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Treatment of diarrhoea in human immunodeficiency virus-infected patients with immunoglobulins from bovine colostrum

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Summary. Diarrhoea and weight loss are found in more than 50% of patients with the acquired immunodeficiency syndrome (AIDS). In some patients the symptoms can be very severe, leading to death even in the absence of opportunistic infections. In 30% of these patients, enteric pathogens cannot be identified, and approximately only half of the identifiable aetiologic agents of diarrhoea in patients infected with the human immunodeficiency virus (HIV) were treatable with antibiotics. Immunoglobulins from bovine colostrum (Lactobin, Biotest, Dreieich, FRG) contain high titers of antibodies against a wide range of bacterial, viral and protozoal pathogens as well as against various bacterial toxins. Lactobin (LIG) is quite resistant to 24-h incubation with gastric juice. In a multi-center pilot study 37 immunodeficiency patients with chronic diarrhoea [29 HIV-infected patients, 2 patients with common variable immunodeficiency (CVID), one unidentified immunodeficiency, five patients with graft versus host disease (GvHD) following bone marrow transplantation] were treated with oral LIG (10 g/day for 10 days). Good therapeutic effects were observed. Out of 31 treatment periods in 29 HIV-infected patients 21 gave good results leading to transient (10 days) or long-lasting (more than 4 weeks) normalisation of the stool frequency. The mean daily stool frequency decreased from 7.4 to 2.2 at the end of the treatment. Eight HIV-infected patients showed no response. The diarrhoea recurred in 12 patients within 4 weeks (32.4%), while 19 patients were free of diarrhoea for at least 4 weeks (51.3%). In 5 patients intestinal cryptosporidiosis disappeared following oral LIG treatment. LIG treatment was also beneficial in 4 out of 5 GvHD patients. No serious side effects were recorded in any of the treated patients.

Key words: Diarrhoea – Colostrum-acquired immunodeficiency syndrome – Human immunodeficiency virus – Cryptosporidiosis

Abbreviations: AIDS = acquired immunodeficiency syndrome; ALL/3 = acute lymphoblastic leukaemia (FAB classification type 3); AML/1 = acute myeloblastic leukaemia (FAB classification type 1); CDC = center of disease control; CML/CP = chronic myelocytic leukaemia (chronic phase); CMV = cytomegalovirus; CVID = common variable immunodeficiency; DHPG = 1,3-dihydroxy-2-propoxymethyl-guanine (gancyclovir); ELISA = enzyme-linked immunosorbent assay; GvHD = graft versus host reaction; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INH = isoniazid; LIG = Lactobin; MAI = mycobacterium avium intracellulare; RAEB-T = refractory anaemia with excess of blasts-transformation; SD = standard deviation

The immunoglobulin preparation from bovine colostrum was obtained from Biotest Pharma GmbH, Dreieich, FRG

Chronic non-bloody diarrhoea with wasting is one of the major therapeutic problems of acquired immunodeficiency syndrome (AIDS) patients. Diar-

rhoea and weight loss are found in more than 50% of patients with AIDS (Cone et al. 1986). The cellular immune deficiency causes a high susceptibility to intestinal infections with *Cryptosporidium* (Conolly et al. 1988), *Giardia lamblia* (Quinn et al. 1983), *Salmonella* (Jacobs et al. 1985) and other pathogens. Diarrhoeal illness is also frequently present in those patients with less severe clinical manifestations of immunodeficiency (Santangelo and Kreis 1986; Cello 1988; Laughon et al. 1988; Smith et al. 1988). Serwadda et al. reported in 1985 the extremely high incidence and mortality of diarrhoea, the so-called "slim" disease, in AIDS patients in Uganda.

