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Short communication

Strongyloides disseminated infection successfully treated with parenteral ivermectin: case report with drug concentration measurements and review of the literature

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ABSTRACT

We report the case of an immunosuppressed patient with *Strongyloides* disseminated infection who was successfully treated with the veterinary parenteral form of ivermectin. A kidney transplant recipient developed disseminated infection with *Strongyloides stercoralis*. Because oral treatment with ivermectin was not possible, subcutaneous ivermectin (75 μg/kg/day, then 200 μg/kg/day) was given for 9 days, with clinical improvement and disappearance of all larvae. Serum ivermectin concentrations were between 15.6 ng/mL and 19.7 ng/mL during the 9 days of therapy; however, drug accumulation (plasma levels >40 ng/mL) 48 h after discontinuation of therapy was associated with the development with encephalopathy. We also review all cases of human disseminated *Strongyloides* infection treated with parenteral ivermectin.

1. Introduction

Strongyloidiasis, an intestinal infection caused by the nematode *Strongyloides stercoralis*, affects 30–100 million people yearly in the world, mostly in tropical and subtropical areas [1]. The autoinfection cycle allows the parasite to persist even in patients who have moved from endemic countries [2]. Immunosuppression can increase this autoinfection cycle, with a large number of larvae concomitantly present in several organs such as the lungs and gastrointestinal system (hyperinfection), or in unusual sites (disseminated infection) [3–6]. Ivermectin is the most effective treatment for immunocompetent and immunosuppressed patients [7] but is only available as an oral formulation for human treatment. We report the case of an immunosuppressed patient with *Strongyloides* disseminated infection who was successfully treated with the veterinary parenteral form of ivermectin.

2. Case report

A 56-year-old male on immunosuppressive therapy for 8 years following kidney transplantation was admitted to the intensive care unit of Erasme Hospital (Brussels, Belgium) for acute pancreatitis with septic shock. An abdominal computed tomography (CT) scan showed several abdominal collections that required surgical drainage and broad-spectrum antibiotic treatment. After initial improvement, the clinical status worsened, with intra-abdominal hypertension and respiratory failure. Because the patient was originally from Congo, and although he had arrived in Belgium 10 years earlier he still travelled frequently to Africa, parasites were specifically looked for in clinical specimens. Numerous filariform *S. stercoralis* larvae were found in his stools, respiratory specimens and abdominal fluid obtained from abdominal drains. As enteral treatment was not possible because of severe gastroparesis, the patient was given a subcutaneous veterinary formulation of parenteral ivermectin (Ecomectin®, 10 mg/mL; ECO Animal Health, New Malden, UK) at an initial dose of 75 μg/kg/day (6 mg). After 5 days the dose was increased to 200 μg/kg/day (16 mg) because of persistence of mobile larvae in abdominal fluid samples. Most larvae were poorly mobile by Day 7 and all were immobile by Day 9 of therapy. On Day 9 of therapy, ivermectin was discontinued because of acute encephalopathy, with increasing confusion, somnolence and ataxia, rapidly evolving to coma, which was considered to be a possible adverse drug event.

The patient did not present any other concomitant metabolic abnormalities; a cerebral CT scan showed no pathological findings. The patient's neurological status slowly improved with return to baseline condition within 10 days. All infected sites were free of parasites by Day 12 after the start of therapy. The patient

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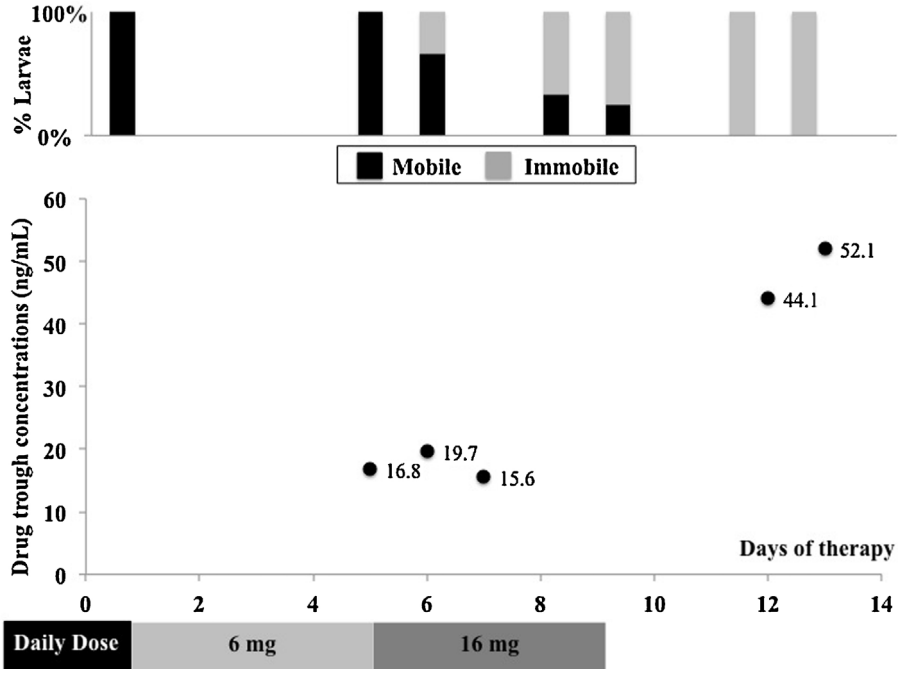

