9 Current therapeutic approaches to cryptosporidiosis

9.1 Introduction

9.1.1 Infection by Cryptosporidium parvum causes self-limiting gastroenteritis of approximately two weeks duration in immunocompetent hosts. After an incubation period of 7-10 days the patient presents with watery diarrhoea, nausea and vomiting and abdominal pain in about 50% of cases. In a minority (36%) there is a febrile illness (Fayer and Ungar 1986). In immunosuppressed hosts, such as patients with AIDS and CD4 counts of ≤ 200 x 106/L, the disease is much more severe (Current and Garcia 1991; Flanigan et al 1992). The patients usually develop severe malabsorption and most patients with AIDS never clear the infection. Although asymptomatic infection of such patients has been documented, more than half develop a chronic illness, and about 10% develop fulminant disease (Blanshard et al 1992).

9.1.2 Specific treatment for cryptosporidial gastroenteritis is generally not needed for immunocompetent patients, but such therapy would potentially benefit immunosuppressed patients or those developing a febrile illness. At present there is no accepted specific therapy for cryptosporidiosis.

9.2 Pathogenesis

9.2.1 Infection is initiated by ingestion of the oocyst with subsequent excystation and release of sporozoites upon exposure to bile salts, although spontaneous excystation can occur. It is found primarily in the small bowel and is located at the luminal surface of the epithelial cells or occasionally just within the brush border of the intestinal epithelium (Clayton et al 1994).

9.2.2 Both cellular and humeral immunity play a role in infection. In adult BALB/c mice it has been shown that both CD4 + lymphocytes and interferon-γ are required to prevent initiation of infection, while CD4 cells also can limit duration and interferon-γ limits intensity (Ungar et al 1991; Chen et al. 1993). Experiments have shown that both colchicine and vinblastine inhibit C. parvum infection in a concentration dependent manner, which suggests that microtubules are important in host-cell invasion and may represent targets for development of new therapeutic drugs (Wiest et al 1993).

9.3 Cell cultures and animal models

9.3.1 Cell cultures and animal models have been widely used to identify pathophysioligic mechanisms involved in human cryptosporidiosis and to screen candidate therapeutic agents (Woods et al 1996). In vitro, permissive cell lines provide useful models for the study of their interactions with the parasite, their regulatory consequences such as mediator secretion and the influence of other systems such as cells and mediators of the immune compartment. Ex vivo systems (for instance isolated ileum) provide useful clues to the understanding of alterations of
electrolyte secretions by intestinal mucosa infected with *C. parvum*. In rodent (mouse and rat) models of cryptosporidiosis, the role of immune response in the control of the infection has been established, although differences with human illness (such as the absence of diarrhoea) preclude direct comparisons. Screening of potential anti-cryptosporidial agents performed *in vitro* using enterocytic lines (HCT-8 or Caco-2) needs to be confirmed in rodent models which involve pharmacokinetics characteristics. Moreover, these models of intestinal, biliary or respiratory cryptosporidiosis mimic histological, but not functional alterations of human cryptosporidiosis. In this context, models of goat or calf cryptosporidiosis may provide a better approach for pathophysiologic and pharmacologic studies.

### 9.4 Therapy

#### 9.4.1 Therapy

Therapy can be either non-specific (for example fluid replacement) or specific (the addition of an antiprotozoal agent). The majority of cryptosporidial infections in immunocompetent patients are self-limiting and usually resolve spontaneously. However, there are exceptions which require the maintenance of fluid balance and such treatment for cryptosporidiosis as is currently available. The majority of immunocompromised patients (for example those with AIDS) have severe chronic diarrhoea and debilitating illness which will require specific drug therapy.

#### 9.4.2 Although more than 95 compounds have been tested in patients with cryptosporidiosis, only a very limited number have been shown to have activity against *Cryptosporidium parvum*; these agents are usually suppressive rather than curative. Antiprotozoal agents with some clinical efficacy are described below.

- **Albendazole** – high dose albendazole (800 mg) twice daily for two weeks has been reported to improve symptoms and eradicate the parasite in four Zambian AIDS patients (Kelly *et al* 1998). This is a preliminary study and requires confirmation by larger controlled trials;

- **Azithromycin** – the first of the azalide antibiotics, has demonstrated good effectiveness to date in immunocompetent animal models of cryptosporidiosis. It also has shown modest activity at a dosage of 600 mg/d in HIV-positive patients who have active cryptosporidial infection, and a rapid clinical and parasitologic cure at a dosage of 1200 mg/d in an immunocompetent patient (Bessette and Amsden 1995).

- **Diclazuril** – a benzeneacetonitrile derivative which is used as an anticoccidial agent in poultry. Its use was associated with anecdotal reports of subjective improvement, but eventually proved ineffective when tested in controlled studies.

- **Letrazuril** – a diclazuril analogue with enhanced bioavailability, has been shown to be somewhat effective but many patients experienced adverse reactions. Development of the drug has ceased and it is no longer available.
Nitazoxanide – a 5-nitrothiazole derivative which has broad anti-parasitic spectrum which includes coccida and flagellate protozoa, amoeba, nematodes, cestodes and trematodes. In a preliminary open study in AIDS patients in Mali, nitazoxanide (500 mg) twice daily for seven days eradicated or produced a >90% reduction in *C. parvum* oocyst excretion in 7 of 12 patients with cryptosporidiosis and stage IV AIDS (Doumba *et al.*, 1997). Further studies are underway to confirm the efficacy of this drug against cryptosporidiosis.