Enteropathic AIDS with long-lasting, therapy-refractory diarrhoea is also a very common syndrome in human immunodeficiency virus (HIV)-infected patients in the USA and Europe (Kotler et al. 1984). In recent studies (Conolly et al. 1989) as well as in the case of our patients, only 30% of the stool specimens of HIV-infected patients were positive for diarrhoea-causing pathogens, indicating the unsuccess fulness of antibiotic therapy. In cases of cryptosporidiosis, chemotherapeutic drugs such as spiramycin have generally proved to be ineffective (Casemore et al. 1985). Thus, there is a need for alternate therapy regimens in cases of chronic diarrhoea in HIV-infected patients with or without proof of enteropathogenic organisms.

The first milk produced by cows after calving is called colostrum. It contains high titers of antibodies against a wide range of bacterial, viral and protozoal pathogens as well as against various bacterial toxins (Table 1). These antibodies protect the calf from intestinal infections during its early life, when the immune system is still immature. Usually, the newborn calf deprived of colostrum soon dies of colisepticaemia (Seto et al. 1976).

In a multi-center, open and uncontrolled "pilot study", we treated 37 patients suffering from chronic diarrhoea [29 HIV-infected patients, 2 patients with common variable immunodeficiency (CVID), 1 unidentified immunodeficiency, 5 patients with intestinal graft verus host disease (GvHD) following allogeneic bone marrow transplantation with oral immunoglobulins from bovine colostrum (Lactobin, LIG, Biotest, Dreieich). LIG was given as a 10% drinking solution (10 g/100 ml) daily for 10 days.

Although this study was uncontrolled, it was our aim to investigate the beneficial effects of LIG on the frequency and duration of diarrhoea. In some cases the therapeutic effects of LIG on specific stool pathogens, notably *Cryptosporidium*, could be demonstrated.

Table 1. Protein composition of lactimmunglobulin (LIG; 10% solution, g/100 ml). Each value represents the mean from 3 batches

Constituent	Concentration (g/100 ml)
IgG	6.0
IgA	0.4
IgM	1.95
Lactose	0.65
Lipids	<0.1

Ig = immunoglobulin

Methods

This "pilot study" was open and uncontrolled. The main end-point of the study presented here was the stool frequency and the body weight of patients under therapy. The following immunocompromised patients were included in the study: 27 adult HIV-infected patients (CDC IV A, 7; CDC IV C, 19; CDC III, 1), 2 paediatric HIV-positives (P2, 2), 2 CVID, 1 unidentified immunodeficiency with intestinal cryptosporidiosis, 5 intestinal GvHD following allogeneic bone marrow transplantation. The mean age was 34.7 years (range 1–54 years), 31 were male and 6 were female. Two HIV-infected patients were intravenous drug users, 23 were homosexual, 2 were haemophiliacs, and the 2 children were infected in utero.

Colostrum was obtained from non-immunized cows within the first 10 h after calving. It was taken only from healthy animals, which were under regular veterinary supervision. The entire preparation was performed using the customary techniques of the diary industry (Stephan et al. 1990). After the removal of fat, the casein was precipitated with HCL, and the whey was spray-dried. The protein composition of the product is shown in Table 1. More than 80% of the protein is represented by immunoglobulins (Ig) G, A and M. A large proportion of IgA is present in the secretory form. Antibody titres against bacterial antigens were determined by passive haemagglutination (Neter 1956) or immunoblotting tests. Antibodies to *Cryptosporidia* species were performed by enzyme-linked immunosorbent assay (ELISA) using *Cryptosporidia* oocysts as antigen (Dr. R. Watson, University of Arizona, Tucson). Antitoxin activities were measured by the inhibition of haemolysis as described previously (Stephan et al. 1990). The results are shown in Table 2. The resistance of Lactobin against proteolytic digestion was tested by in-

Table 2. Antibody activities and antitoxin activities in LIG (50 g/l). Each value represents the mean from 3 batches