Fig. 1. Evolution of drug serum concentrations and presence and mobility of larvae over time.

died 1 month later from severe septic shock associated with extremely drug-resistant *Pseudomonas aeruginosa* infection. Post-mortem examination showed diffuse necrotic lesions in all organs but no parasite was eventually found.

Concomitant sequential trough serum samples for drug concentration analysis were performed on Days 5, 6, 7, 12 and 13 after the start of ivermectin therapy; all samples were taken at 08:00 h before any drug administration (when the therapy was ongoing), centrifuged and serum was stored at −80 °C until processing. Ivermectin concentrations were analysed 2 months thereafter using high-performance liquid chromatography (HPLC) by means of a modified assay with tandem mass spectrometric detection. The lower limit of quantitation for this method is 5 ng/mL. Serum concentrations during therapy ranged between 15.6 ng/mL and 19.7 ng/mL, but were >40 ng/mL within 4 days after therapy had been discontinued (Fig. 1).

3. Discussion

Hyperinfection and disseminated syndromes are dramatic and often life-threatening complications of *Strongyloides* infection in immunosuppressed patients. Mortality rates as high as 80% have been reported despite treatment [8]. Clinical manifestations of disseminated infection may be non-specific because larvae can invade any organ and hypereosinophilia is usually absent [9]. Diagnosis is made by detection of numerous larvae in faeces and body fluids (sputum, bronchial lavage, duodenal aspirate) [7,10]. Ivermectin mediates paralysis of the nematodes by increasing membrane permeability to chloride ions, with eventual cellular swelling. Importantly, ivermectin has been demonstrated to be the most effective and well-tolerated drug for the treatment of chronic strongyloidiasis [11,12], with a recommended dose of 200 μg/kg given orally once daily for 1–2 days [13]. Furthermore, in patients with hyperinfection syndrome or disseminated infection, ivermectin is still considered as the first-line agent, with longer courses of treatment (up to several weeks) indicated until microscopic clearance of larvae from all infected sites is documented [6,13].

In disseminated diseases, the bioavailability of ivermectin and therefore its efficacy is frequently compromised by the coexistence of paralytic or functional ileus and hence the unpredictable absorption of oral drugs [14]. However, a parenteral form of ivermectin is available only in veterinary medicine in which it is commonly used for routine antihelmintic treatment of livestock. As there are no licensed parenteral antihelmintic drugs for human use, this veterinary formulation has been used in life-threatening human infections [15]. Use of the intravenous route has been reported in only one patient, who eventually died with persistence of active larvae, but no information about the daily dose or the total number of administrations was provided. In all the other reports, including the present case, patients were treated with subcutaneous injections of ivermectin. Importantly, we used an initial dose of 75 μg/kg of ivermectin, as scarce data on the safety of subcutaneous administration are available. The characteristics of these patients are summarised in Table 1. Doses ranged from 75 μg/kg to 200 μg/kg given daily or up to every 72 h. Only 8 of the 17 patients survived, although parasitic eradication was also obtained among 4 of the non-survivors. The most frequent side effects were encephalopathy or seizures (three patients), pain at the site of injection (two patients) and increased liver enzyme levels (two patients; alanine aminotransferase was reported to increase up to 84 U/L and γ-glutamyl transferase presented a 6-fold increase). Serum or plasma concentrations of ivermectin were determined in six patients treated with a dose of 200 μg/kg given once daily in five patients and every 2 days in one patient; the reported concentrations ranged from 2 ng/mL to 99.8 ng/mL.

In the patient described here, serum concentrations were <20 ng/mL during therapy, with trough serum concentrations similar to those observed in healthy volunteers; after a single 12 mg oral dose, the peak plasma concentrations in healthy volunteers ranged from 13.9 ng/mL to 101.1 ng/mL [26]. In this patient, higher concentrations were found 3 days and 4 days after drug discontinuation, a finding also reported by other authors [27,28] and related to the depot effect from subcutaneous administration and prolonged release.