Octreotide – a somatostatin synthetic analogue that inhibits secretory diarrhoea, has been associated only with symptomatic improvement, not parasitic cure.

Paromomycin – a non-absorbable, oligosaccharide aminoglycoside, has demonstrated symptomatic improvement, and possible parasitological cure in a small series of patients, but patients required maintenance therapy to prevent relapse (see paragraph 9.4.4 below).

Spiramycin – a macrolide antibiotic that has been used for various types of infections in Europe for the past 20 years, had anecdotal reports of putative cure or symptomatic improvement in enteric cryptosporidiosis patients by 1983, but controlled clinical trials in patients infected with HIV demonstrated poor efficacy of both oral and intravenous formulations.

9.4.3 Only paromomycin and, to a lesser extent, azithromycin have shown some benefit for patients. Paromomycin has been shown to have an anti-cryptosporidial effect in *in vitro* assays (Datry *et al* 1992; Marshall and Flanigan 1992), animal models (Fayer and Ellis 1993a,b, Regh 1994, Tzipori *et al* 1994, Verdon *et al* 1994), and uncontrolled clinical evaluations (Armitage *et al* 1992; Bissuel *et al* 1991; Fichtenbaum *et al* 1993; Gathe *et al* 1990). Paromomycin in a dose of 25 to 35 mg/kg/day has a beneficial but limited effect upon oocyst shedding and stool frequency in AIDS patients (White *et al* 1994). Paromomycin is probably the most promising compound for human treatment.

9.4.4 In the dexamethasone-treated rat model of cryptosporidiosis paromomycin has been shown to be effective at a dosage of 50mg/kg/day or more for ileal infection, and 200mg/kg/day or more for caecal infection. The effect was thus shown to differ according to the anatomical site of the infection. At one and three weeks after treatment, a persistent infection was demonstrated in all rats, indicating that no eradication of the parasite could be observed even when high-dosage regimens up to 400mg/kg/day were used (Verdon *et al* 1995). These results confirm the anti-cryptosporidial activity of paromomycin and underscore the limitations of this compound because of its potential toxicity at such high dosages and its inability to eradicate the infection. They suggest that only a beneficial effect on symptoms rather than a clearing of the infection may be expected from increasing the dose in humans. This was borne out in a prospective trial for cryptosporidiosis in forty four severely immunocompromised individuals with HIV-related cryptosporidiosis. Although almost half of all patients had a clear clinical response, only 4 (9%) had resolution of diarrhoea and clearance of oocysts. Paromomycin often resulted in symptomatic improvement, but rarely ‘cured’ infection (Flanigan *et al* 1996).
9.4.5 Azithromycin was active in the dexamethasone-treated rat model (Regh 1991), but few data for human patients are available (Vargas et al 1993). However, azithromycin treatment of four children with AIDS who had severe diarrhoeal illnesses in which Cryptosporidium parvum was the sole pathogen detected was reported recently to be favourable (Hicks et al 1996). Three of these children had a marked decrease in stool volume and frequency within 36 hours of initiating therapy and resolution of diarrhoea within five days; Cryptosporidium became undetectable on examination of stool or colonic biopsy or by both after therapy was discontinued. A fourth patient however required prolonged therapy with azithromycin to achieve clearance.

9.4.6 Other chemical compounds have been shown to reduce the intensity of the infection by C. parvum in animal models, but such agents are not available for use in humans (Brasseur et al 1993).

9.4.7 Immunotherapy. Preliminary data suggest that administration of hyperimmune colostrum can decrease diarrhoea and may in some instances result in oocyst eradication (Tzipori et al 1986; Greenberg & Cello, 1996). Further trials are required to confirm efficacy and wider applicability to the treatment of cryptosporidiosis.

9.5 Prevention of recurrence

9.5.1 While primary exposure frequently results in proven infection and symptomatic disease in healthy immunocompetent adults previously seronegative for C.parvum (DuPont et al 1995), the resulting susceptibility to reinfection and illness is unknown. Although seroconversion may occur, the C.parvum serum antibody response does not appear to correlate with the presence or absence of infection (Okhuysen et al 1998). Epidemiological data obtained for Brazilian children suggest that primary infection with C.parvum does not completely block reinfection upon subsequent exposure (Newman et al 1994) but may protect the host against clinical illness (Current and Bick 1989). However, in these studies, recurrent infections were described in healthy adults and in high risk populations in areas with high seroprevalence for the disease, suggesting that repeated infection may result in clinical disease. In immunocompromised patients the protective nature of the antibodies to Cryptosporidium that may still be present, remains uncertain. No drug regimens are known to be effective in preventing the recurrence of cryptosporidiosis.

9.6 Overall conclusion

9.6.1 No antimicrobial agent has yet proved curative in adequate randomised double-blind controlled trials. However, there have been a number of encouraging reports on the use of paromomycin, and albendazole and nitazoxanide may have some clinical use in cryptosporidiosis. A number of other agents including azithromycin, have shown some limited therapeutic effect. No drug regimens are known to be effective in preventing the recurrence of cryptosporidiosis.

Recommendation

9.6.2 The Department of Health should continue to keep work in progress under review and encourage further controlled trials of new agents as they become available.
References