Antigen	Reciprocal antibody titres
Escherichia coli[a]	640
Escherichia coli J5[a]	640
Pseudomonas aeruginosa[a]	640
Klebsiella pneumonia[a]	640
Proteus vulgaris[a]	80
Serratia marcescens HY[a]	1280
Salmonella typhimurium[a]	160
Staphylococcus aureus[a]	640
S. epidermidis[a]	160
Streptococcus pyogenes[a]	160
S. faecalis[a]	160
S. viridans[a]	640
S. B[a]	80
Cryptosporidia oocysts[b]	100
Candida albicans[c]	320
Campylobacter jejuni[c] (outer surface antigens)	1280
Helicobacter pylori[c]	640
Yersinia enterocolitica YOP1[c] (outer membrane proteins)	1280
Shiga-like toxin I[c]	1600
Shiga-like toxin II[c]	3200
E. coli heat unstable enterotoxin (LT)[c]	100
Rotavirus[c]	32

[a] Detected by passive haemagglutination
[b] Detected by enzyme-linked immunosorbent assay
[c] Detected by immunoblotting

cubation of the product with artificial gastric juice (pH 2.4–4.0) for 24 h (Präparate Information 1989).

Stool examination and culture

Fresh stools were immediately examined by microscopy for parasites such as *Entamoeba histolytica* and *Giardia lamblia* in a saline wet preparation. Cryptosporidial oocysts were demonstrated by acid-fast staining of the unconcentrated stool, using carbol-fuchsin and a methylene blue counterstain (Heine et al. 1982; Garcia et al. 1983). Controls were performed by a modified Ziehl-Neelsen technique (Henriksen et al. 1981). Fresh stools were cultured on *Shigella-Salmonella*-selective agar media and on selective media for mycobacteria, *Campylobacter* and *Versinia* species. These examinations were performed before and after LIG therapy. Endoscopy of the colon was performed in 5 cases, so we cannot exclude an intestinal cytomegalovirus (CMV) infection in all treated patients.

In HIV-infected patients and the CVID patients, the daily stool frequency and body weight were examined before and after LIG therapy. In GvHD patients the stool frequency as well as the grade of GvHD involvement of the skin and the liver were examined during therapy. In one GvHD patient the daily stool frequency was below 4 per day (no. 2). One patient (no. 5) was treated on day 4 after the second bone marrow transplantation.

Treatment

Patients with diarrhoea (more than 4 stools per day) for longer than 2 weeks were treated daily with 100 ml of a 10% solution for 10 days. LIG was taken orally 30 min before breakfast. Patients who had a relapse of diarrhoea after the treatment period were treated a second time.

Thirteen of the 29 HIV-infected patients and the two CVID patients were treated in addition to the LIG treatment with one or more of the following drugs: azidothymidin (13), trimetoprim, sulfamethoxazol (2) because of *Pneumocystis carinii* infection, i.v. gamma-globulins (2), fluconazol (1), ciprofloxacin (1) because of bronchopneumonia, isoniazid (INH)/rifampicin/myambuthol (1), 1,3-dihydroxy-2-propoxymethyl guanine (DHPG) (1). The following anti-diarrhoeal drugs were used without any benefit before starting the LIG therapy: metronidazol (2), ciprofloxacin (3), trimethoprim sulfamethoxazol (3), spiramycin (1) and 5-aminosalicylic acid (1).

Results

Stool frequency

Twenty-one out of 31 treatment periods of 29 HIV-infected patients, 5 out of 6 treatment periods in 5 GvHD patients and all 3 treatments of the other 3 immunodeficient patients gave good results, leading to transient or long-lasting normalisation of their stool frequency. The mean daily stool frequency decreased from 7.4 ± 3.8 before therapy to 2.8 ± 2.8 after 5 days of therapy. The daily stool frequency was nearly normalized (2.2 ± 3.2) at the end of the LIG treatment. After a pause in the LIG therapy for an interval of 10 days, the mean stool frequency rose from 2.8 to 4.7 ± 4.8 per day, indicating that relapses took place (Fig. 1).

