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Nitazoxanide Treatment of *Cryptosporidium parvum* in Human Immunodeficiency Virus-Infected Children

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To the Editors:

C*ryptosporidium parvum* is a significant cause of diarrhea and wasting in human immunodeficiency virus (HIV)-infected individuals.[1] Chronic cryptosporidiosis represents a common, serious problem in less developed countries, particularly among HIV-infected children. Several studies showed the prevalence of cryptosporidiosis in African countries and Thailand to range from 6% to 25.6%.[2–3] Whereas nitazoxanide (NTZ) is the drug of choice for immunocompetent individuals with diarrhea caused by *C. parvum*, it is not approved for HIV-infected patients. NTZ and its metabolites have a wide range of activity against protozoal infections, including *C. parvum*.[4]

A randomized double-blind placebo-controlled trial of NTZ was conducted in Zambian children, 12 to 36 months of age, with *C. parvum* diarrhea. Children were randomized to receive NTZ (100 mg twice daily orally for 3 days) or placebo. Three days of NTZ treatment significantly improved resolution of diarrhea, parasitologic response, and mortality in non–HIV-infected children. HIV-infected children did not benefit from 3 days of treatment, but after 3 more days of open-label treatment, 77% showed clinical responses. The trial suggested that HIV-infected children may benefit from longer courses of therapy.[5]

The Pediatric AIDS Clinical Trials Group 369 protocol, a collaborative study to determine the pharmacokinetic profile of oral NTZ in HIV-infected children with *C. parvum* diarrhea, terminated early because of slow accrual. Six subjects enrolled, but pharmacokinetic results were available for 3 subjects. The 3 subjects (6 months to 3 years of age) received NTZ 22.5 mg/kg every 12 hours for 56 days. Pharmacokinetic samples were collected on day 7 and predose pharmacokinetic samples were collected on days 14, 28, and 56 to assess drug accumulation. Samples were analyzed for nitazoxanide metabolites, tizoxanide (TZ) and tizoxanide-glucuronide (TZG).

Our study demonstrated significant variability in TZ exposure with the range of area under the curves (AUCs) from 2.29 to 31.53 mcg*h/mL. These values were significantly lower than the AUC of 144 mcg*h/mL reported in adults following 1000 mg, but consistent with reduced concentrations reported in HIV patients. The observed TZ maximum concentrations (C_{max}: 1.04–5.86 mcg/mL), were less variable than AUCs. These values were also lower than the C_{max} of 14 mcg/mL seen in adults and below the reported inhibition concentration for intracellular replicating cryptosporidia in vitro.[4] The TZG AUC ranged from 30.20 to 68.52 mcg*h/mL.

Although the study terminated early, pharmacokinetic analysis of 3 subjects suggests the dosage of NTZ used may not be as sufficient as the doses used in adults. The approved dose for NTZ for the treatment of diarrhea caused by *C. parvum* in immunocompetent children from 1 to 3 years of age is 100 mg every 12 hours. Because the dosages used in our study

were weight based and were higher at 22.5 mg/kg every 12 hours, the effective dosage would probably be much higher than that approved for non–HIV-infected children. While NTZ treatment may be considered in HIV-infected children with *C. parvum* diarrhea, the dosage required for children should be further investigated as a larger dosage will likely be needed to achieve the adult AUC values.

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