phism is accumulating more rapidly than simple nucleotide variation. Also, restricted allelic diversity means that it is probable that only nominal amino acid variation will occur in proteins that are of potential immunoprophylaxis or virulence interest. To gain further insight into the molecular evolutionary genetics of *M. tuberculosis*, it will be necessary to determine the level of sequence variation present in the other closely allied members of the *M. tuberculosis* complex (*M. bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*) and the related slowly growing pathogen *Mycobacterium leprae*, for which there is a report of limited chromosomal diversity based on restriction endonuclease analysis [14].

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Effectiveness of Aminosidine (Paromomycin) Sulfate in Chronic *Cryptosporidium* Diarrhea in AIDS Patients: An Open, Uncontrolled, Prospective Clinical Trial

Colleagues—All treatments for cryptosporidial diarrhea to date have given poor results, including the use of antidiarrheal, antimicrobial, antiparasitic, and immunomodulatory compounds. By contrast, aminosidine (paromomycin), a non–orally absorbable aminoglycoside antibiotic, was shown to be effective in vitro at concentrations achievable in the bowel [1, 2] as well as in experimentally infected animals [3]. Data from various patient series and noncomparative trials have indicated that symptomatic benefits and suppression of parasite growth are associated with the use of oral aminosidine [1, 4–10].

Various aminoglycoside antibiotics belonging to the catenulin group were marketed in the late 1950s and originally thought to be separate entities. The identity of those compounds was clarified later. Oral formulations of aminosidine (paromomycin) are available with different trade names, but the source of the raw material is the same. Therefore, although referred to by either name in the various publications, paromomycin and aminosidine are synonymous.

On the basis of encouraging preliminary results and of the availability of comprehensive information on the tolerability of oral aminosidine for treating intestinal protozoan and helminth infections, we set up a prospective, uncontrolled trial in human immunodeficiency virus–infected patients with chronic cryptosporidial diarrhea.

Forty-one AIDS patients met the eligibility criteria (chronic diarrhea caused by *Cryptosporidium parvum*, three or more bowel movements per day, lasting for at least 1 month) and received aminosidine (Gabbroral; Farmitalia Carlo Erba, Milan) at 2000 mg for 4 weeks and at 1000 mg for the subsequent 4 weeks. No concomitant antidiarrheal or antiviral therapies were allowed. Mean age was 31.2 years; most patients were male (n = 32) and intravenous drug users (n = 28). CD4 cell counts averaged 39.3/mm^3 (range, 4–208) at baseline and remained unchanged during treatment.

This study was conducted when P.O. was employed at Farmitalia Carlo Erba, Research & Development Antiinfectives, Milan; no financial support was received for the study, but aminosidine was provided by Farmitalia Carlo Erba under compassionate plea.

Informed consent was obtained for all patients.

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At the start of aminosidine treatment, 11 patients had concomitant extraintestinal opportunistic infections, including *Pneumocystis carinii* pneumonia, atypical disseminated mycobacteriosis, neurotoxoplasmosis, cerebral abscess, and bacterial pneumonia; 3 had a concomitant intestinal parasitic infection (entamebiasis, giardiasis, trichocephalosis) and 4 had gastrointestinal bacterial infections (i.e., due to *Helicobacter pylori*, *Proteus* species, *Clostridium difficile*, nontuberculous mycobacteria).

Thirty-five patients were deemed evaluatable for efficacy, and 22 (62.8%) completed the 8-week treatment course. The clinical and parasitologic status improved dramatically in most patients (table 1).

With the initial dose, a complete response to therapy (parasitologic plus clinical) was achieved in 7 (20%) of the 35 patients in 7–28 days. The result was confirmed by duodenal biopsy and remained consistently negative in 3 patients at 12 weeks of follow-up. Of the remaining 4 patients, 2 relapsed parasitologically and clinically after treatment discontinuation, and 2 recrudesced when the dosage was reduced to 1000 mg/day.

An additional 15 patients (42.8%) had a partial response, 3 patients died, and 10 (28.5%) did not respond to the aminosidine treatment (4 worsened, 6 showed inadequate response). Of the latter, 2 had extraintestinal *C. parvum* infection. In no case was death or treatment interruption attributed to the use of aminosidine.

When the aminosidine dosage was reduced to 1000 mg/day, symptoms gradually reappeared or increased in 9 of the 15 partial responders and in 2 complete responders. Resumption of the original dosage (2000 mg/day) in recrudescent patients for 28–42 days (mean, 31.6) restored the previous clinical status and reduced the number of oocysts in the stools of 9 of the 17 patients. In the case of treatment failure, the addition of symptomatic antidiarrheals (loperamide, octreotide) did not lead to any substantial improvement.

Concomitant intestinal parasitic infections were also definitively cured.

All responders had significantly better baseline conditions than those who did not respond to therapy: CD4 cell counts $>150/mm^3$, mean of four or fewer bowel movements/day, ≤ 5 oocysts/microscopic field $\times$ 1000.

Treatment was well tolerated: 6 patients reported transient constipation on the higher dosage. No significant change was observed in the clinical laboratory parameters.

Like prior studies, the present trial has limitations due to the open, uncontrolled nature of the trial and the relatively small size. However, the results indicate a role for aminosidine in cryptosporidial diarrhea and are substantiated by a randomized, placebo-controlled study [8].

Consistent with findings in other patients, administration of aminosidine was associated in most patients with suppression of parasite growth rather than killing, and the effect was dose-related. Some patients with less advanced disease and lower parasite load were definitively cured, thus indicating the advantage of early diagnosis and intervention and suggesting a possible preventive role of aminosidine for cryptosporidiosis [3]. Moreover, the broad spectrum of activity, encompassing protozoa and helminths, makes aminosidine a drug of potential interest for wide coverage of noninvasive intestinal parasitic infections in immunocompromised patients.

Table 1. Change from baseline in parasitologic and clinical parameters in patients receiving aminosidine therapy.

Parameter	No. (%) of patients who		
	Worsened	Remained constant	Improved
Bowel movements*	6 (17.2)	3 (8.6)	26 (74.2)
Consistency of stool	6 (17.2)	6 (17.2)	23 (65.5)
Volume of stools	6 (17.2)	5 (14.2)	24 (68.6)
No. of oocysts†	3 (8.5)	8 (22.9)	24 (68.6)
Body weight	8 (22.9)	9 (25.7)	18 (51.4)
Abdominal pain	8 (22.9)	9 (27.7)	18 (51.4)
Nausea or vomiting	5 (14.2)	8 (22.9)	22 (62.9)

* Ten patients had normal bowel movements after a mean of 5.3 days of therapy (range, 3–18); 6 reported constipation (one movement every second or third day) after a mean of 6.1 (5–16) days of treatment with 2 g/day.

† Mean/10 microscopic fields $\times$ 1000 (modified Ziehl-Nielsen staining). Ten patients cleared oocysts after a mean of 18.6 days of therapy; complete parasitologic cure was confirmed in 3 by duodenal biopsy at 12 weeks of follow-up.

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