Eight HIV-infected patients showed no decrease of their initial stool frequency. Four of them had

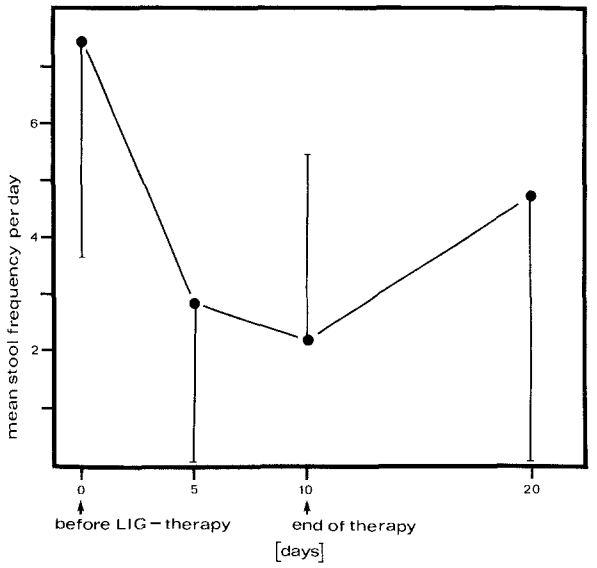

Fig. 1. LIG treatment in immunodeficiency-associated diarrhoea. Forty treatment periods in 37 immunocompromised patients [29 human immunodeficiency virus (HIV)-infected patients, 2 common variable immunodeficiency (CVID), 1 unidentified immunodeficiency, 5 graft vs. host disease (GvHD)]. Mean daily stool frequency before (day 0), after 5 days (day 5), after 10 days (day 10) of therapy and 10 days after stopping the LIG therapy (day 20). The 10 g LIG was given in a 10% solution. Data represents mean ± SD

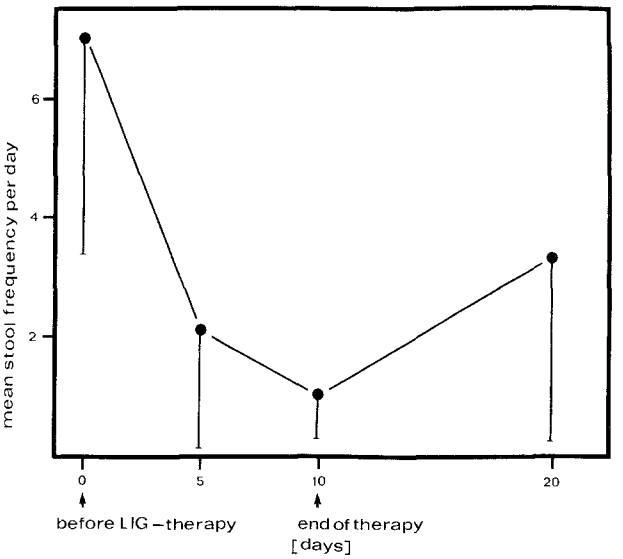

Fig. 2. LIG treatment in immunodeficiency-associated diarrhoea. Twenty-nine treatment periods in 25 immunocompromised patients (18 HIV-infected patients, 2 CVID, 1 unidentified immunodeficiency, 4 GvHD). Responders only, defined as patients whose stool frequency dropped below 3 stools per day. Mean daily stool frequency before (day 0), after 5 days (day 5), after 10 days (day 10) of therapy and 10 days after stopping the LIG therapy (day 20). The 10 g LIG was given in a 10% solution. Data represent mean ± SD

more than 10 stools per day after 10 days of therapy. Two of these patients suffered from an intestinal Kaposi's sarcoma, so that a reduction of the daily stool frequency could not be expected by LIG therapy in these cases. One patient was treated successfully 8 weeks after the first LIG cycle had failed; the fourth patient continued to have 10–15 stools per day, but *Cryptosporidium* oocysts were no longer detectable at the end of LIG therapy.

Looking at the group of responders only (21 HIV-infected patients, 2 CVID, 1 unidentified immunodeficiency, 4 GvHD), defined as patients whose stool frequency decreased below 3 stools per day, we saw a reduction of the mean stool frequency from 7.0 ± 3.6 before therapy to 2.1 ± 2.0 after 5 days of LIG therapy. In this selected group the mean stool frequency was normal (1.1 ± 0.7) on day 10 (Fig. 2).

