CASE REPORT: NITAZOXANIDE TREATMENT FAILURE IN CHRONIC ISOSPORIASIS

RALF BIALEK, DIETRICH OVERKAMP, INGO RETTIG, AND JÜRGEN KNOBLOCH

Institute for Tropical Medicine and Department of Medicine, Division IV Endocrinology, University Hospital Tübingen, Tübingen, Germany

Abstract. We report a 60-year-old immunocompetent patient with chronic biliary isosporiasis who failed to respond to orally administered cotrimoxazole prophylaxis and orally administered treatment with nitazoxanide, a 5-nitrothiazole benzamide compound. Severe malabsorption was regarded as responsible for the subtherapeutic levels of nitazoxanide in plasma and bile, resulting in treatment failure. Intravenously administered cotrimoxazole stopped the shedding of Isospora belli oocysts in bile within 5 days, excluding initially suspected resistance to cotrimoxazole. Patients with malabsorption and cholangitis due to Coccidia such as Isospora belli and Cryptosporidium spp. or due to protozoa that cause microsporidiasis seem to be predisposed to fail to respond to otherwise effective treatment.

INTRODUCTION

Nitazoxanide, a 5-nitrothiazole benzamide compound, is reported to be effective against a variety of parasites, including Isospora belli, and especially in otherwise untreatable infections with microspora and coccidia in patients with human immunodeficiency virus (HIV).1-4 Fascioliasis has been successfully treated with this compound, suggesting therapeutic drug levels in the bile, which have not been determined in humans so far.5

CASE REPORT

A 60-year-old Greek man reported that he used to work as a shepherd in Greece before emigrating to Germany in 1970. In 1974, he underwent cholecystectomy because of symptomatic gallstones. Later, a destructive cholangitis due to fascioliasis was diagnosed and repeatedly treated with praziquantel. In 1991, Isospora belli oocysts were found in bile gained by endoscopic retrograde cholangiopancreatography. A course of cotrimoxazole was given and repeated either orally or intravenously several times in the next few years because of recurrent isosporiasis, defined as diarrhea and excretion of I. belli oocysts in the stool.

We found I. belli in duodenal aspirates and bile in 1996, when specimens of this patient were sent to our laboratory for the first time. According to the patient’s file, he was treated with intravenously administered cotrimoxazole for 7 days, then discharged on orally administered treatment for another 3 months, followed by orally administered cotrimoxazole for 5 days every month. Prophylaxis has been shown to be effective in HIV-infected patients with isosporiasis.6

In February 1998, the patient was admitted with severe diarrhea, a 10-kg loss of weight despite 3.6 g cotrimoxazole orally per day, typical signs of vitamin A and D deficiencies, and an eosinophilia of 18% (1,250/µL). Malabsorption was indicated by pathological results of xylose and lactose absorption assays. Endoscopy disclosed a destructive cholangitis. A severe villous atrophy and oocysts of I. belli were demonstrated in small-bowel biopsies. A nasobiliary tube was placed in his right ductus hepaticus. Coccidial oocysts were found in the bile by microscopy. A resistance to cotrimoxazole was suspected, and after informed consent was obtained from the patient, nitazoxanide was started with 2 × 1 g per day (compassionate use program by Romark Laboratories, Tampa, FL). Plasma and bile samples obtained at 16 hr before, at the time of treatment, and 1, 2, 4, 8, and 12 hr after orally administered treatment were analyzed by chromatography (Dr. Stockis, Bio-Pharma S.A., Wavre, Belgium). In all 7 plasma and corresponding bile samples, the concentration of nitazoxanide was below the limit of detection (0.05 µg/mL). The active metabolite desacetyl-nitazoxanide peaked at 3.2 µg/mL in plasma at 1 hr and at 0.1 µg/mL in the bile 2 hr after treatment, declining to 0.12 µg/mL and to undetectable levels at 8 hr after treatment, respectively.

Despite clinical improvement within 24 hr and despite treatment with nitazoxanide, I. belli oocysts were continuously shed in the bile, as identified in bile recovered from the nasobiliary tube and controlled daily for the next 15 days. The concentration of eosinophils peaked at 47% (4,800/µL). After adding cotrimoxazole 120 mg/kg tid to the treatment, the excretion of oocysts in the bile stopped within 5 days. The patient was discharged after 14 days of intravenous treatment, with a weight gain of 7 kg. The eosinophil count dropped to 985/µL, and the patient remained asymptomatic for the next 3 months under our observation.

DISCUSSION

Extraintestinal isosporiasis has been demonstrated only in immunocompromised patients, but no immunodeficiency could be found in our patient. He never experienced any infection other than the reported fascioliasis and the proven chronic isosporiasis. The damaged biliary tree might have been permissive for the invasion of I. belli. Biopsies of the bile ducts to demonstrate intraendothelial growth were unavailable, but the constant detection in bile drained by a tube placed in the right ductus hepaticus is highly suggestive of extraintestinal replication of this protozoon. We concluded that the villous atrophy with malabsorption caused the failure of nitazoxanide treatment, leading to only subtherapeutic drug levels in plasma and bile. Therefore, we changed to an intravenously administered cotrimoxazole instead of trying another recommended orally administered treatment with pyrimethamine.7 Nitazoxanide is not available for intravenous administration.

The parasite elimination after starting intravenous treatment and the failure of orally administered cotrimoxazole before admittance further support our hypothesis of malabsorption and excludes cotrimoxazole resistance. High con-
centrations of cotrimoxazole in the bile can be achieved by intravenous application and after successful absorption of orally administered medication.

Cholangitis and malabsorption occur in patients with acquired immune deficiency syndrome with cryptosporidiosis and microsporidiosis. According to our observation, these patients might be predisposed to treatment failure with orally administered nitazoxanide.

In conclusion, we recommend intravenously administered cotrimoxazole in patients with isosporiasis and malabsorption who fail to respond to orally administered therapy.

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Authors’ addresses: Ralf Bialek and Jürgen Knobloch, Institut für Tropenmedizin, Universitätsklinikum Tübingen, Keplerstraße 15, D-72074 Tübingen, Germany. Dietrich Overkamp and Ingo Rettig, Medizinische Universitätsklinik, Otfried-Müller-Straße 10, D-72076 Tübingen, Germany.

Reprint requests: Ralf Bialek, Institut für Tropenmedizin, Universitätsklinikum Tübingen, Keplerstraße 15, D-72074 Tübingen, Germany, Telephone: +49-7071-2982367, Fax: +49-7071-295267, e-mail: ralf.bialek@med.uni-tuebingen.de.

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