 mg) with 100% methanol with doramectin internal standard. After centrifugation, air-dried deproteinized supernatants were derivatized with *N*-methylimidazole and trifluoroacetic anhydride. Ivermectin B1a was measured with a 4-point calibration curve with  $< 8\%$  inter-run imprecision.

Plasma ivermectin concentration reached 50  $\mu\text{g/L}$  on day 7 after doubling subcutaneous doses on days 5 and 6, and then increased to 140  $\mu\text{g/L}$  on day 12 after doubling subcutaneous doses on days 10, 11, and 12 (Figure 2A). Brain ivermectin concentration was  $< 1\%$  of that detected in fat (Figure 2B). Liver ivermectin concentration could not be determined because of unidentifiable assay interference, possibly bilirubin.

DISCUSSION

Islands of *Strongyloides* hyperendemicity exist in rural indigenous Australian communities<sup>10</sup> probably visited by this

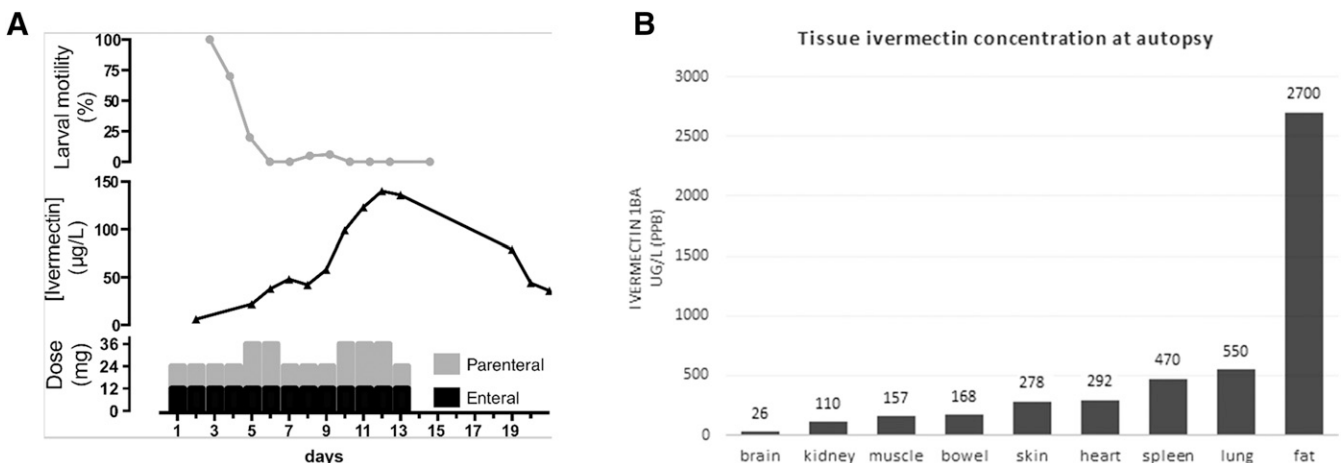


FIGURE 2. (A) Ivermectin treatment timeline demonstrating relationship between days of subcutaneous and nasogastric ivermectin doses, plasma ivermectin 1Ba concentration, and bronchial larval motility. (B) Postmortem tissue analysis of ivermectin 1Ba concentration.

patient. Men who have sex with men are also at increased risk of acquisition.<sup>11</sup> A combination of unrecognized exposure to *Strongyloides*, HIV, and HCV in preceding months; an initial, not uncommon, histological misdiagnosis of inflammatory bowel disease,<sup>12</sup> leading to further immunosuppression with corticosteroids; absence of eosinophilia and late recognition of a characteristic purpuric rash, all contributed to delayed diagnosis, secondary sepsis, and death. Screening for *Strongyloides* where exposure may have occurred recently or remotely in time or geographically, particularly if immunosuppressed, is an important consideration.

Ivermectin is highly lipophilic and protein bound, metabolized by hepatic CYP3A4, and excreted in feces with < 1% renal excretion.<sup>6,13</sup> Parasitocidal action is mediated by high affinity binding to glutamate-gated chloride channels in invertebrate nerve and muscle cells with less affinity for mammalian gamma-aminobutyric acid-gated chloride channels. Mammalian blood-brain barrier penetration is inhibited by P-glycoprotein.<sup>14</sup> It has a wide margin of safety with no adverse effects reported, with serum levels up to 260 ng/mL in healthy adult volunteers exposed to 1,000 µg/kg three times weekly and single doses up to 2,000 µg/kg.<sup>15</sup>

Serum ivermectin levels have been reported in eight cases of hyperinfection.<sup>7,8</sup> In this analysis, serum ivermectin concentration between 50 and 100 µg/L was larvicidal in the lung. The slow increase in serum concentration was also observed by others. In animal studies, the ivermectin formulation's solvent vehicle significantly affects its pharmacokinetics.<sup>16</sup> Ivermectin may be more slowly released from the nonaqueous formulation of Ivomec™ (60% propylene glycerol/40% glycerol). In addition, there may be a larger volume of distribution in hyperinfection because of hypoalbuminemia. As such, a loading dose may be beneficial while a target concentration in this condition is not yet established. In this analysis, a serum ivermectin concentration between 30 and 50 ng/mL correlated with abolition of bronchial larval motility. Postmortem tissue analysis confirmed that ivermectin is highly concentrated in fat but does not readily cross the blood-brain barrier in disseminated strongyloidiasis. Although axonal degeneration, myopathy, and biliary stasis may be attributable to ivermectin toxicity, levels in muscle were lower than those in other unaffected tissue and are more likely to be explained by severe sepsis.

## CONCLUSION

Disseminated *Strongyloides* infection is frequently fatal, particularly if diagnosis is delayed. Serum ivermectin analysis in this case supports the role of an initial loading dose in disseminated infection with blood-brain barrier protection even at high serum ivermectin concentration. Further human parenteral ivermectin pharmacokinetic data are needed.

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