Patients lost up to 10% of their body weight due to long lasting diarrhoea. Before entering the study the mean body weight was 60.1 ± 14.5 kg and it remained stable during LIG therapy (59.8 ± 14.4 kg).

Recurrence of diarrhoea

Diarrhoea recurred after 12 treatment periods (32.4%) within 4 weeks, so that the daily stool frequency increased to 4.8 ± 4.6 in the first 10 days after the end of LIG therapy (Fig. 1). After 19 treatment periods the patients were free of diarrhoea for at least 4 weeks (51.3%). Data concerning the recurrence of diarrhoea were not available in 6 treatments of immunodeficiency or HIV and in the 6 treatment periods in GvHD patients. Three patients with recurrent diarrhoea were treated a second time with LIG for 10 days. Again, a reduction of the daily stool frequency from 5 to 1 stools per day (patient 1 and 2) and from 6 to 2 stools per day (patient 3) occurred.

Side effects

Three patients complained about nausea and 4 about flatulence following the LIG drink. Of the 37 treated patients 29 complained about the unattractive taste of LIG. No serious side effects were recorded in any of the treated patients.

Stool pathogens

Only one-third of our patients had detectable pathogens as a possible cause of their diarrhoea (Table 3). *Gardia lamblia*, *Blastomyces hominis* and *Campylobacter hominis* disappeared after LIG therapy. Similarly, 5 of 7 patients with intestinal crypto-

Table 3. Causes of diarrhoea in 37 treatment periods in 29 HIV-infected patients, 2 CVID and 1 unidentified immunodeficiency

Identified pathogen	Positive stool examinations	
	before therapy	after therapy
Gardia lamblia	2[a]	0
Blastomyces hominis	1	0
Spiral bacteria	1	n.t.
Campylobacter jejuni	1	0
Cryptosporidia species	7	2[b]
No infectious agent identified	23	

[a] In one patient *Gardia lamblia* and cryptosporidia were detectable

[b] After the second cycle of LIG treatment cryptosporidia were no longer detectable

Table 4. Stool frequency after LIG treatment in 29 HIV-infected patients, 2 CVID and 1 unidentified immunodeficiency. Evaluation of 34 treatment periods. (A) Treatment periods without proven stool pathogens, (B) with detectable stool pathogens, (C) all treatment periods

	Daily stool frequency			
	<3/day	3–4/day	4–10/day	>10/day
A	16	3	3	1
B	5	2	3	1
C	21	5	6	2

sporidiosis were free of the pathogens after 10 days of LIG treatment. Two patients did not respond. One of them cleared the cryptosporidiosis after a second cycle of LIG treatment (Table 3).

In patients without proven stool pathogens, 16 out of 23 treatment periods resulted in a normalisation of stool frequency. In 3 patients a reduction of the previously existing diarrhoea to 3 stools per day was recorded. No change during therapy was observed with 3 patients, while an exacerbation of diarrhoea occurred in 1 patient (Table 4). Since endoscopy of the colon was not performed in all treated cases, an intestinal cytomegalovirus (CMV) infection cannot be excluded. In 11 patients with proven stool pathogens, 5 treatment periods resulted in a normalisation of stool frequency. Four of them cleared cryptosporidia and one patient cryptosporidia and *Gardia lamblia* infection.

Therapy in GvHD

Five patients suffering from intestinal GvHD following allogeneic bone marrow transplantation also gained a benefit from LIG treatment. All patients were treated for 10 days between day 4 and 86 after bone marrow transplantation. The treatment resulted in a normalisation of stool frequencies in 4 treatments and reduction in 1 treatment period. Only 1 patient had 5 stools before and 8 stools at the end of the LIG treatment period. Surprisingly, GvHD involvement of the skin decreased from grade IV to grade I with therapy in this case; liver involvement dropped from grade II to grade I.

Discussion

Chronic diarrhoea is a very common problem in the outpatient care of HIV-infected patients. Due to their cellular immunodeficiency these patients are predisposed to a number of opportunistic gastrointestinal infections such as *Cryptosporidium, Salmonella,* CMV and *Mycobacterium avium intracellulare* (MAI).

