Anticryptosporidial Activity of Sulfadimethoxine

Cryptosporidiosis, caused by the protozoan Cryptosporidium sp., is recognized as a significant enteric disease in animals and humans (11). In immunocompetent hosts, the disease is usually self-limiting (2), whereas in hosts with compromised immunity, it can have a protracted course with symptoms and oocyst shedding continuing for several weeks after initial infection (2, 9). Symptoms include diarrhea, abdominal pain, vomiting, and weight loss. Therapy for cryptosporidial infections has been generally unsatisfactory (5, 8, 12). We present evidence that sulfadimethoxine has prophylactic anticryptosporidial activity in an immunosuppressed-rat model.

A dexamethasone-treated-rat model for cryptosporidiosis (J. E. Rehg, M. Hancock, and D. Woodmansee, J. Infect. Dis., in press) was used to evaluate antiprotozoan compounds for anticryptosporidial activity. After determining the daily water consumption for female Sprague-Dawley rats (200 to 250 g [body weight]), we gave dexamethasone (0.25 mg/kg [body weight] per day) in the drinking water to groups of 16 rats for 10 days before inoculating them with 10⁶ bovine Cryptosporidium parvum oocysts. The animals continued to receive dexamethasone for 11 days after oocyst inoculation; on day 10 they began to receive antiprotozoan test compounds, which were administered in the drinking water or feed for 11 days. The weights of the animals and the weights of the food and the volumes of drinking water they consumed were measured every other day to ensure that the animals received the drug doses planned. All of the test compounds were consumed at the anticipated rates.

After 11 days of test-drug treatment, the animals were sacrificed. Immediately following death, the terminal 2 cm of ileum was fixed in 10% neutral buffered Formalin for histologic evaluation. After 24 h of fixation, ileal specimens were embedded in paraffin, sectioned at 4 µm parallel to the longitudinal axis of the ileal lumen, and stained with hematoxylin and eosin.

The terminal 2 cm of the ileum, previously shown to be the intestinal section most heavily infected with cryptosporidia (Rehg et al., J. Infect. Dis., in press), was used to assess the severity of infection in both control and drug-treated animals. The severity of ileal infections, expressed as the mean number of cryptosporidia per villus, was determined by microscopic examination of hematoxylin-and-eosin-stained ileal sections and enumeration of the cryptosporidia, in various developmental stages, that were attached to the microvillous portion of the enterocytes of 10 ileal villi.

The anticryptosporidial activities of seven compounds were assessed by comparing the severities of infection in controls and drug-treated animals. In our initial drug screen, sulfadimethoxine (120 mg/kg per day) was the only drug that had significant anticryptosporidial activity compared with controls. Subsequently, a test of four doses (80, 40, 20, and 10 mg/kg per day) was conducted to determine the minimal effective dose for anticryptosporidial activity. Each treatment group consisted of 13 animals. Sulfadimethoxine anticryptosporidial activity at the three higher doses, but not at 10 mg/kg per day, was statistically different from controls (Table 1). Although there were mild reductions in the villi: crypt ratio in some animals, there was no statistically significant difference in this ratio between the drug-treated and control groups. Both the sulfadimethoxine-treated rats and the dexamethasone-treated controls that died during the experiment had similar visceral lesions. The animals had one or more of the following lesions: multifocal pulmonary consolidations, renal abscesses, and focal ulcers in the cecum and colon.

Although sulfadimethoxine did not completely eradicate the infection, it was highly effective in reducing the severity of cryptosporidial infection in immunosuppressed rats. The very mild infection observed in drug-treated animals may have been associated with reinfection from the environment. Another possibility is that 11 days of drug therapy may be inadequate to eradicate infection. Others suggest that sulfonamides need to be administered longer than 7 to 10 days to be curative for Isospora bellii infection, especially in immunocompromised patients; otherwise, clinical disease may recur (3, 10, 13).

Adverse reactions, such as erythema multiforme and toxic epidermal necrolysis, have been associated with sulfadimethoxine therapy in humans. Consequently, the drug may have limited application in humans with clinical cryptosporidiosis. However, the evaluation of other sulfonamides for anticryptosporidial activity should be pursued, since a variety of sulfa drugs are known to have activity against one or more of the coccidians Toxoplasma, Eimeria, and Isospora species (4, 6, 7, 13).

Although sulfadimethoxine use against cryptosporidiosis in humans may be limited, field trials to evaluate its effectiveness against clinical disease in animals may be warranted, since no effective drugs are available for treatment of cryptosporidiosis.

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| TABLE 1. Comparison of different doses of sulfadimethoxine for anticryptosporidial activity |
| Dose (mg/kg per day) | No. of animalsa | No. of cryptosporidia/villus |
| | | Median | Range |
| None (control)b | 11 | 24.8 | 0–66.2 |
| 80 | 11 | 0.1c | 0–25.3 |
| 40 | 13 | 1.0d | 0–30.6 |
| 20 | 13 | 1.2d | 0–28.9 |
| 10 | 12 | 3.4 | 1.8–10.7 |

* Each group initially contained 13 animals.

* This group consisted of oocyst-inoculated, dexamethasone-treated rats that did not receive sulfadimethoxine in the drinking water.

* Differences significantly from control (alpha = 0.01; Kruskal-Wallis test [1]).

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LITERATURE CITED

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