Conolly et al. reported that about 70% of their patients with AIDS related complex treated in St. Stephens Hospital in London complained of intermittant diarrhoea (Conolly et al. 1989). If enteropathogenic organisms are demonstrable, there is often no sufficient treatment available; for example, in cases of cryptosporidiosis or MAI infections chemotherapeutic drugs have generally proved to be ineffective (Casemore et al. 1985).

As an alternate therapy we tried to treat these patients orally with immunoglobulins from bovine colostrum (LIG). It has been shown by others that bovine colostral milk can protect against enterotoxigenic *E. coli* and infantile *Rotavirus* infections, *E. coli* gastroenteritis (Mietens et al. 1979; Barnes et al. 1982; Ebina et al. 1985; Losonski et al. 1985; Tacket et al. 1988), cryptosporidiosis (Tzipori et al. 1986) and gastrointestinal candidosis (Smith 1988). In addition, bovine colostrum orally administered has anticholera toxin activity and is effective in patients with cholera diarrhoea (McClead and Butter 1988).

In the open and uncontrolled pilot study presented here, the clinical benefit of the patients treated with LIG was evident. Diarrhoea patients with and without a positive proof of intestinal pathogens showed a decrease in frequency and quantity of diarrhoea. The mean body weight remained stable during therapy with LIG, in contrast to a weight loss up to 10% due to the long-lasting diarrhoea before entering the study. However the beneficial effects of Lactobin therapy usually lasted only for short periods of time, so that repeated or continued LIG treatments will be necessary to control diarrhoea in HIV-infected patients.

The resistance of the colostral immunoglobulins to proteolysis in the gastrointestinal tract has been shown by de Rham and Isliker (1977), Hilpert et al. (1975) and McClead and Gregory (1984). Moreover, bovine colostral milk contains a trypsin inhibitor that may protect the bovine immunoglobulins from proteolysis (Pineiro et al. 1978). Thus, it can be supposed that specific antibodies from colostrum which lend protection against the abovementioned pathogens remain active in the gastrointestinal tract of the treated patients in reasonable concentrations.

Cryptosporidiosis is a major problem in HIV-infected patients. This protozoan parasite infects immunocompetent and immunocompromised patients. Cryptosporidia species are readily eliminated by an healthy immune system and may lead to a short diarrhoeal episode. Cryptosporidiosis was first described in CVID patients, in whom it may lead to chronic malabsorption and severe weight loss (Lasser et al. 1979; Sloper et al. 1982). In HIV-infected patients *Cryptosporidia* species are highly virulent and lead to chronic diarrhoea in spite of treatment with other antimicrobial agents (Laughon et al. 1988). Since cryptosporidiosis is very common in bovine animals, Lactobin contains high antibody titers against this pathogen (see Table 2). We could demonstrate, as others in individual cases (Tzipori et al. 1986), that in 5 out of 7 patients with *Cryptosporidia*-associated diarrhoea a therapy with Lactobin was effective. Therefore, bovine colostrum appears to be a useful adjunct in the treatment of diarrhoea due to infection with *Cryptosporidium* in patients with immunodeficiency disorders, particularly in cases where treatment with antibiotics has failed.

The beneficial effects of LIG treatment in allogeneic bone marrow transplantation recipients suffering from intestinal GvHD and diarrhoea were also demonstrable. Whether or not these effects are pathogen-specific, similar to those seen after sterilisation of the gut by antibiotics, needs further investigation.

In summary, LIG therapy of diarrhoea associated with HIV infection is safe and free of any side effects, and it was at least transitorily efficient in most of the treated patients. We admit that the validity of this pilot study is reduced by the lack of a placebo control group and the missing colon diagnostic by endoscopy. Nevertheless, one can speculate from these data that besides in cases of HIV-associated diarrhoea, Lactobin might also be useful in other forms of diarrhoea, for instance in chronic inflammatory bowel diseases.

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